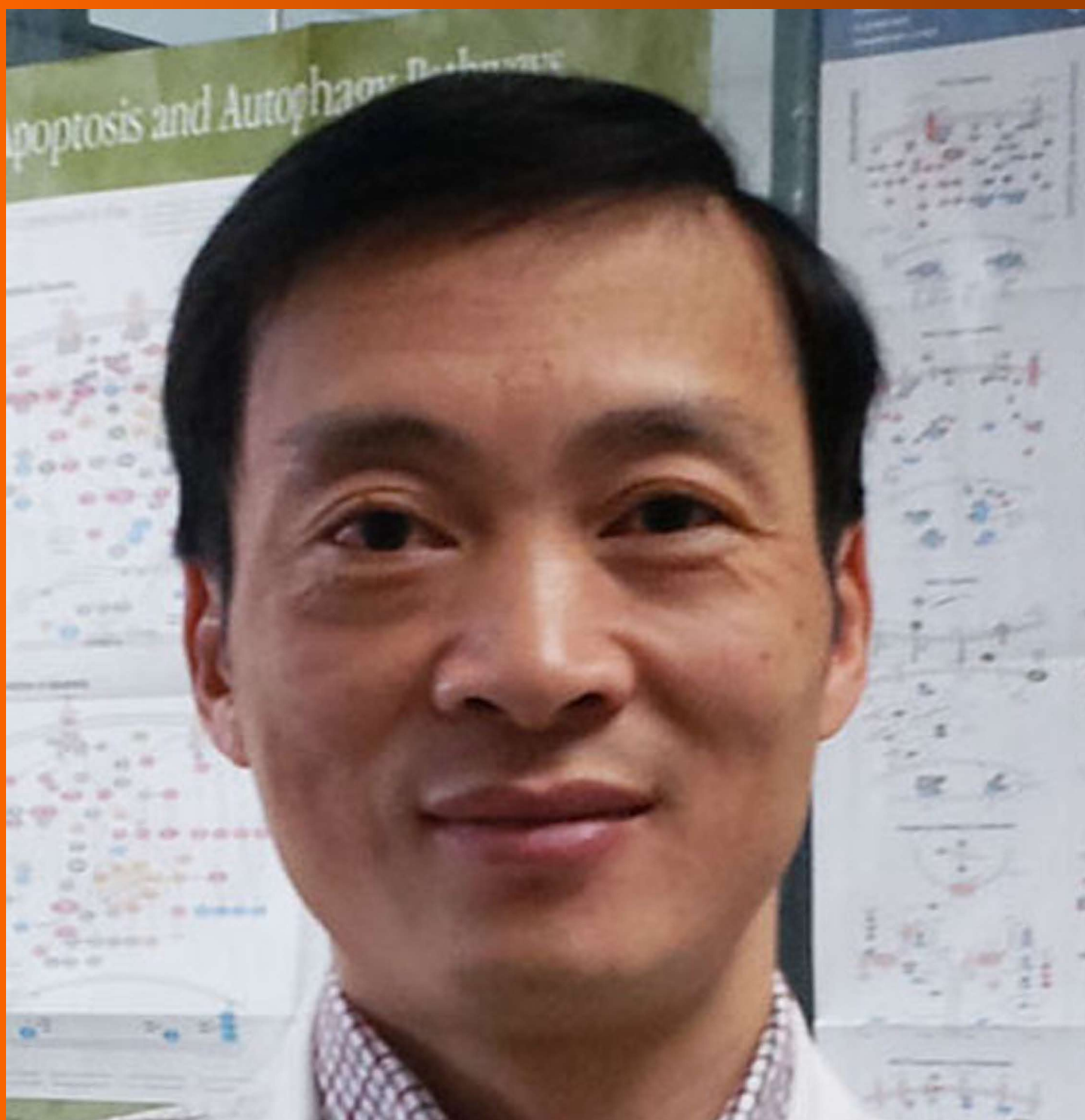


World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 January 10; 8(1): 1-29





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmänn, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hirotoshi Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hirotoshi Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



EDITORIAL

- 1 Confocal endomicroscopy: Is it time to move on?
Robles-Medrandá C

REVIEW

- 4 Bowel cleansing before colonoscopy: Balancing efficacy, safety, cost and patient tolerance
Harrison NM, Hjelkrem MC
- 13 Role of endoscopic clipping in the treatment of oesophageal perforations
Lázár G, Paszt A, Mán E

MINIREVIEWS

- 23 Role of self-expanding metal stents in the management of variceal haemorrhage: Hype or hope?
Hogan BJ, O'Beirne JP

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 1 January 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Yong-Liang Zhu, PhD, Assistant Professor, Second Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, China

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Thomson Reuters Web of Science Emerging Sources Citation Index, PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jin-Xin Kong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
January 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Confocal endomicroscopy: Is it time to move on?

Carlos Robles-Medranda

Carlos Robles-Medranda, Gastroenterology and Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas, University Hospital OMNI, Guayaquil 090505, Ecuador

Author contributions: Robles-Medranda C solely contributed to this work.

Conflict-of-interest statement: The author has no conflict of interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Carlos Robles-Medranda, MD, Head of the Endoscopy Division, Gastroenterology and Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas, University Hospital OMNI, Av. Abel Romeo Castillo y Av. Juan Tanca Marengo, Torre Vitalis, Mezanine 3, Guayaquil 090505, Ecuador. carlosoakm@yahoo.es
Telephone: +593-4-2109180
Fax: +593-4-2109180

Received: May 28, 2015

Peer-review started: May 31, 2015

First decision: August 16, 2015

Revised: September 5, 2015

Accepted: November 13, 2015

Article in press: November 17, 2015

Published online: January 10, 2016

Abstract

Confocal laser endomicroscopy permits *in-vivo* microscopy evaluation during endoscopy procedures. It can be used in all the parts of the gastrointestinal tract and includes: Esophagus, stomach, small bowel, colon, biliary tract through and endoscopic retrograde

cholangiopancreatography and pancreas through needles during endoscopic ultrasound procedures. Many researches demonstrated a high correlation of results between confocal laser endomicroscopy and histopathology in the diagnosis of gastrointestinal lesions; with accuracy in about 86% to 96%. Moreover, in spite that histopathology remains the gold-standard technique for final diagnosis of any diseases; a considerable number of misdiagnosis rate could be present due to many factors such as interpretation mistakes, biopsy site inaccuracy, or number of biopsies. Theoretically; with the diagnostic accuracy rates of confocal laser endomicroscopy could help in a daily practice to improve diagnosis and treatment management of the patients. However, it is still not routinely used in the clinical practice due to many factors such as cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist. These limitations are relative, and solutions could be found based on new researches focused to solve these barriers.

Key words: Confocal laser endomicroscopy; *In-vivo* microscopy; Barret esophagus; Gastrointestinal cancer; Confocal laser endomicroscopy probe

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Confocal laser endomicroscopy (CLE) permits *in-vivo* microscopy evaluation during endoscopy procedures. It can be used in all the parts of the gastrointestinal tract with accuracy in about 86% to 96%. In spite of its high accuracy as well as several clinical applications, CLE is still not used in routine clinical practice. This could be correlated to many factors such as: cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist. However, these limitations are relative, and solutions could be found

based on new research leading to increased consensus overcoming present barriers.

Robles-Medranda C. Confocal endomicroscopy: Is it time to move on? *World J Gastrointest Endosc* 2016; 8(1): 1-3 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i1/1.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i1.1>

INTRODUCTION

Confocal laser endomicroscopy (CLE) is an advanced endoscopic imaging modality that provides histology-like images at 1000-fold magnification for *in-vivo* microscopy evaluation^[1]. Since the first publication about the use of CLE in the gastrointestinal tract, ten years have passed^[2].

The technology was initially developed for an endoscope-integrated CLE system (e-CLE) (EC3870K, Pentax Medical, Japan) with specific applications to upper and lower endoscopy, and a few years later for a probe-based CLE system (p-CLE) (Cellvizio, Mauna Kea Technologies, France)^[1,2].

Nowadays only p-CLE is commercially available, with the advantage that it can be used in other parts of gastrointestinal tract as in bilio-pancreatic diseases through endoscopic retrograde cholangiopancreatography and endoscopic ultrasound.

Several studies have demonstrated a high correlation of results between CLE and histopathology in gastrointestinal lesions^[1,2]. In fact, CLE has overcome some of the limitations found in endoscopy (macroscopy) and histopathology (microscopy), thus improving patient management.

In spite of its high accuracy and several clinical applications, CLE is still not routinely used in the clinical practice due to many barriers.

CLINICAL EVIDENCE AND APPLICATIONS

It has been demonstrated that white light endoscopy is not accurate for predicting histological inflammation or other alterations such as nonspecific erythema, nodularity, erosions, etc.^[3].

Moreover, the limits between neoplastic and inflammatory areas are very narrow/unclear due to the coexistence of these processes together.

When using CLE during endoscopy we can clearly understand why the correlation between standard videoendoscopy and histopathology is not higher than 70% in most cases^[4].

Many studies evidence an accuracy of 81.5% using p-CLE for the diagnosis of dysplasia in Barrett esophagus^[5].

In gastric diseases, CLE has had an accuracy of 94%-96% for diagnosis of malignancy when compared directly with histological biopsies^[6]; and 88% for pre-malignant conditions such as intestinal metaplasia^[7].

In colon conditions, CLE has had an accuracy of 82%

for predicting polyp histology *in-vivo*, increasing to 94% if used in combination with digital chromoendoscopy with narrow band imaging during procedures^[8]. Moreover, in inflammatory bowel diseases (IBDs), various studies have examined the role of CLE in surveillance of IBD patients, assessing the extent of disease, targeting biopsies, earlier detection of dysplasia, assessment of mucosal healing, and defining treatment protocols^[9,10].

Recently, new applications in the biliary tract and for diagnosing subtypes of pancreatic cysts have been studied showing a mean accuracy of 85% for diagnosis of neoplastic and non-neoplastic lesions^[11,12].

IS IT TIME TO MOVE ON?

In spite of its high accuracy as well as several clinical applications, CLE is still not used in routine clinical practice. This could be correlated to many factors such as: cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist.

However, these limitations are relative, and solutions could be found based on new research leading to increased consensus overcoming present barriers. Examples of this could be: cost-effective studies and analysis, meta-analysis, learning curve studies, etc.

A recent study performed at our institution demonstrated the benefit of using CLE in cases of "diagnostic doubts", causing changes in diagnostic and therapeutic approach in 40% of cases, in the performance of target biopsies in 100% of cases (17/17) and making other diagnostic or therapeutic methods unnecessary in all cases^[13].

In this regard, a patient with Barrett esophagus and dysplasia at histopathology but without dysplasia criteria at high definition with chromoendoscopy could have diagnosis benefits using CLE. Other examples are: patients with biliary tract stenosis of unknown origin where citobrush did not evidence neoplasia, and the difficult management during follow-up repetitions. In both cases, need of newer tests and examinations, biopsies, etc., will be unnecessary, reducing the cost management of these patients.

One of the biggest problems when using CLE, is that histopathology remains the gold-standard technique for final diagnosis of diseases. However, histopathology could have a 20% to 30% misdiagnosis rate due to many factors such as interpretation mistakes, biopsy site inaccuracy, or number of biopsies^[4].

Another suggestion would be to use CLE in cases where other investigative procedures have shown an absence of malignancy as a method of confirmation of the negative results. This would eliminate many of the medical and cost-related problems mentioned above. The rationale for this is based on the fact that 9 out of 10 biopsies are benign and that the accuracy of CLE to confirm non-neoplastic lesions is higher than its

accuracy for confirming positive neo-plastic results.

FUTURE PERSPECTIVES

New studies focused on solving the relative barriers in using CLE are currently necessary. The results obtained during the last ten years validate the use of CLE in clinical practice, and the first step to doing this could be dealing with patients with diagnostic uncertainties. This could improve and solve many unclear diagnoses as well as improve therapeutic decisions and/or follow-up procedures in this kind of patient.

REFERENCES

- 1 **Choi KS**, Jung HY. Confocal laser endomicroscopy and molecular imaging in barrett esophagus and stomach. *Clin Endosc* 2014; **47**: 23-30 [PMID: 24570880 DOI: 10.5946/ce.2014.47.1.23]
- 2 **Wang KK**, Carr-Locke DL, Singh SK, Neumann H, Bertani H, Galmiche JP, Arsenescu RI, Caillol F, Chang KJ, Chaussade S, Coron E, Costamagna G, Dlugosz A, Ian Gan S, Giovannini M, Gress FG, Haluszka O, Ho KY, Kahaleh M, Konda VJ, Prat F, Shah RJ, Sharma P, Slivka A, Wolfsen HC, Zfass A. Use of probe-based confocal laser endomicroscopy (pCLE) in gastrointestinal applications. A consensus report based on clinical evidence. *United European Gastroenterol J* 2015; **3**: 230-254 [PMID: 26137298 DOI: 10.1177/2050640614566066]
- 3 **Elta GH**, Appelman HD, Behler EM, Wilson JA, Nostrant TJ. A study of the correlation between endoscopic and histological diagnoses in gastroduodenitis. *Am J Gastroenterol* 1987; **82**: 749-753 [PMID: 3300278]
- 4 **Deutsch JC**. The optical biopsy of small gastric lesions. *Gastrointest Endosc* 2014; **79**: 64-65 [PMID: 24342587 DOI: 10.1016/j.gie.2013.07.035]
- 5 **Gaddam S**, Mathur SC, Singh M, Arora J, Wani SB, Gupta N, Overhiser A, Rastogi A, Singh V, Desai N, Hall SB, Bansal A, Sharma P. Novel probe-based confocal laser endomicroscopy criteria and interobserver agreement for the detection of dysplasia in Barrett's esophagus. *Am J Gastroenterol* 2011; **106**: 1961-1969 [PMID: 21946283 DOI: 10.1038/ajg.2011.294]
- 6 **Kitabatake S**, Niwa Y, Miyahara R, Ohashi A, Matsuura T, Iguchi Y, Shimoyama Y, Nagasaka T, Maeda O, Ando T, Ohmiya N, Itoh A, Hirooka Y, Goto H. Confocal endomicroscopy for the diagnosis of gastric cancer in vivo. *Endoscopy* 2006; **38**: 1110-1114 [PMID: 17111332 DOI: 10.1055/s-2006-944855]
- 7 **Lim LG**, Yeoh KG, Srivastava S, Chan YH, Teh M, Ho KY. Comparison of probe-based confocal endomicroscopy with virtual chromoendoscopy and white-light endoscopy for diagnosis of gastric intestinal metaplasia. *Surg Endosc* 2013; **27**: 4649-4655 [PMID: 23892761 DOI: 10.1007/s00464-013-3098-x]
- 8 **Shahid MW**, Buchner AM, Heckman MG, Krishna M, Raimondo M, Woodward T, Wallace MB. Diagnostic accuracy of probe-based confocal laser endomicroscopy and narrow band imaging for small colorectal polyps: a feasibility study. *Am J Gastroenterol* 2012; **107**: 231-239 [PMID: 22068663 DOI: 10.1038/ajg.2011.376]
- 9 **Neumann H**, Vieth M, Atreya R, Neurath MF, Mudter J. Prospective evaluation of the learning curve of confocal laser endomicroscopy in patients with IBD. *Histol Histopathol* 2011; **26**: 867-872 [PMID: 21630216]
- 10 **Kiesslich R**, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterology* 2007; **132**: 874-882 [PMID: 17383417 DOI: 10.1053/j.gastro.2007.01.048]
- 11 **Slivka A**, Gan I, Jamidar P, Costamagna G, Cesaro P, Giovannini M, Caillol F, Kahaleh M. Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary strictures: results of a prospective multicenter international study. *Gastrointest Endosc* 2015; **81**: 282-290 [PMID: 25616752 DOI: 10.1016/j.gie.2014.10.009]
- 12 **Napoléon B**, Lemaistre AI, Pujol B, Caillol F, Lucidarme D, Bourdariat R, Morellon-Mialhe B, Fumex F, Lefort C, Lepilliez V, Palazzo L, Monges G, Filoche B, Giovannini M. A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy. *Endoscopy* 2015; **47**: 26-32 [PMID: 25325684 DOI: 10.1055/s-0034-1390693]
- 13 **Robles-Medranda C**, Ospina J, Puga-Tejada M, Soria Alcivar M, Bravo Velez G, Robles-Jara C, Lukashok HP. Clinical impact of confocal laser endomicroscopy probe (p-cle) in the management of gastrointestinal neoplastic and non-neoplastic lesion. *Gastrointest Endosc* 2015; **81**: AB243 [DOI: 10.1016/j.gie.2015.03.283]

P- Reviewer: Gupta RA, Tada M **S- Editor:** Gong ZM

L- Editor: A **E- Editor:** Lu YJ



Bowel cleansing before colonoscopy: Balancing efficacy, safety, cost and patient tolerance

Nicole M Harrison, Michael C Hjelkrem

Nicole M Harrison, Department of Medicine, Fort Belvoir Community Hospital, Fort Belvoir, VA 22060, United States

Michael C Hjelkrem, Department of Gastroenterology, Fort Belvoir Community Hospital, Fort Belvoir, VA 22060, United States

Author contributions: Harrison NM and Hjelkrem MC contributed solely to this paper.

Conflict-of-interest statement: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Michael C Hjelkrem, MD, Department of Gastroenterology, Fort Belvoir Community Hospital, 9300 DeWitt Loop, Fort Belvoir, VA 22060, United States. mhjelkrem@yahoo.com
Telephone: +1-571-2312014

Received: June 23, 2015

Peer-review started: June 24, 2015

First decision: August 25, 2015

Revised: September 15, 2015

Accepted: November 10, 2015

Article in press: November 11, 2015

Published online: January 10, 2016

Abstract

Effective colorectal cancer screening relies on reliable colonoscopy findings which are themselves dependent on adequate bowel cleansing. Research has consistently demonstrated that inadequate bowel preparation adversely affects the adenoma detection rate and leads gastroenterologists to recommend earlier follow up than is consistent with published guidelines. Poor preparation affects as many as 30% of colonoscopies and contributes to an increased cost of colonoscopies. Patient tolerability is strongly affected by the preparation chosen and manner in which it is administered. Poor tolerability is, in turn, associated with lower quality bowel preparations. Recently, several new developments in both agents being used for bowel preparation and in the timing of administration have brought endoscopists closer to achieving the goal of effective, reliable, safe, and tolerable regimens. Historically, large volume preparations given in a single dose were administered to patients in order to achieve adequate bowel cleansing. These were poorly tolerated, and the unpleasant taste of and significant side effects produced by these large volume regimens contributed significantly to patients' inability to reliably complete the preparation and to a reluctance to repeat the procedure. Smaller volumes, including preparations that are administered as tablets to be consumed with water, given as split doses have significantly improved both the patient experience and efficacy, and an appreciation of the importance of the preparation to colonoscopy interval have produced additional cleansing.

Key words: Bowel preparation; Colonoscopy; Adenoma detection rate; MiraLAX; Polyethylene glycol; Sodium picosulfate; Oral sulfate solution

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Improvements in efficacy and tolerability of

bowel preparation include new formulations that are more tolerable to patients without sacrificing efficacy or safety, and a better understanding of the ideal timing of bowel preparation administration.

Harrison NM, Hjelkrem MC. Bowel cleansing before colonoscopy: Balancing efficacy, safety, cost and patient tolerance. *World J Gastrointest Endosc* 2016; 8(1): 4-12 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i1/4.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i1.4>

INTRODUCTION

Many patients describe the bowel preparation prior to colonoscopy as the most unpleasant part of the whole procedure and the biggest deterrent to repeating it. Unfortunately, in addition to being the most loathed aspect, the bowel preparation is one of the most critical components of effective screening for colon cancer. The ideal bowel preparation, though this has not yet been developed, is one that is safe, highly effective and reliable, convenient, and tolerable enough that patients are not deterred from repeating the procedure.

Inadequate bowel preparations lead to lower adenoma detection rates and more frequent follow up intervals than would otherwise be recommended by guidelines based on colonoscopy findings. The European Panel of Appropriateness of Gastrointestinal Endoscopy found that polyp detection was related to the quality of bowel cleansing^[1]. Relative to a low quality preparation, a high quality or intermediate quality preparation produced a 1.46 and 1.73 odds ratio (OR) of polyp detection^[1]. Sherer *et al*^[2] found a lower detection rate of advanced histology in the setting of poor preparation, though the number of polyps 6-9 mm detected was not different. In studies that have looked at early repeat colonoscopy following a suboptimal preparation, the quality of preparation is strongly associated with incidence of missed polyps and adenomas^[3-5]. Lebwahl *et al*^[3] found a 42% overall miss rate after inadequate bowel prep with a 47% miss rate for adenomas less than 10 mm and 27% miss rate for adenomas greater or equal to 10 mm. Hong *et al*^[4] found that the adenoma detection rate decreased as the quality of bowel prep decreased with a precipitous drop off seen as the quality decreased from fair to poor. Ultimately, the adenoma detection rate was associated with patient tolerability with an OR of 0.39 in the setting of poorly tolerated preparations^[6].

The evidence for the benefit of bowel preparation prior to colorectal surgery is less convincing. While it remains the overwhelming practice of surgeons to prescribe a mechanical bowel preparation, studies have not convincingly showed that it reduces the incidence of mortality, skin and soft tissue infections, or peritonitis as compared to no preparation^[7]. Recent studies have supported the use of oral and parenteral antibiotics prior

to procedure. As with the preparation for endoscopy, there is no clear superiority of one regimen over another.

Poor preparation is not an uncommon occurrence. Rates of inadequate bowel preparation are estimated to be as high as 30.2% with as many as 10% being so poor as to preclude any further evaluation^[8]. Due to the increased risk of missed polyps and decreased efficacy of screening in the face of a poor bowel prep, research has found that, in patients with a poor bowel prep, gastroenterologists are less likely to adhere to recommended screening intervals and more frequently recommend closer follow up than would otherwise be appropriate based on intra-procedure findings^[9-11]. Shortened follow up intervals translate into increased screening costs, estimated to be as much as a 12% to 22% increase, and greater inconvenience to patients^[12].

A 4 L preparation of polyethylene glycol (PEG) has been considered the gold standard in terms of prep efficacy but is reviled by patients due to its poor taste and discomfort associated with the larger volumes. Alternate formulations have been developed, but these have had other drawbacks in terms of safety, tolerability, or efficacy. Recently, new options have received Food and Drug Administration (FDA) approval and these may offer improved tolerability without sacrificing efficacy (Table 1).

POLYETHELENE GLYCOL

Four liters PEG-ELS (electrolyte lavage solution) administered in split doses is considered by most to be the standard against which all other bowel preparations are judged^[13]. A systemic review and meta-analysis by Enestvedt *et al*^[13] found an OR of 3.46 that a split dose 4 L PEG-ELS preparation would produce a good or excellent bowel preparation compared with other methods. The pooled analysis did not reveal any other significant differences in performance measures such as overall experience or willingness of patients to repeat the procedure, or in side effects such as nausea.

Nonetheless, many studies conclude that patients prefer lower volume preparations to the full 4 L PEG. Often preceded by a stimulant laxative such as bisacodyl or magnesium citrate, 2 L PEG preparations have been found to achieve equivalent levels of bowel cleansing with enhanced patient experience^[14-19]. A 1994 study comparing single dose preparations of 4 L PEG-ELS with 2 L PEG-ELS preceded by bisacodyl found comparable cleansing^[14]. The subjects in the 2 L PEG-ELS group rated the preparation more tolerable and more patients were able to complete the preparation than in the 4 L group (93% vs 66%). Sharma *et al*^[15] found similar results in a trial comparing 4 L PEG-ELS with 2 L PEG-ELS with bisacodyl or magnesium citrate. The quality of preparation was rated better with 2 L PEG-ELS with bisacodyl or magnesium citrate than with 4 L PEG-ELS (8.1 vs 7.8 vs 7.3). This was coupled with lower procedure times and higher patient

Table 1 Relative effectiveness and cost of available bowel preparations

Prep		% Adequate	Lesion detection rate	Cost ¹
4 L PEG	Single	51%-88% ^[16,64]	PDR 50.5%-51% ^[26,51]	PEG 3350 with electrolytes 4 L
	Split	71.3%-92.1% ^[23,51]	ADR 27.8%-34.3% ^[51,70]	\$26.59
2 L PEG	Single	83.5%-91% ^[45,64]	ADR 18.8% ^[70]	Moviprep 100 g/1 kit
	Split	74.4%-93.5% ^[45,48]		\$91.55
MiraLAX	Single	67.8%-81.8% ^[29,31]	PDR 47% ^[26]	MiraLAX 8.3oz/238 g
	Split			\$13.99
Sodium Phosphate		84.3%-90% ^[35,37]	Not Available	OsmoPrep 32 tabs
				\$163.05
Sodium Picosulfate	Single	61.5%-82.6% ^[49,51]	PDR 38.5%-42.9% ^[51,53]	Prepopik, 2 pkts
	Split	81.6%-87.9% ^[49,50]	ADR 23.8%-31.3% ^[51,53]	\$121.31
Oral Sulfate Solution	SuPrep	94.7%-98.4% ^[44,53]	PDR 50.9% ^[53]	SuPrep 1 kit
				\$49.09
	Suclear	93.5% ^[45]	ADR 26% ^[53]	Suclear
				\$76.38

¹Prices from RxPriceQuotes.com as listed for CVS w/exception of MiraLAX which was priced at local CVS. PEG: Polyethylene glycol; PDR: Polyp detection rate; ADR: Adenoma detection rate.

satisfaction scores. Of 24 subjects who had a previous bowel prep with 4 L PEG-ELS, 88% of those in the 2 L PEG-ELS plus magnesium citrate and 56% of those in the 2 L PEG-ELS plus bisacodyl preferred the low volume preparation. A follow up study by the same group found small, likely clinically insignificant serum electrolyte changes following low dose PEG-ELS with stimulant laxatives^[20]. A low volume PEG plus ascorbic acid in comparison with 4 L PEG-ELS produced an equivalent number of adequate bowel preps (94.6% vs 90%), was better tolerated and produced fewer adverse events (80.2% vs 89.9%)^[21]. Similar results have been obtained in other studies though some have shown that cleansing in the right colon was superior with the 4 L PEG preparation^[22,23].

The relative efficacy of the 2 L PEG preparations is undiminished when it is administered as a split dose^[24,25]. A 2013 study of 2 L PEG-citrate plus bisacodyl and simethicone found that successful preps were achieved in 92.8% vs 92.1% of patients using the 2 L PEG and 4 L PEG respectively^[24]. A higher percentage of excellent right colon preps were observed in the 4 L PEG group. The 2 L PEG prep was better tolerated (31.6% reporting symptoms vs 45.2%) and more patients expressed willingness to repeat the same procedure in the future (90.6% vs 77%). Similar results were obtained using split dose 2 L PEG-ascorbic acid alone^[25]. There was no significant difference in the quality of bowel prep or number of patients achieving an adequate bowel prep in 2 L vs 4 L groups (7.0 ± 2.1 vs 7.1 ± 2.0 and 73.2% vs 76.3%)^[25]. The low volume preparation was rated significantly more tolerable with 14.3% of subjects reporting difficulty in taking the preparation vs 30.7% with the 4 L PEG preparation^[25].

MIRALAX

Though it has not been FDA approved for the purpose, MiraLAX (Bayer Healthcare, Leverkusen, Germany)

has come into widespread use as a bowel prep agent in spite of equivocal evidence supporting its efficacy as compared to FDA approved alternatives due to the convenience of using an over the counter product and superior palatability. A recent survey of practicing gastroenterologists found that one third regularly recommend some sort of MiraLAX based bowel prep to their patients with rates as high as 50% in suburban practices and a positive correlation between the number of colonoscopies performed and the likelihood of recommending a MiraLAX based bowel prep^[26]. MiraLAX based bowel preps, typically 238 mg of MiraLAX in 64oz of Gatorade, has generally, though not universally, been found to be more tolerable to patients^[27-30].

The data regarding the cleansing achieved with MiraLAX is more mixed. McKenna *et al.*^[30] found that single dose MiraLAX was non-inferior compared to 4 L of PEG-ELS, both taken the night before procedure. Both MiraLAX and PEG-ELS produced equivalent BBPS (7.0 vs 7.2) and had similar percentages of patients achieving adequate bowl preps (BBPS ≥ 6, 81.3% vs 84.3%). The authors found no difference in time to cecal intubation or withdrawal time. MiraLAX was preferred by study subjects. Similar results were obtained in a study by Samarasena *et al.*^[28] comparing split dose MiraLAX with split dose PEG-ELS. Again, no significant difference in BBPS (8.01 vs 8.33) was observed and the MiraLAX based prep was given significantly better ratings in terms of taste and tolerability with 96.8% vs 75% of subjects willing to repeat the prep in the future. A comparison of MiraLAX in Gatorade plus bisacodyl with 4 L PEG-ELS found superior results overall (93.3% vs 89.3% with excellent/good cleansing) and equivalent results when the analysis was limited to only ASA class 1 patients of which there were more in the 4 L PEG-ELS group^[31]. The authors noted that the increased rate of adequate preparations derived primarily from more frequent good and less frequent fair preparations.

Other researchers have found inferior bowel prep

with MiraLAX based regimens compared with PEG-ELS. Hjelkrem *et al.*^[27] compared split doses of 4 L PEG-ELS with MiraLAX (alone and with either bisacodyl or lubiprostone) and demonstrated inferior preps with all of the MiraLAX based preps (Ottawa score of 5.1 vs 6.9, 6.3, and 6.8). Cleansing was adequate with all preps, but there was a higher incidence of excellent preps in the Golytely arm (49% vs 15%, 20%, and 19%). No difference in adenoma detection rates was observed. A lower rate of excellent prep and overall inferior BBPS was also observed by Enesvedt *et al.*^[29] when comparing MiraLAX with 4 L PEG-ELS. PEG-ELS produced a mean BBPS of 9% and 70% of preps were rated excellent which was superior to a mean BBPS of 8% and 55% of preps rated excellent for MiraLAX. A follow up study by Enesvedt *et al.*^[32] comparing MiraLAX with PEG-ELS showed that, in addition to less frequently achieving a BBPS greater than or equal to 7, MiraLAX was associated with a lower adenoma detection rate (16.1% vs 26.2% with PEG-ELS).

There have been concerns about the safety of MiraLAX for bowel preparation after reports of severe hyponatremia^[33]. Unlike the electrolyte solutions used for prescription bowel preps, the sports drink (typically Gatorade) is not osmotically balanced and is relatively hypotonic. Two randomized controlled trials have since demonstrated comparable safety with standard 4 L PEG preparations^[28,30]. Neither trial detected a clinically or statistically significant difference in serum electrolytes. Though, the study populations were relatively small and may not detect very infrequent adverse events, it is reassuring that not even a trend toward greater electrolyte abnormalities was observed.

SODIUM PHOSPHATE

Sodium phosphate (NaP) is an osmotic laxative that was initially prescribed as a more tolerable alternative to whole gut lavage with PEG preparations. It was widely used and well tolerated by patients as a much smaller volume of fluid was required for successful prep; however, concerns about safety and confounding mucosal changes have limited the use of this agent more recently. Because of concerns of significant electrolyte disturbances and even acute renal failure, the use of sodium phosphate preps is not recommended in multiple populations including patients over the age of 55, patients taking certain medications such as angiotensin converting enzyme inhibitors (ACEi), and those with pre-existing renal disease, heart failure, and liver disease. Sodium phosphate carries a black box warning regarding the risk of acute phosphate nephropathy.

In comparison to single dose 4 L PEG-ELS, NaP produced equivalent to superior bowel cleansing with improved patient tolerability^[34-38]. The greater tolerability of NaP as compared to PEG preparation has been nearly universal^[35-38]. Subjects, including 37 who had been prepped with PEG for prior colonoscopy, rated NaP easier

to complete and less uncomfortable^[35].

Unfortunately, in spite of its superior tolerability, NaP is not without significant adverse side effects^[39]. Hyperphosphatemia following NaP has been well documented in patients with both normal and impaired renal function and has been associated with hypocalcemia. Cases of acute phosphate nephropathy have largely occurred in patients with pre-existing renal disease, but have also occurred in setting of dehydration in patients with otherwise normal renal function^[40]. NaP is thought to cause renal injury by precipitating nephrocalcinosis^[39,40]. The risk of adverse events is increased patients taking ACEi or angiotensin receptor blockers and who are of advanced age^[39]. Additional suspected risk factors include existing renal disease, female gender, volume depletion, and abnormal bowel motility^[39].

NaP has also been reported to cause mucosal inflammation and ulcerations that give the appearance of inflammatory bowel disease. A randomized control trial compared patients receiving PEG-ELS with NaP and found an association between NaP use and the presence of nonspecific aphthoid like mucosal lesions^[41]. Lesions were present in 24.5% of subjects receiving NaP vs 2.3% of those receiving PEG. Though pathological evaluation of the lesions was not consistent with IBD, the authors reported that they were endoscopically similar to those seen in Crohn's disease. This association was substantiated in a larger observational trial of 730 patients who were administered a NaP bowel prep and followed for 3 years after the procedure^[42]. In this study, only 3.3% of patients exposed to NaP demonstrated mucosal lesions on endoscopy, but these lesions were of the type seen in anti-inflammatory drug induced injury and in IBD. As a result of these observations, NaP is not recommended in patients undergoing colonoscopy to evaluate for suspected IBD^[41,42].

ORAL SULFATE SOLUTION

Sulfate is a poorly absorbed anion that does not cause significant fluid or electrolyte shifts^[43,44]. In comparison with sodium phosphate, sodium sulfate produced more liquid stool and, unlike phosphate, did not increase the propensity for calcium to precipitate in renal tubules^[43]. Oral sulfate solution (OSS) is available in two formulations: SuPrep (two doses of sodium, phosphate, and magnesium sulfate; Braintree Laboratories, Braintree, MA) and Suclear (one dose of sodium, phosphate, and magnesium sulfate followed by a second dose of PEG 3350 in 2 L of water; Braintree Laboratories, Braintree, MA).

A 2009 study by Di Palma *et al.*^[44] demonstrated equivalent bowel cleansing with OSS and 2 L PEG-ELS given as single and split doses. Split dosing was superior to single dose for both preparations (82.4% and 80.3% vs 97.2% and 95.6% for OSS and PEG-ELS respectively). OSS was associated with a higher frequency of excellent preparations in the split dose arm

(63.3% vs 52.5%). A subsequent study by this group comparing split dose OSS (SuPrep) with single dose 4 L sulfate free PEG-ELS found a significantly higher rate of adequate and excellent preparations in the OSS group (98.4% vs 89.6% and 71.4% vs 34.4%)^[45]. OSS also resulted in less residual stool in the right colon. There were small changes in serum electrolytes with OSS which the authors reported as clinically insignificant. A third study by this group compared split dose OSS plus PEG-ELS (Suclear) with split dose 2 L PEG-ELS and OSS plus PEG-ELS given the night before procedure with 10 mg bisacodyl followed by 2 L PEG-ELS^[46]. The split dose administration produced equivalent rates of successful prep (93.5% in both arms). Single dose OSS with PEG-ELS was non-inferior to PEG-ELS given with bisacodyl (89.8% vs 83.5%) and associated with significantly more excellent preparations (47.7% vs 35.6%). In both arms of the study, OSS plus PEG-ELS was associated with a higher incidence of side effects (vomiting in the split dose arm and overall discomfort in single dose arm.) The authors looked specifically at the efficacy in the elderly (age ≥ 65) and found that the split dose OSS with PEG-ELS produced more successful preparations (93% vs 86%) in this population. Patients with pre-existing comorbidities (cardiac or renal disease, diabetes, and hypertension) had similar rates of adverse events with both preps.

SODIUM PICOSULFATE

Sodium picosulfate (PMC) is a stimulant laxative given in combination with an osmotic laxative component such as magnesium citrate or magnesium oxide and citric acid which combine to form magnesium citrate. PMC has been used extensively in Canada and Europe for the past 20 years, but was only recently approved for use as a bowel preparative agent in the United States. The formulation available in the United States, Prepik (Ferring Pharmaceuticals, Parsippany, NJ), is given as a split dose. Like sodium phosphate, this is a hyperosmolar preparation may not be suitable for patients with heart failure, renal insufficiency, end stage liver disease, or baseline electrolyte abnormalities. There have been reports of clinically significant hyponatremia following PMC bowel preparations and a retrospective cohort study by Weir *et al.*^[47] confirmed that use of PMC in patients older than 65 years was associated with an increased risk of 30 d hospitalization for hyponatremia, but not with increased risk of acute neurological symptoms or mortality.

Katz *et al.*^[48] compared PMC, given as single and split doses, with single dose 2 L PEG and bisacodyl administered the day before. Single dose PMC compared favorably with single dose PEG producing successful cleansing in 83.0% vs 79.7% or patients and comparable cleansing seen throughout all segments of the colon. Adverse events were similar between the two groups, and patient acceptability was significantly greater in the PMC arm. With split dose administration,

PMC performed significantly better than single dose 2 L PEG with bisacodyl^[49]. Good or excellent Aronchick scores were more frequent in the PMC arm in both the overall colon (84.2% vs 74.4%) and in the individual segments. Again, PMC was rated more tolerable than 2 L PEG. Similar results were observed by Kojecy *et al.*^[50] in a comparison of PMC and 4 L PEG in single and split doses. Split dose regimens were preferable regardless of the agent. Single dose PMC produced a higher percentage of acceptable preps compared to PEG (82.6% vs 73%). There was no significant difference in the number of subjects with adequate prep among the remaining study arms; split dose PMC (81.6%), single dose PMC (82.6%), and split dose PEG (87.3%). Both PMC based regimens were rated more tolerable than either PEG based prep. Single dose PEG was most associated with nausea and bloating. Single dose PMC had the least abdominal pain reported, but split dose PMC had the highest association with incontinence. There was a slight preference for the single dose PMC preparation among older subjects and for the split preparation in younger subjects. These findings have been replicated in other studies with PMC achieving similar percentages of adequate bowel cleansing compared with PEG while being significantly preferred by study subjects^[51,52]. Another study evaluated PMC alone versus in combination with PEG found little additional benefit with PEG^[53]. Only in the right colon was there a significant difference in Ottawa bowel prep scores between the PMC alone and PMC plus 2 L PEG groups (1.34 ± 1.022 vs 1.11 ± 0.97). As in other studies, the PMC alone regimen was preferred by patients (89% vs 72.3%) and had less associated nausea.

There has been only one study directly comparing PMC with OSS^[54]. Rex *et al.*^[54] found a higher rate of successful and excellent preparations with OSS in comparison with PMC (94.7% vs 85.7% and 54% vs 26%). Unlike the OSS arm, there were 4 patients in the PMC arm who required additional preparation before the procedure could be attempted and 9 patients in whom the cecum was not reached. There was no significant difference in the polyp detection rate (50.9% vs 42.9%), adenoma detection rate (26.0% vs 23.8%), or flat lesion detection rate (9.5% vs 4.8%), and no difference in the procedure duration (mean 16.5 min vs 16.6 min). There was no difference in adverse events in the two arms and, though nausea was generally mild in both arms, subjects taking PMC reported better scores for nausea (Table 2).

TIMING OF PREP

Regardless of the preparation used, the quality of preparation has proven higher with split dose vs day before administration. This has been demonstrated most clearly with PEG based preparations. A 2005 study compared 4 L PEG preparations given as a single dose with dietary restrictions on the evening before the procedure or as a split dose without dietary restrictions

Table 2 Advantages and disadvantages of available bowel preparations

Prep	Advantages	Disadvantages
4 L PEG	Effective Safe in most populations	Poor taste Very high volumes Poorly tolerated by patients
2 L PEG	Effective Safe in most populations	Poor taste High volumes High cost
MiraLAX	Well tolerated by patients Available over the counter Existing studies indicate it is safe	Not as effective as prescription PEG preparations Rare reports of hyponatremia
Sodium phosphate	Available as oral tab	Inappropriate for use in patients with renal disease, volume depletion, heart or liver failure, or who are taking ACEi or NSAIDs
Sodium picosulfate	Well tolerated by patients	Risk of acute phosphate nephropathy and subsequent chronic kidney disease Cost
OSS	Well tolerated by patients Small volumes to be ingested	Not as effective as PEG or OSS Inappropriate for patients with heart failure, renal insufficiency, end stage liver disease, or baseline electrolyte abnormalities
	Pleasant taste Well tolerated by patients Highly effective Available as oral tab	High cost High cost Not as well studied

PEG: Preparation of polyethylene glycol; ACEi: Angiotensin converting enzyme inhibitors; NSAIDs: Nonsteroidal anti-inflammatory drugs; OSS: Oral sulfate solution.

and found that, even without dietary restrictions, the split dose preparation produced significantly better preps^[55]. A randomized control trial of evening before vs split dose PEG preparations that included both high and low volume preparations found that, regardless of the volume of preparation, split dose administration produced significantly more successful preps (75.2% vs 43.0%) and a lower rate of aborted procedures (6.9% vs 21.2%)^[56]. A pre-post study by the Veteran's Health Administration assessed efficacy and acceptance of split dose bowel preps in an elderly populations with multiple co-morbidities and found that the split dose preparations were better tolerated by patients and produced superior results^[57]. Both right and left colon preparations were improved with split dose administration (excellent/good preps achieved in 81.4% vs 63% and 85.9% vs 71.6% respectively)^[57].

These results were validated in 2 meta-analyses^[58,59]. Kilgore *et al*^[58] included 5 trials in an analysis which found split dose PEG produced an OR of 3.7 of a satisfactory bowel preparation as well as improved patient tolerability. Martel *et al*^[59] obtained similar results in an analysis of 47 trials. In this study which included split dose preparations of PEG, NaP, and PMC, the OR of a successful prep with split vs evening before preparation was 2.51. Subjects reported greater willingness to repeat the split dose preparation.

Concerns have been raised about the risk of peri-procedural aspiration with split dose regimens. In 2010, Huffman *et al*^[60] examined 712 patients with EGD of which 254 had received split dose bowel preps for concurrent colonoscopy. While the residual gastric volume was higher in patients who received the split dose preparation as compared with patients scheduled

for EGD only (19.7 mL vs 14.6 mL), there was no difference between when compared with patients who received day before preparation (20.2 mL) and the 5 mL difference is unlikely to be clinically significant^[60].

Recent studies have shed light on the reason for the improved cleansing seen with split dose preparations and highlighted the importance of a short duration between the completion of a bowel prep and the start of the colonoscopy^[61-64]. A prospective analysis of colonoscopy start times and the time of the last dose of bowel prep showed an inverse relationship between the degree of cleansing and the length of this interval^[64]. Subsequent studies have reinforced this finding and clarified the ideal time interval between bowel prep and colonoscopy. Eun *et al*^[62] compared intervals of more and less than 7 h and of more and less than 4 h and found that, in each case, superior cleansing was seen with the shorter interval. A 3 to 5 h interval produced the best cleansing throughout the colon in a prospective study by Seo *et al*^[61], though the association was not as high as with the amount of PEG ingested (OR 1.85 for prep to colonoscopy time vs 4.34 for quantity of PEG ingested).

Following from these findings, researchers have looked at the feasibility of preparations completed entirely on the morning of the planned procedure^[65-67]. Varughese *et al*^[65] compared morning only preparation with preparation completed entirely the evening prior and, consistent with the finding that the interval between preparation and procedure is a determinant of the quality of preparation, found that morning only preparation is superior to evening before preparation. Matro *et al*^[66] compared morning only to split dose administration of PEG-ELS and found equivalent cleansing and adenoma detection with improved tolerability in the morning only

group. Similar findings were obtained by Longcroft-Wheaton *et al*^[67] in comparing morning only to split dose sodium picosulfate.

CONCLUSION

Effective, safe, and reliable options for bowel preparation are becoming increasingly available though the most tolerable options remain the most costly. Improved efficacy has also been achieved with alterations in the dosing schedule, namely split dose administration and a better understanding of the optimal interval between preparation and the colonoscopy. These adjustments have proven more tolerable as well as more effective. The consensus of the major Gastrointestinal Societies is that the choice of agent should be tailored to the individual patient, but that a split dose regimen can be recommended in all cases^[68,69]. Additional research is needed to develop tools to assist providers in choosing an optimal regimen for their patients as factors such as age and comorbid conditions may affect the efficacy and safety of a particular agent. The optimal choice of bowel preparation must be guided by the circumstances of the individual patient undergoing procedure; however, low volume PEG preparations would appear to come closest to being the ideal preparatory agent in that it is effective, generally well tolerated, has an excellent safety record in a population of patients with a range of comorbid conditions, and is relatively inexpensive. Ongoing studies are evaluating the impact of interventions such as improved pre-procedure patient education and smart phone based applications that remind patients of when to take their prep are showing promise with regard to improved patient tolerability and adherence and may offer a path toward both patient and endoscopist satisfaction.

ACKNOWLEDGMENTS

The opinion or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the view of the US Department of the Army or the United States Department of Defense.

REFERENCES

- 1 **Froehlich F**, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005; **61**: 378-384 [PMID: 15758907 DOI: 10.1016/S0016-5107(04)02776-2]
- 2 **Sherer EA**, Imler TD, Imperiale TF. The effect of colonoscopy preparation quality on adenoma detection rates. *Gastrointest Endosc* 2012; **75**: 545-553 [PMID: 22138085 DOI: 10.1016/j.gie.2011.09.022]
- 3 **Lebwohl B**, Kastrinos F, Glick M, Rosenbaum AJ, Wang T, Neugut AI. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest Endosc* 2011; **73**: 1207-1214 [PMID: 21481857 DOI: 10.1016/j.gie.2011.01.051]
- 4 **Hong SN**, Sung IK, Kim JH, Choe WH, Kim BK, Ko SY, Lee JH, Seol DC, Ahn SY, Lee SY, Park HS, Shim CS. The Effect of the Bowel Preparation Status on the Risk of Missing Polyp and Adenoma during Screening Colonoscopy: A Tandem Colonoscopic Study. *Clin Endosc* 2012; **45**: 404-411 [PMID: 23251889 DOI: 10.5946/ce.2012.45.4.404]
- 5 **Chokshi RV**, Hovis CE, Hollander T, Early DS, Wang JS. Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. *Gastrointest Endosc* 2012; **75**: 1197-1203 [PMID: 22381531 DOI: 10.1016/j.gie.2012.01.005]
- 6 **Holt EW**, Yimam KK, Ma H, Shaw RE, Sundberg RA, Verhille MS. Patient tolerability of bowel preparation is associated with polyp detection rate during colonoscopy. *J Gastrointest Liver Dis* 2014; **23**: 135-140 [PMID: 24949604]
- 7 **Kumar AS**, Kelleher DC, Sigle GW. Bowel Preparation before Elective Surgery. *Clin Colon Rectal Surg* 2013; **26**: 146-152 [PMID: 24436665 DOI: 10.1055/s-0033-1351129]
- 8 **Kazarian ES**, Carreira FS, Toribara NW, Denberg TD. Colonoscopy completion in a large safety net health care system. *Clin Gastroenterol Hepatol* 2008; **6**: 438-442 [PMID: 18304886 DOI: 10.1016/j.cgh.2007.12.003]
- 9 **Hillyer GC**, Basch CH, Lebwohl B, Basch CE, Kastrinos F, Insel BJ, Neugut AI. Shortened surveillance intervals following suboptimal bowel preparation for colonoscopy: results of a national survey. *Int J Colorectal Dis* 2013; **28**: 73-81 [PMID: 22885884 DOI: 10.1007/s00384-012-1559-7]
- 10 **Menees SB**, Elliott E, Govani S, Anastassiades C, Judd S, Urganus A, Boyce S, Schoenfeld P. The impact of bowel cleansing on follow-up recommendations in average-risk patients with a normal colonoscopy. *Am J Gastroenterol* 2014; **109**: 148-154 [PMID: 24496417 DOI: 10.1038/ajg.2013.243]
- 11 **Ben-Horin S**, Bar-Meir S, Avidan B. The impact of colon cleanliness assessment on endoscopists' recommendations for follow-up colonoscopy. *Am J Gastroenterol* 2007; **102**: 2680-2685 [PMID: 17714555 DOI: 10.1111/j.1572-0241.2007.01486.x]
- 12 **Rex DK**, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and cost of colonoscopy. *Am J Gastroenterol* 2002; **97**: 1696-1700 [PMID: 12135020]
- 13 **Enestvedt BK**, Tofani C, Laine LA, Tierney A, Fennerty MB. 4-Liter split-dose polyethylene glycol is superior to other bowel preparations, based on systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 1225-1231 [PMID: 22940741 DOI: 10.1016/j.cgh.2012.08.029]
- 14 **Adams WJ**, Meagher AP, Lubowski DZ, King DW. Bisacodyl reduces the volume of polyethylene glycol solution required for bowel preparation. *Dis Colon Rectum* 1994; **37**: 229-233; discussion 233-234 [PMID: 8137669 DOI: 10.1007/BF02048160]
- 15 **Sharma VK**, Chockalingham SK, Ugheoke EA, Kapur A, Ling PH, Vasudeva R, Howden CW. Prospective, randomized, controlled comparison of the use of polyethylene glycol electrolyte lavage solution in four-liter versus two-liter volumes and pretreatment with either magnesium citrate or bisacodyl for colonoscopy preparation. *Gastrointest Endosc* 1998; **47**: 167-171 [PMID: 9512283 DOI: 10.1016/S0016-5107(98)70351-7]
- 16 **Ker TS**. Comparison of reduced volume versus four-liter electrolyte lavage solutions for colon cleansing. *Am Surg* 2006; **72**: 909-911 [PMID: 17058733]
- 17 **Park SS**, Sinn DH, Kim YH, Lim YJ, Sun Y, Lee JH, Kim JY, Chang DK, Son HJ, Rhee PL, Rhee JC, Kim JJ. Efficacy and tolerability of split-dose magnesium citrate: low-volume (2 liters) polyethylene glycol vs. single- or split-dose polyethylene glycol bowel preparation for morning colonoscopy. *Am J Gastroenterol* 2010; **105**: 1319-1326 [PMID: 20485282 DOI: 10.1038/ajg.2010.79]
- 18 **Jansen SV**, Goedhard JG, Winkens B, van Deursen CT. Preparation before colonoscopy: a randomized controlled trial comparing different regimens. *Eur J Gastroenterol Hepatol* 2011; **23**: 897-902 [PMID: 21900786 DOI: 10.1097/MEG.0b013e32834a3444]
- 19 **Kao D**, Lalor E, Sandha G, Fedorak RN, van der Knoop B, Doornweerd S, van Kooten H, Schreuders E, Midodzi W, Veldhuyzen van Zanten S. A randomized controlled trial of four precolonoscopy bowel cleansing regimens. *Can J Gastroenterol* 2011; **25**: 657-662 [PMID: 22175055]

- 20 **Sharma VK**, Schaberg JW, Chockalingam SK, Vasudeva R, Howden CW. The effect of stimulant laxatives and polyethylene glycol-electrolyte lavage solution for colonoscopy preparation on serum electrolytes and hemodynamics. *J Clin Gastroenterol* 2001; **32**: 238-239 [PMID: 11246353 DOI: 10.1097/00004836-200103000-00013]
- 21 **Ponchon T**, Boustière C, Heresbach D, Hagege H, Tarrerias AL, Halphen M. A low-volume polyethylene glycol plus ascorbate solution for bowel cleansing prior to colonoscopy: the NORMO randomised clinical trial. *Dig Liver Dis* 2013; **45**: 820-826 [PMID: 23769755 DOI: 10.1016/j.dld.2013.04.009]
- 22 **Mathus-Vliegen EM**, van der Vliet K. Safety, patient's tolerance, and efficacy of a 2-liter vitamin C-enriched macrogol bowel preparation: a randomized, endoscopist-blinded prospective comparison with a 4-liter macrogol solution. *Dis Colon Rectum* 2013; **56**: 1002-1012 [PMID: 23838870 DOI: 10.1097/DCR.0b013e3182989f05]
- 23 **Gentile M**, De Rosa M, Cestaro G, Forestieri P. 2 L PEG plus ascorbic acid versus 4 L PEG plus simethicon for colonoscopy preparation: a randomized single-blind clinical trial. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 276-280 [PMID: 23751992 DOI: 10.1097/SLE.0b013e31828e389d]
- 24 **Valiante F**, Bellumat A, De Bona M, De Boni M. Bisacodyl plus split 2-L polyethylene glycol-citrate-simethicone improves quality of bowel preparation before screening colonoscopy. *World J Gastroenterol* 2013; **19**: 5493-5499 [PMID: 24023492 DOI: 10.3748/wjg.v19.i33.5493]
- 25 **Lee KJ**, Park HJ, Kim HS, Baik KH, Kim YS, Park SC, Seo HI. Electrolyte changes after bowel preparation for colonoscopy: A randomized controlled multicenter trial. *World J Gastroenterol* 2015; **21**: 3041-3048 [PMID: 25780304 DOI: 10.3748/wjg.v21.i10.3041]
- 26 **Hillyer GC**, Lebowitz B, Basch CH, Basch CE, Kastrinos F, Insel BJ, Neugut AI. Split dose and MiraLAX-based purgatives to enhance bowel preparation quality becoming common recommendations in the US. *Therap Adv Gastroenterol* 2013; **6**: 5-14 [PMID: 23320046 DOI: 10.1177/1756283X12464100]
- 27 **Hjelmkrem M**, Stengel J, Liu M, Jones DP, Harrison SA. MiraLAX is not as effective as GoLyteLy in bowel cleansing before screening colonoscopies. *Clin Gastroenterol Hepatol* 2011; **9**: 326-332.e1 [PMID: 21115134 DOI: 10.1016/j.cgh.2010.11.007]
- 28 **Samarasena JB**, Muthusamy VR, Jamal MM. Split-dosed MiraLAX/Gatorade is an effective, safe, and tolerable option for bowel preparation in low-risk patients: a randomized controlled study. *Am J Gastroenterol* 2012; **107**: 1036-1042 [PMID: 22565162 DOI: 10.1038/ajg.2012.115]
- 29 **Enestvedt BK**, Fennerty MB, Eisen GM. Randomised clinical trial: MiraLAX vs. Golytely - a controlled study of efficacy and patient tolerability in bowel preparation for colonoscopy. *Aliment Pharmacol Ther* 2011; **33**: 33-40 [PMID: 21083586 DOI: 10.1111/j.1365-2036.2010.04493.x]
- 30 **McKenna T**, Macgill A, Porat G, Friedenber FK. Colonoscopy preparation: polyethylene glycol with Gatorade is as safe and efficacious as four liters of polyethylene glycol with balanced electrolytes. *Dig Dis Sci* 2012; **57**: 3098-3105 [PMID: 22711499 DOI: 10.1007/s10620-012-2266-5]
- 31 **Shieh FK**, Gunaratnam N, Mohamud SO, Schoenfeld P. MiraLAX-Gatorade bowel prep versus GoLyteLy before screening colonoscopy: an endoscopic database study in a community hospital. *J Clin Gastroenterol* 2012; **46**: e96-e100 [PMID: 23060223 DOI: 10.1097/MCG.0b013e3182617bfb]
- 32 **Enestvedt BK**, Brian Fennerty M, Zaman A, Eisen GM. MiraLAX vs. Golytely: is there a significant difference in the adenoma detection rate? *Aliment Pharmacol Ther* 2011; **34**: 775-782 [PMID: 21848798 DOI: 10.1111/j.1365-2036.2011.04795.x]
- 33 **Schoenfeld P**. Safety of MiraLAX/Gatorade bowel preparation has not been established in appropriately designed studies. *Clin Gastroenterol Hepatol* 2013; **11**: 582 [PMID: 23376319 DOI: 10.1016/j.cgh.2013.01.017]
- 34 **Huppertz-Hauss G**, Bretthauer M, Sauar J, Paulsen J, Kjelleveid Ø, Majak B, Hoff G. Polyethylene glycol versus sodium phosphate in bowel cleansing for colonoscopy: a randomized trial. *Endoscopy* 2005; **37**: 537-541 [PMID: 15933926 DOI: 10.1055/s-2005-861315]
- 35 **Vanner SJ**, MacDonald PH, Paterson WG, Prentice RS, Da Costa LR, Beck IT. A randomized prospective trial comparing oral sodium phosphate with standard polyethylene glycol-based lavage solution (Golytely) in the preparation of patients for colonoscopy. *Am J Gastroenterol* 1990; **85**: 422-427 [PMID: 2183591]
- 36 **Cohen SM**, Wexner SD, Binderow SR, Nogueras JJ, Daniel N, Ehrenpreis ED, Jensen J, Bonner GF, Ruderman WB. Prospective, randomized, endoscopic-blinded trial comparing precolonoscopy bowel cleansing methods. *Dis Colon Rectum* 1994; **37**: 689-696 [PMID: 8026236 DOI: 10.1007/BF02054413]
- 37 **Golub RW**, Kerner BA, Wise WE, Meesig DM, Hartmann RF, Khanduja KS, Aguilar PS. Colonoscopic bowel preparations--which one? A blinded, prospective, randomized trial. *Dis Colon Rectum* 1995; **38**: 594-599 [PMID: 7774469 DOI: 10.1007/BF02054117]
- 38 **Kastenber D**, Chasen R, Choudhary C, Riff D, Steinberg S, Weiss E, Wruble L. Efficacy and safety of sodium phosphate tablets compared with PEG solution in colon cleansing: two identically designed, randomized, controlled, parallel group, multicenter phase III trials. *Gastrointest Endosc* 2001; **54**: 705-713 [PMID: 11726845 DOI: 10.1067/mge.2001.119733]
- 39 **Heher EC**, Thier SO, Rennke H, Humphreys BD. Adverse renal and metabolic effects associated with oral sodium phosphate bowel preparation. *Clin J Am Soc Nephrol* 2008; **3**: 1494-1503 [PMID: 18596115 DOI: 10.2215/CJN.02040408]
- 40 **Desmeules S**, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003; **349**: 1006-1007 [PMID: 12954755 DOI: 10.1056/NEJM200309043491020]
- 41 **Zwas FR**, Cirillo NW, el-Serag HB, Eisen RN. Colonic mucosal abnormalities associated with oral sodium phosphate solution. *Gastrointest Endosc* 1996; **43**: 463-466 [PMID: 8726758 DOI: 10.1016/S0016-5107(96)70286-9]
- 42 **Rejchrt S**, Bures J, Siroký M, Kopáková M, Slezák L, Langr F. A prospective, observational study of colonic mucosal abnormalities associated with orally administered sodium phosphate for colon cleansing before colonoscopy. *Gastrointest Endosc* 2004; **59**: 651-654 [PMID: 15114307 DOI: 10.1016/S0016-5107(04)00158-0]
- 43 **Patel V**, Nicar M, Emmett M, Asplin J, Maguire JA, Santa Ana CA, Fordtran JS. Intestinal and renal effects of low-volume phosphate and sulfate cathartic solutions designed for cleansing the colon: pathophysiological studies in five normal subjects. *Am J Gastroenterol* 2009; **104**: 953-965 [PMID: 19240703 DOI: 10.1038/ajg.2008.124]
- 44 **Di Palma JA**, Rodriguez R, McGowan J, Cleveland Mv. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. *Am J Gastroenterol* 2009; **104**: 2275-2284 [PMID: 19584830 DOI: 10.1038/ajg.2009.389]
- 45 **Rex DK**, Di Palma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc* 2010; **72**: 328-336 [PMID: 20646695 DOI: 10.1016/j.gie.2010.03.1054]
- 46 **Rex DK**, McGowan J, Cleveland Mv, Di Palma JA. A randomized, controlled trial of oral sulfate solution plus polyethylene glycol as a bowel preparation for colonoscopy. *Gastrointest Endosc* 2014; **80**: 482-491 [PMID: 24830577 DOI: 10.1016/j.gie.2014.03.043]
- 47 **Weir MA**, Fleet JL, Vinden C, Shariff SZ, Liu K, Song H, Jain AK, Gandhi S, Clark WF, Garg AX. Hyponatremia and sodium picosulfate bowel preparations in older adults. *Am J Gastroenterol* 2014; **109**: 686-694 [PMID: 24589671 DOI: 10.1038/ajg.2014.20]
- 48 **Katz PO**, Rex DK, Epstein M, Grandhi NK, Vanner S, Hookey LC, Alderfer V, Joseph RE. A dual-action, low-volume bowel cleanser administered the day before colonoscopy: results from the SEE CLEAR II study. *Am J Gastroenterol* 2013; **108**: 401-409 [PMID: 23318484 DOI: 10.1038/ajg.2012.441]
- 49 **Rex DK**, Katz PO, Bertiger G, Vanner S, Hookey LC, Alderfer V, Joseph RE. Split-dose administration of a dual-action, low-volume bowel cleanser for colonoscopy: the SEE CLEAR I study. *Gastrointest*

- Endosc* 2013; **78**: 132-141 [PMID: 23566639 DOI: 10.1016/j.gie.2013.02.024]
- 50 **Kojecky V**, Dolina J, Kianicka B, Misurec M, Varga M, Latta J, Vaculin V. A single or split dose picosulfate/magnesium citrate before colonoscopy: comparison regarding tolerance and efficacy with polyethylene glycol. A randomized trial. *J Gastrointest Liver Dis* 2014; **23**: 141-146 [PMID: 24949605 DOI: 10.15403/jgld.2014.1121.232.vk1]
 - 51 **Kim HG**, Huh KC, Koo HS, Kim SE, Kim JO, Kim TI, Kim HS, Myung SJ, Park DI, Shin JE, Yang DH, Lee SH, Lee JS, Lee CK, Chang DK, Joo YE, Cha JM, Hong SP, Kim HJ. Sodium Picosulfate with Magnesium Citrate (SPMC) Plus Laxative Is a Good Alternative to Conventional Large Volume Polyethylene Glycol in Bowel Preparation: A Multicenter Randomized Single-Blinded Trial. *Gut Liver* 2015; **9**: 494-501 [PMID: 25287163 DOI: 10.5009/gnl14010]
 - 52 **Kang MS**, Kim TO, Seo EH, Jung da K, Kim MS, Heo NY, Park JH, Park SH, Moon YS. Comparison of the Efficacy and Tolerability between Same-day Picosulfate and Split-dose Polyethylene Glycol Bowel Preparation for Afternoon Colonoscopy: A Prospective, Randomized, Investigator-blinded Trial. *Intest Res* 2014; **12**: 53-59 [PMID: 25349564 DOI: 10.5217/ir.2014.12.1.53]
 - 53 **Song KH**, Suh WS, Jeong JS, Kim DS, Kim SW, Kwak DM, Hwang JS, Kim HJ, Park MW, Shim MC, Koo JI, Kim JH, Shon DH. Effectiveness of Sodium Picosulfate/Magnesium Citrate (PICO) for Colonoscopy Preparation. *Ann Coloproctol* 2014; **30**: 222-227 [PMID: 25360429 DOI: 10.3393/ac.2014.30.5.222]
 - 54 **Rex DK**, DiPalma JA, McGowan J, Cleveland Mv. A comparison of oral sulfate solution with sodium picosulfate: magnesium citrate in split doses as bowel preparation for colonoscopy. *Gastrointest Endosc* 2014; **80**: 1113-1123 [PMID: 25028274 DOI: 10.1016/j.gie.2014.05.329]
 - 55 **Aoun E**, Abdul-Baki H, Azar C, Mourad F, Barada K, Berro Z, Tarchichi M, Sharara AI. A randomized single-blind trial of split-dose PEG-electrolyte solution without dietary restriction compared with whole dose PEG-electrolyte solution with dietary restriction for colonoscopy preparation. *Gastrointest Endosc* 2005; **62**: 213-218 [PMID: 16046981 DOI: 10.1016/S0016-5107(05)00371-8]
 - 56 **Marmo R**, Rotondano G, Riccio G, Marone A, Bianco MA, Stroppa I, Caruso A, Pandolfo N, Sansone S, Gregorio E, D'Alvano G, Procaccio N, Capo P, Marmo C, Cipolletta L. Effective bowel cleansing before colonoscopy: a randomized study of split-dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions. *Gastrointest Endosc* 2010; **72**: 313-320 [PMID: 20561621 DOI: 10.1016/j.gie.2010.02.048]
 - 57 **Cohen B**, Tang RS, Groessl E, Herrin A, Ho SB. Effectiveness of a simplified "patient friendly" split dose polyethylene glycol colonoscopy prep in Veterans Health Administration patients. *J Interv Gastroenterol* 2012; **2**: 177-182 [PMID: 23687605 DOI: 10.4161/jig.23748]
 - 58 **Kilgore TW**, Abdinoor AA, Szary NM, Schowengerdt SW, Yust JB, Choudhary A, Matteson ML, Puli SR, Marshall JB, Bechtold ML. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc* 2011; **73**: 1240-1245 [PMID: 21628016 DOI: 10.1016/j.gie.2011.02.007]
 - 59 **Martel M**, Barkun AN, Menard C, Restellini S, Kherad O, Vanasse A. Split-Dose Preparations Are Superior to Day-Before Bowel Cleansing Regimens: A Meta-analysis. *Gastroenterology* 2015; **149**: 79-88 [PMID: 25863216 DOI: 10.1053/j.gastro.2015.04.004]
 - 60 **Huffman M**, Unger RZ, Thatikonda C, Amstutz S, Rex DK. Split-dose bowel preparation for colonoscopy and residual gastric fluid volume: an observational study. *Gastrointest Endosc* 2010; **72**: 516-522 [PMID: 20646700 DOI: 10.1016/j.gie.2010.03.1125]
 - 61 **Seo EH**, Kim TO, Park MJ, Joo HR, Heo NY, Park J, Park SH, Yang SY, Moon YS. Optimal preparation-to-colonoscopy interval in split-dose PEG bowel preparation determines satisfactory bowel preparation quality: an observational prospective study. *Gastrointest Endosc* 2012; **75**: 583-590 [PMID: 22177570 DOI: 10.1016/j.gie.2011.09.029]
 - 62 **Eun CS**, Han DS, Hyun YS, Bae JH, Park HS, Kim TY, Jeon YC, Sohn JH. The timing of bowel preparation is more important than the timing of colonoscopy in determining the quality of bowel cleansing. *Dig Dis Sci* 2011; **56**: 539-544 [PMID: 21042853 DOI: 10.1007/s10620-010-1457-1]
 - 63 **Rodríguez De Miguel C**, Serradesanferm A, Del Manzano S, Cárdenas A, Fernández-Esparrach G, Ginés A, Ricart E, Sendino O, González-Suárez B, López-Cerón M, Llach J, Grau J, Castells A, Pellisé M. [Timing of polyethylene glycol administration is a key factor in the tolerability and efficacy of colon preparation in colorectal cancer screening]. *Gastroenterol Hepatol* 2012; **35**: 236-242 [PMID: 22445938 DOI: 10.1016/j.gastrohep.2012.01.012]
 - 64 **Siddiqui AA**, Yang K, Specchler SJ, Cryer B, Davila R, Cipher D, Harford WV. Duration of the interval between the completion of bowel preparation and the start of colonoscopy predicts bowel preparation quality. *Gastrointest Endosc* 2009; **69**: 700-706 [PMID: 19251013 DOI: 10.1016/j.gie.2008.09.047]
 - 65 **Varughese S**, Kumar AR, George A, Castro FJ. Morning-only one-gallon polyethylene glycol improves bowel cleansing for afternoon colonoscopies: a randomized endoscopist-blinded prospective study. *Am J Gastroenterol* 2010; **105**: 2368-2374 [PMID: 20606677 DOI: 10.1038/ajg.2010.271]
 - 66 **Matro R**, Shnitser A, Spodik M, Daskalakis C, Katz L, Murtha A, Kastenber D. Efficacy of morning-only compared with split-dose polyethylene glycol electrolyte solution for afternoon colonoscopy: a randomized controlled single-blind study. *Am J Gastroenterol* 2010; **105**: 1954-1961 [PMID: 20407434 DOI: 10.1038/ajg.2010.160]
 - 67 **Longcroft-Wheaton G**, Bhandari P. Same-day bowel cleansing regimen is superior to a split-dose regimen over 2 days for afternoon colonoscopy: results from a large prospective series. *J Clin Gastroenterol* 2012; **46**: 57-61 [PMID: 22064553 DOI: 10.1097/MCG.0b013e318233a986]
 - 68 **Johnson DA**, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, Robertson DJ, Richard Boland C, Giardello FM, Lieberman DA, Levin TR, Rex DK. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2014; **109**: 1528-1545 [PMID: 25223578 DOI: 10.1053/j.gastro.2014.07.002]
 - 69 **Saltzman JR**, Cash BD, Pasha SF, Early DS, Muthusamy VR, Khashab MA, Chathadi KV, Fanelli RD, Chandrasekhara V, Lightdale JR, Fonkalsrud L, Shergill AK, Hwang JH, Decker GA, Jue TL, Sharaf R, Fisher DA, Evans JA, Foley K, Shaikat A, Eloubeidi MA, Faulx AL, Wang A, Acosta RD. Bowel preparation before colonoscopy. *Gastrointest Endosc* 2015; **81**: 781-794 [PMID: 25595062 DOI: 10.1016/j.gie.2014.09.048]
 - 70 **Pontone S**, Angelini R, Standoli M, Patrizi G, Culasso F, Pontone P, Redler A. Low-volume plus ascorbic acid vs high-volume plus simethicone bowel preparation before colonoscopy. *World J Gastroenterol* 2011; **17**: 4689-4695 [PMID: 22180711 DOI: 10.3748/wjg.v17.i42.4689]

P- Reviewer: Fogli L, Kotwal VS, Talmon GA, Zaltman C

S- Editor: Ji FF L- Editor: A E- Editor: Lu YJ



Role of endoscopic clipping in the treatment of oesophageal perforations

György Lázár, Attila Paszt, Eszter Mán

György Lázár, Attila Paszt, Eszter Mán, Department of Surgery, University of Szeged, Szeged 6720, Hungary

Author contributions: Lázár G wrote the article and analyzed the data; Paszt A and Mán E collected and analyzed the data and created the tables.

Conflict-of-interest statement: The authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: György Lázár, MD, PhD, Head, Department of Surgery, University of Szeged, H-6720 Szeged, Szókefalvi-Nagy Béla u. 6., Szeged 6720, Hungary. gylazar@gmail.com
Telephone: +36-62-545701
Fax: +36-62-545701

Received: July 28, 2015

Peer-review started: July 30, 2015

First decision: September 14, 2015

Revised: September 25, 2015

Accepted: November 10, 2015

Article in press: November 11, 2015

Published online: January 10, 2016

Abstract

With advances in endoscopic technologies, endoscopic clips have been used widely and successfully in the treatment of various types of oesophageal perforations, anastomosis leakages and fistulas. Our aim was to summarize the experience with two types of clips: The

through-the-scope (TTS) clip and the over-the-scope clip (OTSC). We summarized the results of oesophageal perforation closure with endoscopic clips. We processed the data from 38 articles and 127 patients using PubMed search. Based on evidence thus far, it can be stated that both clips can be used in the treatment of early (< 24 h), iatrogenic, spontaneous oesophageal perforations in the case of limited injury or contamination. TTS clips are efficacious in the treatment of 10 mm lesions, while bigger (< 20 mm) lesions can be treated successfully with OTSC clips, whose effectiveness is similar to that of surgical treatment. However, the clinical success rate is significantly lower in the case of fistulas and in the treatment of anastomosis insufficiency. Tough prospective randomized multicentre trials, which produce the largest amount of evidence, are still missing. Based on experience so far, endoscopic clips represent a possible therapeutic alternative to surgery in the treatment of oesophageal perforations under well-defined conditions.

Key words: Oesophageal perforation; Endoscopic clipping; Upper gastrointestinal perforation; Endoscopy; Over-the-scope clip

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: With advances in endoscopic technologies, endoscopic clips have been used successfully in the treatment of various types of oesophageal perforations, anastomosis leakages and fistulas. We summarized the results of oesophageal perforation closure with endoscopic clips [the through-the-scope (TTS) clip and the over-the-scope clip (OTSC)]. We processed the data from 38 articles and 127 patients using PubMed search. Based on the evidence, TTS clips are efficacious in the treatment of 10 mm lesions, while bigger (< 20 mm) lesions can be treated successfully with OTSC clips. Based on experience so far, endoscopic clips represent a possible therapeutic alternative to surgery in the treatment of oesophageal

perforations under well-defined conditions.

Lázár G, Paszt A, Mán E. Role of endoscopic clipping in the treatment of oesophageal perforations. *World J Gastrointest Endosc* 2016; 8(1): 13-22 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i1/13.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i1.13>

INTRODUCTION

Despite remarkable advances in surgery and intensive care, oesophageal perforation is still a life-threatening condition^[1,2]. It is iatrogenic (caused by a device) in a majority of cases; perforation caused by a foreign body or trauma and spontaneous perforation are less frequent. Several well-known factors influence its course: location and cause of perforation, time from diagnosis until care, co-morbidities of the oesophagus, general condition of the patient and selected treatment^[3,4]. In addition to oesophageal perforation, suture insufficiency of the oesophagus and other oesophageal fistulas also pose serious therapeutic challenges nowadays.

With the development of endoscopic technology during the last two decades, endoscopic clips and self-expanding stents have been used successfully and ever more widely in the treatment of oesophageal perforations/fistulas of various origins^[5,6]. Oesophageal injury was first closed endoscopically with the placement of clips in 1995; the injury had occurred as a consequence of pneumatic dilatation in a patient with achalasia^[7]. Since then, this method has been used for oesophageal perforations of various aetiologies, including Boerhaave syndrome^[8-11]. To date, the method has been successful, especially in the treatment of small (< 2 cm) injuries. The following review article describes indications of endoscopy and endoscopic clips in the treatment of oesophageal perforation.

DISCUSSION

Aetiology of oesophageal perforation

Various causes of perforation or rupture of the oesophagus are well-known: iatrogenic, foreign body, postmictic (spontaneous, Boerhaave syndrome) trauma, tumour and surrounding inflammation. Iatrogenic injuries are still the most common cause; the second most common is spontaneous oesophageal rupture. These two types represent more than two-thirds of the perforations based on a number of publications from different countries^[12,13]. Suture insufficiency in the oesophagus (oesophageal/gastric resections and other sutures) and fistulas of various aetiologies fall into a separate group. In recent decades, the appearance and more widespread use of new therapeutic endoscopic methods have significantly increased the incidence of iatrogenic oesophageal perforations. It can be well determined which endoscopic

interventions confer increased risk of perforation: (1) dilatation of the oesophagus (balloon/bougie); (2) endoscopic resections [endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)]; and (3) removal of a foreign body. Dilatation of the oesophagus is almost as old as endoscopy; however, this method is still not without risks. The risk of perforation is greatest in the case of balloon dilatation (especially due to achalasia), with an approximate 2% overall cumulative rate, which can be reduced if endoscopic guidance is provided and if a balloon with a small (30 mm) diameter is used at the beginning of the intervention^[14-16]. The risk of perforation in the dilatation treatment of peptic and other benign strictures is significantly lower with the use of a guide wire and a bougie (0.18%); however, in the case of malignant strictures, the risk of injury is increased again (0.48%)^[17]. In the case of endoscopic resections (EMR and ESD), the risk of perforation is similar to that of balloon dilatation (2%-3%)^[10,18].

Diagnosis of oesophageal perforation

A bidirectional chest X-ray is usually taken in addition to an oesophagogram with water-soluble contrast material to confirm perforation. The oesophagogram is the most common test procedure, but there are a number of false negative results (10%)^[19]. Nowadays, abdominal and thoracic CT examinations are also routine^[20]. The sensitivity of the CT examination is especially important in detecting a small amount of mediastinal/pleural air and/or fluid^[21,22]. If the examination is combined with an oesophagogram, the exact location of extravasation can be determined more precisely. An endoscopic examination^[23] may likewise be helpful in the diagnosis. Endoscopy is not only important in setting up the diagnosis, but also in confirming previously unknown accompanying co-morbidities of the oesophagus (such as tumour and stricture), which may significantly modify the treatment strategy. Endoscopy also offers an immediate treatment option (if the conditions are suitable), and it may also be helpful intraoperatively during surgical intervention (in checking whether the sutures are intact, in inserting a nasogastric/jejunal probe, etc.)^[23]. The diagnosis of a perforation is especially important in the case of an endoscopic intervention (EMS, ESD, balloon dilatation, etc.), which also determines therapy and prognosis^[24].

TREATMENT OF OESOPHAGEAL PERFORATION: GENERAL CONSIDERATIONS

Essential elements in the treatment of oesophageal perforation include resolving the source of the infection, operative or non-operative closure of the defect, and thoracic and mediastinal debridement. Important parts of therapy are controlling sepsis, intensive monitoring, targeted antibiotic/antimycotic treatment, fluid therapy

and strengthening the immune system of the body with enteral nutrition.

Several obvious factors determine treatment strategy and prognosis: (1) time of the diagnosis (delay); (2) localization of the perforation; (3) severity and size of the perforation; (4) presence of septic complications, physiologic reserves of the patient and existing co-morbidity of the oesophagus; and (5) the experience of the professionals providing care.

Primary closure of the oesophagus is successful in more than 90% of cases if the defect is closed within 24 h and there were no co-morbidities in the oesophagus (tumour, stricture, *etc.*)^[25,26]. In this phase, tissues are not oedematic and are easy to suture/close; in addition, there is no active bacterial infection in the thoracic cavity and/or mediastinum. If the perforation occurred more than 24 h beforehand, the prognosis is significantly reduced due to rapidly developing septic complications and less successful surgical/conservative treatment^[12,27].

It is well-known that thoracic transmural injuries of the oesophagus have the worst prognosis due to rapidly developing mediastinitis and sepsis, followed by injury of the abdominal segment, while perforation in the cervical segment has the best prognosis.

Intramural injuries usually respond well to conservative treatment. Transmural and transpleural injuries represent the worst defects. Treatment strategy is also essentially influenced by the size of the defect. These factors are especially important in using the endoscopic technique (see below).

General stress tolerance of the patient, existing co-morbidities and severe septic condition are known to worsen the prognosis^[12,27]. Existing co-morbidities of the oesophagus are especially important in selecting a treatment option, but may also influence the prognosis significantly (such as tumorous perforation).

Today, it is only possible to manage oesophageal perforations with multidisciplinary co-operation. The role of a surgeon experienced in the treatment of perforations and that of a gastroenterologist familiar with new innovative endoscopic techniques are decisive. Treatment has to be administered individually with an understanding of the general principles involved.

TREATMENT OPTIONS FOR OESOPHAGEAL PERFORATION

Endoscopic procedures representing a minimal or significantly lower burden are more widely used not only in the diagnosis of oesophageal perforation, but also in its treatment. A number of publications, especially case histories, demonstrate the successful use of endoscopic clips and self-expanding stents in the treatment of oesophageal injuries^[5,28]. The applicability of endoscopic methods has also been confirmed in experimental animal models (endoscopic clipping vs suturing vs thoracoscopic repair)^[29]. Endoscopic clipping basically results in the immediate resolution of the oesophageal defect, while

various types of stents aid in resolving extravasation from the oesophagus (diversion of enteral contents) and provide further slow healing of the injury. Stent implantation is mainly used in the treatment of large (> 2.5-3 cm) injuries of the middle and lower third segments of the oesophagus, and is especially suitable for the treatment of tumorous perforations where dysphagia is also resolved. Several types of stents are known, such as self-expanding plastic stents and fully and partially covered, self-expanding metal stents. In the case of injuries of the gastro-oesophageal junction, a partially covered stent is recommended with the smallest migration tendency if there is no oesophageal stricture^[30]. The success of the procedure also depends on early application. Any delay in endoscopic treatment significantly reduces the chances of healing of the oesophageal perforation, as is the case with other treatment options^[5]. According to the latest systematic review, the overall technical and clinical success rates of oesophageal stent placement in patient groups were 91% and 81%, respectively, and mortality was also acceptably low at 13%^[31]. One of the most common complications of stent implantation is stent migration, which occurs in 20.8% of cases; this percentage is lower (11%) in the case of metal stents and higher for plastic stents (27%)^[31]. However, stent migration may be reduced significantly with clips (proximal clip fixation^[32]).

Vacuum-assisted technology

A method providing permanent continuous suction/drainage, is used in a number of areas with high efficacy, such as in the treatment of open abdomen, chronic wounds and suture insufficiency (rectum and oesophagus)^[33]. The procedure is suitable for the treatment of chronic fistulas, particularly well-defined peri-oesophageal abscesses. It can also be used for intrathoracic oesophagus anastomosis insufficiency. It may be used to stimulate the formation of granulation tissue; therefore, the duration of prolonged secondary wound healing is decreased significantly^[34-36]. Due to excessive granulation tissue formation, oesophageal stenosis can occur later within a 6%-40% range, but with an incidence of 15% in most cases^[37]. Due to severe mediastinal/intrathoracic infection, the mortality rate is also naturally high (0%-20%) with this method^[37].

ENDOSCOPIC CLIPS

Endoscopic clips have been used in the treatment of oesophageal perforation for 20 years; however, the number of publications on their use has only increased during the last few years. Generally, experience is available with two types of clip: the through-the-scope (TTS) clip and the over-the-scope clip (OTSC). TTS clips were developed for haemostasis and the treatment of mucosal ruptures. However, they may only be used in treating small (< 10 mm) injuries due to their limited (< 11 mm) wingspan.

The wingspan of the OTSC (OVESCO Endoscopy,

Tübingen, Germany) is not significantly larger (11-14 mm), but the system also features a special applicator cap^[38]. The entire thickness of the tissue may be pulled into the cap by suction and/or with graspers, and the tissue may be united with special clamps (a bear claw). Experience shows that this innovative clipping device made of biocompatible nitinol also provides stronger closure of large (1-2 cm) defects^[39]. Nowadays, several types of clips are available (blunt/atraumatic and pointed-teeth/traumatic). There is also a special "anchor" which aids in the closure of fibrotic fistulas. It only takes an experienced endoscopic professional a few minutes to close a defect^[40]. One iatrogenic oesophageal injury has been reported with the use of this device when an endoscopic OTSC was inserted^[40]; the injury may have been caused by the 2 mm rim of the plastic cap. However, experience shows that the device can be used safely, and the complication rate is around 1%^[40,41].

CLOSURE OF OESOPHAGEAL PERFORATION WITH ENDOSCOPIC CLIPS

Tables 1 and 2 summarize the results of the PubMed (Medline) search.

We used the following key words: Oesophageal perforation, gastrointestinal perforation, endoscopic clip (ping) and OTSC (latest search date: 15 March 2015). We processed the data from 38 articles and 127 patients. We placed causes of perforation into three categories in the table: Perforation was defined as an acute iatrogenic or spontaneous defect, leak as an insufficiency/disruption of a surgical anastomosis, and fistula as a chronic residual inflammatory communication between the oesophagus, with a mediastinal or pleural space or tracheobronchial tract under the skin.

Statistical analysis: Categorical data were analyzed using χ^2 and Fisher's exact test [SPSS version 15.0 (© 2007 SPSS Inc.)].

Most publications are case reports or retrospective analyses with heterogeneous indications. The number of publications significantly increased after the first clinical use of the OTSC clip in 2007, first in Europe and then in the United States and other countries as well. Neither randomized nor comparative (TTS vs OTSC) studies have been conducted with the use of clips. One prospective European multicentre study and two retrospective North American multicentre studies have been published on the use of OTSC clips in the treatment of GI perforations^[40-42]. Unfortunately, salient information is missing from numerous articles, and generally there are no reports on the follow-up period at all.

Based on the results, it can be concluded that both clips are suitable for the treatment and early management (< 24 h) of iatrogenic, spontaneous oesophageal perforation in the case of limited injury and contamination.

TTS clips are successfully used for injuries of an average of 10 mm, while OTSC clips may also be successful in the treatment of larger injuries. More clips may also be used to close a defect, and various clips may be combined^[40,43]; in addition, closure with a clip may be repeated^[44]. In accordance with the latest recommendations from the European Society of Gastrointestinal Endoscopy^[30], clips may only be used in the treatment of an injury in the case of safe care, in stable patients, with a clear oesophagus, limited mediastinal contamination and limited injury (intramural/transmural). Certain immediately diagnosed iatrogenic perforations meet this criterion system in particular. If the amount of mediastinal and/or pleural fluid is more significant, mediastinal and/or pleural space drainage/VATS treatment usually cannot be avoided. The treatment algorithm is summarized in Figure 1.

PERFORATIONS

Based on our analysis (Tables 1 and 2), clips were used early (immediate diagnosis, < 24 h), especially in the case of minimally contaminated iatrogenic injuries or spontaneous ruptures, and the success of healing was similar to that of surgical treatment [TTS 88.8% (24/27); OTSC 92.86% (26/28)]. Although TTS and OTSC clips were used for injuries of varying sizes, their success rates did not diverge significantly (88.8% vs 92.85%, $P > 0.12$). Of further interest, clips were used with a similar success rate for the far smaller number of perforations of > 24 h which are only associated with a well-defined mediastinal inflammation/abscess [TTS 100% (8/8) vs OTSC 83.3% (5/6)]. Transoesophageal lavage of the process or even vacuum therapy may be of great aid in resolving the abscessing mediastinal process^[45].

In selected cases of Boerhaave syndrome, closing the oesophageal injury with endoscopic clips might also be successful. TTS clips were used in two cases. In one patient, a minimal transmural oesophageal injury was diagnosed (a little air in the mediastinum), only the mucosal injury was partially closed with endoscopy, and conservative treatment was administered^[46]. In another patient, a 5-7 mm transpleural injury was closed with 3 TTS clips, and additional thoracic drainage and enteral nutrition were administered^[47]. In three additional cases, OTSC clips were used successfully to close a spontaneous transmural injury^[43,48,49]. In the two matured (> 24 h) perforations, additional VATS therapy was necessary. Similarly, only limited cases have been reported on the treatment of injuries caused by foreign bodies^[50,51].

Broad-spectrum antibiotic therapy and suspension of oral nutrition are required in addition to successful early endoscopic care. In the majority of cases, complication-free healing can be expected with careful indication. However, close monitoring of the patient and additional therapy such as mediastinal/pleural drainage or even

Table 1 Published literature reporting endoscopic through-the-scope clip closure for oesophageal perforations

Ref.	Cause	Size/mm	Time to treatment	Im/Tm/Tp	Method	Nr	Clinical success	Additional treatment	Hospital stay /d	Follow-up
Wewalka <i>et al</i> ^[7]	Perforation (1)	< 10	< 24	Tm	Endoclip		1/1 (100%)	None	ND	ND
Rodella <i>et al</i> ^[44]	Leak (7)	10-20	> 24	ND	Endoclip	ND	2/7 (14%)	Yes	ND	9.6 mo avg.
van Bodegraven <i>et al</i> ^[57]	Fistula (1)	12	> 24	ND	Endoclip + argon beam electrocoagulation	ND	1/1 (100%)	Yes	ND	7 mo
Cipolletta <i>et al</i> ^[8]	Perforation (2)	7-8	< 24	Im/Tm	Endoclip	1	1/1 (100%)	No	5	9 mo
		10	< 24	Im/Tm	Endoclip	2	1/1 (100%)	No	6	14 mo
Shimamoto <i>et al</i> ^[50]	Perforation (1)	20	< 24	Tm	Endoclip	3	1/1 (100%)	No	37	ND
Abe <i>et al</i> ^[58]	Perforation (1)	5	> 24	Tm	Endoclip	ND	1/1 (100%)	Yes	36	ND
Mizobuchi <i>et al</i> ^[59]	Fistula (1)	ND	> 24	Tm	Endoclip	1	1/1 (100%)	Yes	> 31	ND
Raymer <i>et al</i> ^[9]	Fistula (3)	≤ 25	> 24	Tm/Tp	Endoclip	ND	3/3 (100%)	Yes	ND	ND
			> 24	Tm/Tp	Endoclip + surgery	ND		Yes	ND	ND
			> 24	Tm/Tp	Endoclip + surgery	ND		Yes	ND	ND
Shimizu <i>et al</i> ^[10]	Perforation (3)	8/10/2008	< 24	Tm	Endoclip	ND	3/3 (100%)	Yes	14	ND
Schubert <i>et al</i> ^[60]	Leak (1)	ND	> 24	Tm	Stent + endoclip	ND	1/1 (100%)	ND	ND	1 mo
Wehrmann <i>et al</i> ^[45]	Perforation (4)	ND	> 24	Tm	Endoclip	ND	4/4 (100%)	Yes	9-22	12 mo
	Leak (3)	ND	> 24	Tm	Endoscopic lavage + endoclip	ND	3/3 (100%)	Yes		
Matsuda <i>et al</i> ^[46]	Perforation (1)	25	< 24	Im	Endoclip	ND	1/1 (100%)	No	ND	ND
Sriram <i>et al</i> ^[11]	Perforation (1)	10	> 24	Tm	Endoclip	ND	1/1 (100%)	Yes	ND	ND
Fischer <i>et al</i> ^[61]	Perforation (4)	20-40	< 24	Tm	Endoclip	2-6	4/4 (100%)	No	7-18	No
			< 24	Tm	Endoclip			No		No
			< 24	Tm	Endoclip			No		No
			< 24	Tm	Endoclip			No		No
Gerke <i>et al</i> ^[62]	Perforation (1)	15	< 24	Tm	Endoclip	3 + 1	1/1 (100%)	No	7	6 mo
Qadeer <i>et al</i> ^[28]	Fistula (1)	3	> 24	Tm	Endoclip + stent	4	1/1 (100%)	Yes	65	17 mo
Luigiano <i>et al</i> ^[56]	Fistula (1)	25	> 24	Tm	Endoclip	5	1/1 (100%)	ND	ND	1 mo
					Endoloop	1				
Ivekovic <i>et al</i> ^[55]	Perforation (1)	15 × 10	≤ 24	Im/Tm	Endoloop	1	1/1 (100%)	ND	ND	4 wk
					Endoclip	4				
Jung <i>et al</i> ^[63]	Perforation (1)	25	> 24	Im/Tm	Endoclip	12	1/1 (100%)	Yes	ND	2 mo
					Endoloop	1				
Rokszin <i>et al</i> ^[47]	Perforation (1)	5-7	< 24	Tp	Endoclip	3	1/1 (100%)	Yes	14	6 mo
Coda <i>et al</i> ^[64]	Perforation (1)	20 (distal)	< 24	Tm	Endoclip	6	1/1 (100%)	Yes	15	6 mo
Sato <i>et al</i> ^[24]	Perforation (1)	ND	< 24	Im/Tm	Endoclip	ND	1/1 (100%)	No	ND	ND
Biancari <i>et al</i> ^[65]	Perforation (4)	8 (median)	< 24	Tm	Endoclip	ND	3/4 (75%)	Yes	32 (median)	No
Huang <i>et al</i> ^[66]	Perforation (4)	ND	< 24	ND	Endoclip	2	4/4 (100%)	ND	ND	ND

Im: Intramural; Tm: Transmural; Tp: Transperural; ND: Non determined; VATS: Video assisted thoracoscopy.

surgical treatment, if necessary, are also essential.

FISTULAS/CHRONIC INJURIES

Fistulizing chronic injuries and treating anastomosis insufficiencies represent a separate group. Experience shows that OTSC clips have provided relatively secure closure so far, but the success rate in acute cases [OTSC 57.7% (15/26) vs TTS 100% (4/4) ($P < 0.05$) for fistulas; OTSC 77.7% (12/18) vs TTS 54.5% (6/11) ($P < 0.05$) for leaks] differed significantly in the groups.

Closure is technically often unfeasible, especially in the case of fibrotizing, scarred fistulas and a severely inflamed environment^[52]. Most problems stem from insufficiency of the oesophageal anastomosis diagnosed in the early postoperative state. These cases are usually subacute, the tissues are extremely fragile, often ischaemic, and therefore the tendency to heal is already decreased^[53]. The success rate for the closure of chronic

fistulas is also reduced by previous radiation therapy. If a TTS clip is used, argon plasma coagulation and other mechanical freshening up (with a cytology brush) may aid in stabilizing the clip. These extra manoeuvres may only increase tissue oedema and the success of clip deployment when OTSC clips are used^[41,52]. There are only a few case reports on successful closure of a chronic spontaneous oesophageal rupture and a consequently developed fistula with endoscopic clips^[9,11].

Endoscopic vacuum therapy may be helpful in reducing the inflammatory cavity and closing the remaining fistula with good localization in the case of chronic injuries and mediastinal/pleural inflammation^[37,45]. Following initial stent placement and removal in the treatment of an early, well-defined injury, a cavity marked by chronic inflammation may remain, one which may not be resolved with primary clipping alone. In these cases, EVT and/or surgical treatment (VATS) represent the primary therapeutic procedure^[34-36,45].

Table 2 Published literature reporting over-the-scope clip closure of oesophageal perforations

Ref.	Cause	Size/mm	Time to treatment (< 24 h <)	Im/Tm/Tp	Method	Nr	Clinical success	Additional treatment	Hospital stay /d	Follow-up
Pohl <i>et al</i> ^[67]	Leak (1)	< 0	> 24	Tp	OTSC	1	1/1(100%)	No	30	ND
	Perforation (1)	ND	> 24	Tp	Surgery + stent + OTSC		0/1(0%)	Yes	Died	ND
von Renteln <i>et al</i> ^[68]	Fistula (2)	ND	> 24	Tm	OTSC	1	0/2(0%)	ND	ND	ND
		ND	> 24	Tm	OTSC	1		Yes	ND	ND
Traina <i>et al</i> ^[69]	Fistula (1)	ND	> 24	Tm	OTSC	1	1/1(100%)	ND	ND	4 wk
Albert <i>et al</i> ^[70]	Fistula (1)	ND	> 24	Tm	OTSC	1	1/1(100%)	ND	ND	46 wk
	Leak (1)	ND	> 24	Tm	OTSC	1	0/1(0%)	Stent	ND	4 wk
	Leak (1)	ND	> 24	Tm	OTSC	1	1/1(100%)	ND	ND	63 wk
Kirschniak <i>et al</i> ^[71]	Leak (1)	ND	> 24	ND	OTSC	ND	1/1(100%)	ND	10	ND
Manta <i>et al</i> ^[72]	Fistula (1)	8 × 4	> 24	Tm	OTSC + standard clips	1+3	1/1(100%)	No	0	ND
Surace <i>et al</i> ^[73]	Leak (1)	ND	> 24	ND	OTSC	ND	1/1(100%)	ND	ND	ND
Baron <i>et al</i> ^[41]	Leak (3)	ND	> 24	Tm	OTSC	4	1/3(33%)	ND	ND	77 avg. (30-330 d)
	Perforation (1)	ND	< 24	Tm			1/1(100%)	ND	ND	
Hadj Amor <i>et al</i> ^[74]	Perforation (1)	20	< 24	Tp	OTSC + stent	1	1/1(100%)	VATS	ND	ND
Hagel <i>et al</i> ^[53]	Leak (2)	28 × 13	> 24	Tm/Tp	OTSC	3	1/2(50%)	Surgery	Died	30 d
		8 × 4						No	12.3 ± 11	30 d
	Perforation (2)	8 × 3	> 24	Tm/Tp	OTSC	1	0/2(0%)	Surgery		30 d
		14 × 3	> 24					Surgery		30 d
Jacobsen <i>et al</i> ^[75]	Perforation (3)	9	> 24	ND	OTSC	2	3/3(100%)	No	ND	ND
		10	> 24	ND		1		No	ND	ND
	(distal)									
		10	> 24	ND		2		No	ND	ND
Markar <i>et al</i> ^[76]	Leak (1)	ND	> 24	Tm	OTSC	2	1/1(100%)	Yes	ND	3 mo
Voermans <i>et al</i> ^[40]	Perforation (5)	< 30	< 24	ND	OTSC	ND	5/5(100%)	No	ND	6 mo
Zolotarevsky <i>et al</i> ^[77]	Fistula (1)	5	> 24	ND	OTSC	ND	1/1(100%)	ND	7	3 mo
Braun <i>et al</i> ^[43]	Perforation (6)	10-40	< 24	Tm/Tp	OTSC	1-4	6/6(100%)	VATS	9-19	6-12 wk
Ferreira <i>et al</i> ^[51]	Perforation (1)	10	> 24	Tm	OTSC	1	1/1(100%)	No	21	3 mo
	(distal)									
Noronha Ferreira <i>et al</i> ^[78]	Leak (1)	10 × 6	> 24	Tm	OTSC	1	1/1(100%)	No	14	ND
Nishiyama <i>et al</i> ^[79]	Perforation (1)	20	> 24	ND	OTSC	ND	1/1(100%)	ND	ND	56 d
Ramhamadany <i>et al</i> ^[49]	Perforation (1)	ND	> 24	ND	OTSC	ND	1/1(100%)	Yes	ND	6 mo
Bona <i>et al</i> ^[48]	Perforation (1)	10	> 24	Tm/Tp	OTSC	1	1/1(100%)	No	28	No
Haito-Chavez <i>et al</i> ^[42]	Perforation (10)	ND	< 24	Tm/Tp	OTSC		10/10(100%)	ND	ND	Median follow-up: 121-207 d
	Leaks (5)	ND	> 24	Tm/Tp			4/5(80%)	ND	ND	
	Fistula (16)	ND	> 24	Tm/Tp			9/16(57%)	ND	ND	
Mönkemüller <i>et al</i> ^[52]	Fistula (4)	10-15	> 24	ND	OTSC	1-2	2/4(50%)	No	ND	10 mo (1-10)
	Leak (1)	10-12	> 24	ND	OTSC		0/1(0%)	No	ND	

Im: Intramural; Tm: Transmural; Tp: Transperal; ND: Non determined; VATS: Video assisted thoracoscopy.

Very few articles report long-term follow-up data. The biggest and most detailed report is a North American study which evaluated gastrointestinal defects in 188 patients treated with OTSC. Success was achieved in 60.2% of the patients in a median follow-up of 146 d. The long-term rate for clinically successful closure of perforations (90%) and leaks (73.3%) was significantly higher than that of fistulas (42.9%). The study also showed significantly greater long-term success when OTSCs were used in primary therapy.

On the whole, it is clear that closure with clips shows the best results in the treatment of early injuries, and the success rate for clinical recovery approaches the result for surgical treatment.

Other uses of clips

Endoscopic clips may also be used with endoloop. The

method was first used for endoscopic mucosal resection to resolve large defects^[54]. Later, it was successful in the treatment of Mallory-Weis syndrome^[55] and in closing oesophageal fistulas^[56]. Due to the limited number of these articles, no conclusions can be drawn about their efficacy.

CONCLUSION

A number of case reports and case series reports have been published on the successful outcome of clip closure of endoscopic perforations, but high-evidence, case-controlled, multicentre studies are still missing. This method can only be used under very strict conditions (Figure 1). The introduction of OTSC clips significantly increases the size of treatable lesions (from 1 to 2-3 cm). However, this technique is only used in a limited

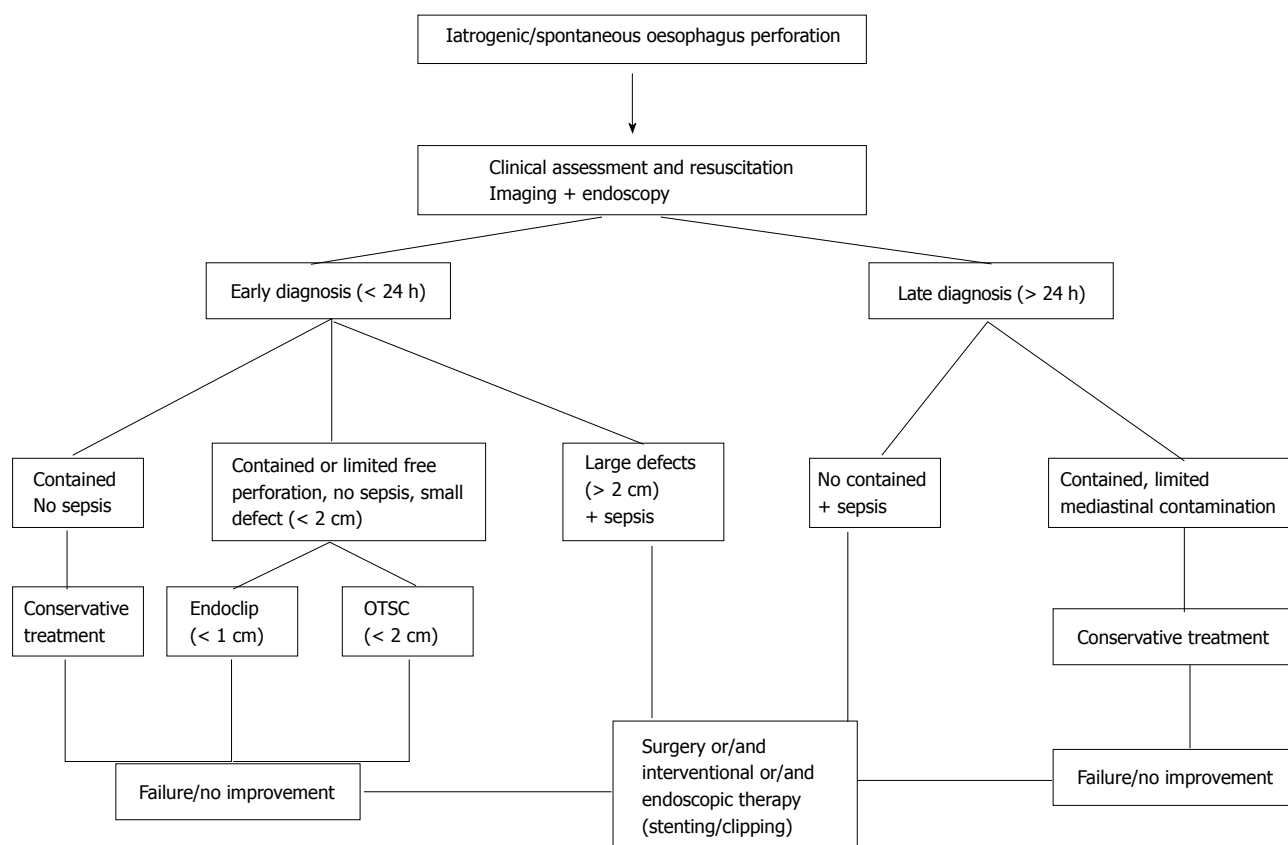


Figure 1 Algorithm for the management of oesophageal perforations.

number of centres. It is important to point out that both conventional TTS and the new OTSC methods are both safe. But a learning curve period and experience will both be necessary in their usage, including the selection of patients suitable for clip treatment. Multidisciplinary teams (surgeon, endoscopy specialist and intensive care therapist) are further important conditions in the successful treatment of oesophageal perforations. Surgical treatment still constitutes the primary therapy in oesophageal perforation. Based on the results so far, we can state that endoscopic closure of early, well-defined oesophageal perforations represents a therapeutic alternative to surgical treatment.

REFERENCES

- 1 **Bufkin BL**, Miller JI, Mansour KA. Esophageal perforation: emphasis on management. *Ann Thorac Surg* 1996; **61**: 1447-1451; discussion 1451-1452 [PMID: 8633957 DOI: 10.1016/0003-4975(96)00053-7]
- 2 **Sakamoto Y**, Tanaka N, Furuya T, Ueno T, Okamoto H, Nagai M, Murakawa T, Takayama T, Mafune K, Makuuchi M, Nobori M. Surgical management of late esophageal perforation. *Thorac Cardiovasc Surg* 1997; **45**: 269-272 [PMID: 9477457 DOI: 10.1055/s-2007-1013747]
- 3 **Skinner DB**, Little AG, DeMeester TR. Management of esophageal perforation. *Am J Surg* 1980; **139**: 760-764 [PMID: 7386730 DOI: 10.1016/0002-9610(80)90379-7]
- 4 **Tilanus HW**, Bossuyt P, Schattenkerk ME, Obertop H. Treatment of oesophageal perforation: a multivariate analysis. *Br J Surg* 1991; **78**: 582-585 [PMID: 2059811 DOI: 10.1002/bjs.1800780519]
- 5 **Fischer A**, Thomusch O, Benz S, von Dobschuetz E, Baier P, Hopt UT. Nonoperative treatment of 15 benign esophageal perforations with self-expandable covered metal stents. *Ann Thorac Surg* 2006; **81**: 467-472 [PMID: 16427833 DOI: 10.1016/j.athoracsur.2005.08.047]
- 6 **Johnsson E**, Lundell L, Liedman B. Sealing of esophageal perforation or ruptures with expandable metallic stents: a prospective controlled study on treatment efficacy and limitations. *Dis Esophagus* 2005; **18**: 262-266 [PMID: 16128784 DOI: 10.1111/j.1442-2050.2005.00476.x]
- 7 **Wewalka FW**, Clodi PH, Haidinger D. Endoscopic clipping of esophageal perforation after pneumatic dilation for achalasia. *Endoscopy* 1995; **27**: 608-611 [PMID: 8608757 DOI: 10.1055/s-2007-1005768]
- 8 **Cipolletta L**, Bianco MA, Rotondano G, Marmo R, Piscopo R, Meucci C. Endoscopic clipping of perforation following pneumatic dilation of esophagojejunal anastomotic strictures. *Endoscopy* 2000; **32**: 720-722 [PMID: 10989998 DOI: 10.1055/s-2000-7032]
- 9 **Raymer GS**, Sadana A, Campbell DB, Rowe WA. Endoscopic clip application as an adjunct to closure of mature esophageal perforation with fistulae. *Clin Gastroenterol Hepatol* 2003; **1**: 44-50 [PMID: 15017516 DOI: 10.1053/jcgh.2003.50007]
- 10 **Shimizu Y**, Kato M, Yamamoto J, Nakagawa S, Komatsu Y, Tsukagoshi H, Fujita M, Hosokawa M, Asaka M. Endoscopic clip application for closure of esophageal perforations caused by EMR. *Gastrointest Endosc* 2004; **60**: 636-639 [PMID: 15472698 DOI: 10.1016/S0016-5107(04)01960-1]
- 11 **Sriram PV**, Rao GV, Reddy ND. Successful closure of spontaneous esophageal perforation (Boerhaave's syndrome) by endoscopic clipping. *Indian J Gastroenterol* 2006; **25**: 39-41 [PMID: 16567897]
- 12 **Bhatia P**, Fortin D, Inculet RI, Malthaner RA. Current concepts in the management of esophageal perforations: a twenty-seven year Canadian experience. *Ann Thorac Surg* 2011; **92**: 209-215 [PMID: 21718846 DOI: 10.1016/j.athoracsur.2011.03.131]
- 13 **Biancari F**, D'Andrea V, Paone R, Di Marco C, Savino G, Koivukangas V, Saarnio J, Lucenteforte E. Current treatment and outcome of

- esophageal perforations in adults: systematic review and meta-analysis of 75 studies. *World J Surg* 2013; **37**: 1051-1059 [PMID: 23440483 DOI: 10.1007/s00268-013-1951-7]
- 14 **Chuah SK**, Wu KL, Hu TH, Tai WC, Changchien CS. Endoscope-guided pneumatic dilation for treatment of esophageal achalasia. *World J Gastroenterol* 2010; **16**: 411-417 [PMID: 20101764 DOI: 10.3748/wjg.v16.i4.411]
- 15 **Campos GM**, Vittinghoff E, Rabl C, Takata M, Gadenstätter M, Lin F, Ciofica R. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 2009; **249**: 45-57 [PMID: 19106675 DOI: 10.1097/SLA.0b013e31818e43ab]
- 16 **Lynch KL**, Pandolfino JE, Howden CW, Kahrilas PJ. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic review of the literature. *Am J Gastroenterol* 2012; **107**: 1817-1825 [PMID: 23032978 DOI: 10.1038/ajg.2012.332]
- 17 **Piotet E**, Escher A, Monnier P. Esophageal and pharyngeal strictures: report on 1,862 endoscopic dilations using the Savary-Gilliard technique. *Eur Arch Otorhinolaryngol* 2008; **265**: 357-364 [PMID: 17899143 DOI: 10.1007/s00405-007-0456-0]
- 18 **Neuhaus H**. ESD around the world: Europe. *Gastrointest Endosc Clin N Am* 2014; **24**: 295-311 [PMID: 24679240 DOI: 10.1016/j.giec.2013.11.002]
- 19 **Giménez A**, Franquet T, Erasmus JJ, Martínez S, Estrada P. Thoracic complications of esophageal disorders. *Radiographics* 2002; **22** Spec No: S247-S258 [PMID: 12376614 DOI: 10.1148/radiographics.22.suppl_1.g02oc18s247]
- 20 **Fadoo F**, Ruiz DE, Dawn SK, Webb WR, Gotway MB. Helical CT esophagography for the evaluation of suspected esophageal perforation or rupture. *AJR Am J Roentgenol* 2004; **182**: 1177-1179 [PMID: 15100114 DOI: 10.2214/ajr.182.5.1821177]
- 21 **Carrott PW**, Low DE. Advances in the management of esophageal perforation. *Thorac Surg Clin* 2011; **21**: 541-555 [PMID: 22040636 DOI: 10.1016/j.thorsurg.2011.08.002]
- 22 **Kowalczyk L**, Forsmark CE, Ben-David K, Wagh MS, Chauhan S, Collins D, Draganov PV. Algorithm for the management of endoscopic perforations: a quality improvement project. *Am J Gastroenterol* 2011; **106**: 1022-1027 [PMID: 21637265 DOI: 10.1038/ajg.2010.434]
- 23 **Kuppusamy MK**, Felisky C, Kozarek RA, Schembre D, Ross A, Gan I, Irani S, Low DE. Impact of endoscopic assessment and treatment on operative and non-operative management of acute oesophageal perforation. *Br J Surg* 2011; **98**: 818-824 [PMID: 21523697 DOI: 10.1002/bjs.7437]
- 24 **Sato H**, Inoue H, Ikeda H, Grace R, Santi E, Yoshida A, Onimaru M, Kudo S. Clinical experience of esophageal perforation occurring with endoscopic submucosal dissection. *Dis Esophagus* 2014; **27**: 617-622 [PMID: 23980646 DOI: 10.1111/dote.12125]
- 25 **Lawrence DR**, Ohri SK, Moxon RE, Townsend ER, Fountain SW. Primary esophageal repair for Boerhaave's syndrome. *Ann Thorac Surg* 1999; **67**: 818-820 [PMID: 10215235 DOI: 10.1016/S0003-4975(99)00043-0]
- 26 **Sabanathan S**, Eng J, Richardson J. Surgical management of intrathoracic oesophageal rupture. *Br J Surg* 1994; **81**: 863-865 [PMID: 8044604 DOI: 10.1002/bjs.1800810623]
- 27 **Lázár G**, Paszt A, Simonka Z, Bársony A, Abraham S, Horváth G. A successful strategy for surgical treatment of Boerhaave's syndrome. *Surg Endosc* 2011; **25**: 3613-3619 [PMID: 21674208 DOI: 10.1007/s00464-011-1767-1]
- 28 **Qadeer MA**, Dumot JA, Vargo JJ, Lopez AR, Rice TW. Endoscopic clips for closing esophageal perforations: case report and pooled analysis. *Gastrointest Endosc* 2007; **66**: 605-611 [PMID: 17725956 DOI: 10.1016/j.gie.2007.03.1028]
- 29 **Fritscher-Ravens A**, Hampe J, Grange P, Holland C, Olagbeye F, Milla P, von Herbay A, Jacobsen B, Seehusen F, Haderl KG, Mannur K. Clip closure versus endoscopic suturing versus thoracoscopic repair of an iatrogenic esophageal perforation: a randomized, comparative, long-term survival study in a porcine model (with videos). *Gastrointest Endosc* 2010; **72**: 1020-1026 [PMID: 21034902 DOI: 10.1016/j.gie.2010.07.029]
- 30 **Paspatis GA**, Dumonceau JM, Barthet M, Meisner S, Repici A, Saunders BP, Vezakis A, Gonzalez JM, Turino SY, Tsiamoulos ZP, Fockens P, Hassan C. Diagnosis and management of iatrogenic endoscopic perforations: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy* 2014; **46**: 693-711 [PMID: 25046348 DOI: 10.1055/s-0034-1377531]
- 31 **Dasari BV**, Neely D, Kennedy A, Spence G, Rice P, Mackle E, Epanomeritakis E. The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. *Ann Surg* 2014; **259**: 852-860 [PMID: 24509201 DOI: 10.1097/SLA.0000000000000564]
- 32 **Vanbiervliet G**, Filippi J, Karimjee BS, Venissac N, Iannelli A, Rahili A, Benizri E, Pop D, Staccini P, Tran A, Schneider S, Mouroux J, Gugenheim J, Benchimol D, Hébuterne X. The role of clips in preventing migration of fully covered metallic esophageal stents: a pilot comparative study. *Surg Endosc* 2012; **26**: 53-59 [PMID: 21792721 DOI: 10.1007/s00464-011-1827-6]
- 33 **Loske G**, Schorsch T, Müller C. Endoscopic vacuum sponge therapy for esophageal defects. *Surg Endosc* 2010; **24**: 2531-2535 [PMID: 20333402 DOI: 10.1007/s00464-010-0998-x]
- 34 **Loske G**, Schorsch T, Müller C. Endoscopic intracavitary vacuum therapy of Boerhaave's syndrome: a case report. *Endoscopy* 2010; **42** Suppl 2: E144-E145 [PMID: 20405387 DOI: 10.1055/s-0029-1244092]
- 35 **Ahrens M**, Schulte T, Egberts J, Schafmayer C, Hampe J, Fritscher-Ravens A, Broering DC, Schniewind B. Drainage of esophageal leakage using endoscopic vacuum therapy: a prospective pilot study. *Endoscopy* 2010; **42**: 693-698 [PMID: 20806153 DOI: 10.1055/s-0030-1255688]
- 36 **Loske G**, Schorsch T, Müller C. Intraluminal and intracavitary vacuum therapy for esophageal leakage: a new endoscopic minimally invasive approach. *Endoscopy* 2011; **43**: 540-544 [PMID: 21448855 DOI: 10.1055/s-0030-1256345]
- 37 **Mennigen R**, Senninger N, Laukoetter MG. Novel treatment options for perforations of the upper gastrointestinal tract: endoscopic vacuum therapy and over-the-scope clips. *World J Gastroenterol* 2014; **20**: 7767-7776 [PMID: 24976714 DOI: 10.3748/wjg.v20.i24.7767]
- 38 **Kirschniak A**, Kratt T, Stüker D, Braun A, Schurr MO, Königsrainer A. A new endoscopic over-the-scope clip system for treatment of lesions and bleeding in the GI tract: first clinical experiences. *Gastrointest Endosc* 2007; **66**: 162-167 [PMID: 17591492 DOI: 10.1016/j.gie.2007.01.034]
- 39 **Parodi A**, Repici A, Pedroni A, Bianchi S, Conio M. Endoscopic management of GI perforations with a new over-the-scope clip device (with videos). *Gastrointest Endosc* 2010; **72**: 881-886 [PMID: 20646699 DOI: 10.1016/j.gie.2010.04.006]
- 40 **Voermans RP**, Le Moine O, von Renteln D, Ponchon T, Giovannini M, Bruno M, Weusten B, Seewald S, Costamagna G, Deprez P, Fockens P. Efficacy of endoscopic closure of acute perforations of the gastrointestinal tract. *Clin Gastroenterol Hepatol* 2012; **10**: 603-608 [PMID: 22361277 DOI: 10.1016/j.cgh.2012.02.005]
- 41 **Baron TH**, Song LM, Ross A, Tokar JL, Irani S, Kozarek RA. Use of an over-the-scope clipping device: multicenter retrospective results of the first U.S. experience (with videos). *Gastrointest Endosc* 2012; **76**: 202-208 [PMID: 22726484 DOI: 10.1016/j.gie.2012.03.250]
- 42 **Haito-Chavez Y**, Law JK, Kratt T, Arezzo A, Verra M, Morino M, Sharaiha RZ, Poley JW, Kahaleh M, Thompson CC, Ryan MB, Choksi N, Elmunzer BJ, Gosain S, Goldberg EM, Modayil RJ, Stavropoulos SN, Schembre DB, DiMaio CJ, Chandrasekhara V, Hasan MK, Varadarajulu S, Hawes R, Gomez V, Woodward TA, Rubel-Cohen S, Fluxa F, Vleggaar FP, Akshintala VS, Raju GS, Khashab MA. International multicenter experience with an over-the-scope clipping device for endoscopic management of GI defects (with video). *Gastrointest Endosc* 2014; **80**: 610-622 [PMID: 24908191 DOI: 10.1016/j.gie.2014.03.049]
- 43 **Braun A**, Richter-Schrag HJ, Fischer A, Hoepfner J. Minimally invasive therapy of perforations at the esophagogastric junction

- by over-the-scope clipping. *Endoscopy* 2013; **45** Suppl 2 UCTN: E133-E134 [PMID: 23716097 DOI: 10.1055/s-0032-1326449]
- 44 **Rodella L**, Laterza E, De Manzoni G, Kind R, Lombardo F, Catalano F, Ricci F, Cordiano C. Endoscopic clipping of anastomotic leakages in esophagogastric surgery. *Endoscopy* 1998; **30**: 453-456 [PMID: 9693892 DOI: 10.1055/s-2007-1001307]
 - 45 **Wehrmann T**, Stergiou N, Vogel B, Riphaut A, Köckerling F, Frenz MB. Endoscopic debridement of paraesophageal, mediastinal abscesses: a prospective case series. *Gastrointest Endosc* 2005; **62**: 344-349 [PMID: 16111949 DOI: 10.1016/j.gie.2005.03.001]
 - 46 **Matsuda A**, Miyashita M, Sasajima K, Nomura T, Makino H, Matsutani T, Katsuno A, Sasaki J, Tajiri T. Boerhaave syndrome treated conservatively following early endoscopic diagnosis: a case report. *J Nippon Med Sch* 2006; **73**: 341-345 [PMID: 17220586]
 - 47 **Rokszin R**, Simonka Z, Paszt A, Szepes A, Kuca K, Lazar G. Successful endoscopic clipping in the early treatment of spontaneous esophageal perforation. *Surg Laparosc Endosc Percutan Tech* 2011; **21**: e311-e312 [PMID: 22146179 DOI: 10.1097/SLE.0b013e31823118ee]
 - 48 **Bona D**, Aiolfi A, Rausa E, Bonavina L. Management of Boerhaave's syndrome with an over-the-scope clip. *Eur J Cardiothorac Surg* 2014; **45**: 752-754 [PMID: 23868954 DOI: 10.1093/ejcts/ezt363]
 - 49 **Ramhamadany E**, Mohamed S, Jaunoo S, Baker T, Mannath J, Harding J, Menon V. A delayed presentation of Boerhaave's syndrome with mediastinitis managed using the over-the-scope clip. *J Surg Case Rep* 2013; **2013**: rjt020 [PMID: 24964437 DOI: 10.1093/jscr/rjt020]
 - 50 **Shimamoto C**, Hirata I, Umegaki E, Katsu K. Closure of an esophageal perforation due to fish bone ingestion by endoscopic clip application. *Gastrointest Endosc* 2000; **51**: 736-739 [PMID: 10840316 DOI: 10.1067/mge.2000.105729]
 - 51 **Ferreira AO**, Lopes J, Velosa J. Snapper fishbone esophageal perforation closed with an over-the-scope-clip. *BMJ Case Rep* 2013; **2013**: bcr2013201614 [PMID: 24163406 DOI: 10.1136/bcr-2013-201614]
 - 52 **Mönkemüller K**, Peter S, Toshniwal J, Popa D, Zabielski M, Stahl RD, Ramesh J, Wilcox CM. Multipurpose use of the 'bear claw' (over-the-scope-clip system) to treat endoluminal gastrointestinal disorders. *Dig Endosc* 2014; **26**: 350-357 [PMID: 23855514 DOI: 10.1111/den.12145]
 - 53 **Hagel AF**, Naegel A, Lindner AS, Kessler H, Matzel K, Dauth W, Neurath MF, Raithel M. Over-the-scope clip application yields a high rate of closure in gastrointestinal perforations and may reduce emergency surgery. *J Gastrointest Surg* 2012; **16**: 2132-2138 [PMID: 22903364 DOI: 10.1007/s11605-012-1983-6]
 - 54 DAVE Project - Gastroenterology. Editors: Kelsey PB, Bounds BC, Raju, GS, Collier DF. Video: Tulip bundle technique: a novel technique for closing perforations caused by endoscopic resection, by placement of clips and approximation with endoloops. Available from: URL: <http://www.podcastchart.com/podcasts/dave-project-gastroenterology/episodes/video-tulip-bundle-technique-a-novel-technique-for-closing-perforations-caused-by-endoscopic-resection-by-placement-of-clips-and-approximation-with-endoloops>
 - 55 **Ivekovic H**, Rustemovic N, Brkic T, Opacic M, Pulanic R, Ostojic R, Vucelic B. The esophagus as a working channel: successful closure of a large Mallory-Weiss tear with clips and an endoloop. *Endoscopy* 2011; **43** Suppl 2 UCTN: E170 [PMID: 21563067 DOI: 10.1055/s-0030-1256273]
 - 56 **Luigiano C**, Ferrara F, Polifemo AM, Fabbri C, Ghersi S, Bassi M, D'Imperio N. Endoscopic closure of esophageal fistula using a novel "clips and loop" method. *Endoscopy* 2009; **41** Suppl 2: E249-E250 [PMID: 19787575 DOI: 10.1055/s-0029-1214430]
 - 57 **van Bodegraven AA**, Kuipers EJ, Bonenkamp HJ, Meuwissen SG. Esophagopleural fistula treated endoscopically with argon beam electrocoagulation and clips. *Gastrointest Endosc* 1999; **50**: 407-409 [PMID: 10462666 DOI: 10.1053/ge.1999.v50.97234]
 - 58 **Abe N**, Sugiyama M, Hashimoto Y, Itoh N, Nakaura H, Izumisato Y, Matsuoka H, Masaki T, Nakashima M, Mori T, Atomi Y. Endoscopic nasomediastinal drainage followed by clip application for treatment of delayed esophageal perforation with mediastinitis. *Gastrointest Endosc* 2001; **54**: 646-648 [PMID: 11677490 DOI: 10.1067/mge.2001.117155]
 - 59 **Mizobuchi S**, Kuge K, Maeda H, Matsumoto Y, Yamamoto M, Sasaguri S. Endoscopic clip application for closure of an esophagomediastinal-tracheal fistula after surgery for esophageal cancer. *Gastrointest Endosc* 2003; **57**: 962-965 [PMID: 12776057 DOI: 10.1016/S0016-5107(03)70054-6]
 - 60 **Schubert D**, Scheidbach H, Kuhn R, Wex C, Weiss G, Eder F, Lippert H, Pross M. Endoscopic treatment of thoracic esophageal anastomotic leaks by using silicone-covered, self-expanding polyester stents. *Gastrointest Endosc* 2005; **61**: 891-896 [PMID: 15933696 DOI: 10.1016/S0016-5107(05)00325-1]
 - 61 **Fischer A**, Schrag HJ, Goos M, von Dobschuetz E, Hopt UT. Nonoperative treatment of four esophageal perforations with hemostatic clips. *Dis Esophagus* 2007; **20**: 444-448 [PMID: 17760660 DOI: 10.1111/j.1442-2050.2007.00652.x]
 - 62 **Gerke H**, Crowe GC, Iannettoni MD. Endoscopic closure of cervical esophageal perforation caused by traumatic insertion of a mucosectomy cap. *Ann Thorac Surg* 2007; **84**: 296-298 [PMID: 17588444 DOI: 10.1016/j.athoracsur.2007.02.027]
 - 63 **Jung JH**, Kim JI, Song JH, Kim JH, Lee SH, Cheung DY, Park SH, Kim JK. A case of Sengstaken-Blakemore tube-induced esophageal rupture repaired by endoscopic clipping. *Intern Med* 2011; **50**: 1941-1945 [PMID: 21921373 DOI: 10.2169/internalmedicine.50.5432]
 - 64 **Coda S**, Antonellis F, Tsagkaropoulos S, Francioni F, Trentino P. Complete endoscopic closure (clipping) of a large esophageal perforation after pneumatic dilation in a patient with achalasia. *J Laparoendosc Adv Surg Tech A* 2012; **22**: 815-818 [PMID: 22973857 DOI: 10.1089/lap.2012.0198]
 - 65 **Biancari F**, Saarnio J, Mennander A, Hypén L, Salminen P, Kuittila K, Victorzon M, Böckelman C, Tarantino E, Tiffet O, Koivukangas V, Søreide JA, Viste A, Bonavina L, Vidarsdóttir H, Gudbjartsson T. Outcome of patients with esophageal perforations: a multicenter study. *World J Surg* 2014; **38**: 902-909 [PMID: 24174169 DOI: 10.1007/s00268-013-2312-2]
 - 66 **Huang J**, Wen W, Tang X, Fan Z, Song H, Wang K. Cap-assisted clip closure of large esophageal perforations caused by a duodenoscope during endoscopic retrograde cholangiopancreatography (with video). *Surg Laparosc Endosc Percutan Tech* 2014; **24**: e101-e105 [PMID: 24710255 DOI: 10.1097/SLE.0b013e318293c4b6]
 - 67 **Pohl J**, Borgulya M, Lorenz D, Ell C. Endoscopic closure of postoperative esophageal leaks with a novel over-the-scope clip system. *Endoscopy* 2010; **42**: 757-759 [PMID: 20806160 DOI: 10.1055/s-0030-1255634]
 - 68 **von Renteln D**, Denzer UW, Schachschal G, Anders M, Groth S, Rösch T. Endoscopic closure of GI fistulae by using an over-the-scope clip (with videos). *Gastrointest Endosc* 2010; **72**: 1289-1296 [PMID: 20951989 DOI: 10.1016/j.gie.2010.07.033]
 - 69 **Traina M**, Curcio G, Tarantino I, Soresi S, Barresi L, Vitulo P, Gridelli B. New endoscopic over-the-scope clip system for closure of a chronic tracheoesophageal fistula. *Endoscopy* 2010; **42** Suppl 2: E54-E55 [PMID: 20157889 DOI: 10.1055/s-0029-1243824]
 - 70 **Albert JG**, Friedrich-Rust M, Woeste G, Strey C, Bechstein WO, Zeuzem S, Sarrazin C. Benefit of a clipping device in use in intestinal bleeding and intestinal leakage. *Gastrointest Endosc* 2011; **74**: 389-397 [PMID: 21612776 DOI: 10.1016/j.gie.2011.03.1128]
 - 71 **Kirschniak A**, Subotova N, Zieker D, Königsrainer A, Kratt T. The Over-The-Scope Clip (OTSC) for the treatment of gastrointestinal bleeding, perforations, and fistulas. *Surg Endosc* 2011; **25**: 2901-2905 [PMID: 21424197 DOI: 10.1007/s00464-011-1640-2]
 - 72 **Manta R**, Manno M, Bertani H, Barbera C, Pigò F, Mirante V, Longinotti E, Bassotti G, Conigliaro R. Endoscopic treatment of gastrointestinal fistulas using an over-the-scope clip (OTSC) device: case series from a tertiary referral center. *Endoscopy* 2011; **43**: 545-548 [PMID: 21409741 DOI: 10.1055/s-0030-1256196]
 - 73 **Surace M**, Mercky P, Demarquay JF, Gonzalez JM, Dumas R, Ah-Soune P, Vitton V, Grimaud J, Barthet M. Endoscopic management of GI fistulae with the over-the-scope clip system (with video). *Gastrointest Endosc* 2011; **74**: 1416-1419 [PMID: 22136786 DOI:

- 10.1016/j.gie.2011.08.011]
- 74 **Hadj Amor WB**, Bonin EA, Vitton V, Desjeux A, Grimaud JC, Barthet M. Successful endoscopic management of large upper gastrointestinal perforations following EMR using over-the-scope clipping combined with stenting. *Endoscopy* 2012; **44** Suppl 2 UCTN: E277-E278 [PMID: 22933253 DOI: 10.1055/s-0032-1309861]
- 75 **Jacobsen GR**, Coker AM, Acosta G, Talamini MA, Savides TJ, Horgan S. Initial experience with an innovative endoscopic clipping system. *Surg Technol Int* 2012; **22**: 39-43 [PMID: 23225590]
- 76 **Markar SR**, Koehler R, Low DE, Ross A. Novel multimodality endoscopic closure of postoperative esophageal fistula. *Int J Surg Case Rep* 2012; **3**: 577-579 [PMID: 22943885 DOI: 10.1016/j.ijscr.2012.08.001]
- 77 **Zolotarevsky E**, Kwon Y, Bains M, Schattner M. Esophagobronchial fistula closure using a novel endoscopic over-the-scope-clip. *Ann Thorac Surg* 2012; **94**: e69-e70 [PMID: 22916783 DOI: 10.1016/j.athoracsur.2012.02.025]
- 78 **Noronha Ferreira C**, Ribeiro LC, Velosa J, Ferreira J, Ferreira C, Freire JP, Marques J, Ruivo A, Bicha Castelo H. Total gastrectomy in an elderly patient complicated by esophageal fistula: rescue by the over-the-scope clip. *Gastrointest Endosc* 2013; **77**: 497-498 [PMID: 23294758 DOI: 10.1016/j.gie.2012.10.031]
- 79 **Nishiyama N**, Mori H, Kobara H, Rafiq K, Fujihara S, Kobayashi M, Oryu M, Masaki T. Efficacy and safety of over-the-scope clip: including complications after endoscopic submucosal dissection. *World J Gastroenterol* 2013; **19**: 2752-2760 [PMID: 23687412 DOI: 10.3748/wjg.v19.i18.2752]

P- Reviewer: Kuehn F, Natsugoe S **S- Editor:** Qi Y **L- Editor:** A
E- Editor: Lu YJ



Role of self-expanding metal stents in the management of variceal haemorrhage: Hype or hope?

Brian J Hogan, James P O'Beirne

Brian J Hogan, James P O'Beirne, Institute for Liver and Digestive Health, UCL, Royal Free Hospital, London NW3 2QG, United Kingdom

James P O'Beirne, the Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust, Royal Free Hospital, London NW3 2QG, United Kingdom

Author contributions: Both authors contributed to this paper.

Conflict-of-interest statement: Brian J Hogan and James P O'Beirne are co-investigators in a multi-centre randomized controlled trial of self-expanding metal stents in the management of variceal haemorrhage. The "Stent Oesophageal Varices" trial has received financial support from Ella CS.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. James P O'Beirne, Consultant Hepatologist, the Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust, Royal Free Hospital, Pond Street, London NW3 2QG, United Kingdom. james.o'beirne@nhs.net
Telephone: +44-20-77940500-33998
Fax: +44-20-74726226

Received: June 29, 2015

Peer-review started: July 2, 2015

First decision: August 4, 2015

Revised: October 8, 2015

Accepted: November 10, 2015

Article in press: November 11, 2015

Published online: January 10, 2016

Abstract

Despite the advances of medical, endoscopic and

radiological therapy over recent years the mortality rates of acute variceal haemorrhage are still 16%-20% and the medium term outcome has not improved in the last 25 years. Early transjugular intrahepatic portosystemic shunt has proved to be an effective therapy for selected groups of patients with a high risk of re-bleeding and moderate liver disease. However, there is an unmet need for a therapy that can be applied in patients with a high risk of re-bleeding and advanced liver disease either as definitive therapy or as a bridge to permanent therapy. Self-expanding metal stents can be placed without the need for endoscopic or fluoroscopic control and, once in place, will provide effective haemostasis and allow a route for oral fluids and nutrition. They can remain in place whilst liver function recovers and secondary prophylaxis is initiated. We review the results of 6 case series including a total of 83 patients and the first randomised controlled trial of self-expanding metal stents *vs* balloon tamponade (BT) in the management of refractory variceal haemorrhage. We report that self-expanding metal stents provide effective haemostasis and perform better than BT in refractory bleeding, where they are associated with fewer complications. Whilst the most effective place for self-expanding metal stents in the management algorithm needs to be determined by further randomised controlled trials, currently they provide an effective alternative to BT in selected patients.

Key words: Esophageal and gastric varices; Stents; Liver cirrhosis; Gastrointestinal haemorrhage; Portal hypertension

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Failure to control bleeding in high-risk patients with variceal haemorrhage is still common, and not all patients are suitable for transjugular intrahepatic portosystemic shunts. Self-expanding metal stents can be placed without the need for endoscopic or fluoroscopic control and, once in place, provide effective haemostasis and allow a route for oral fluids and nutrition. They

can remain in place whilst liver function recovers and secondary prophylaxis is initiated or whilst definitive therapy is provided. Self-expanding metal stents provide effective haemostasis and perform better than balloon tamponade in refractory bleeding, where they are associated with fewer complications.

Hogan BJ, O'Beirne JP. Role of self-expanding metal stents in the management of variceal haemorrhage: Hype or hope? *World J Gastrointest Endosc* 2016; 8(1): 23-29 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i1/23.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i1.23>

INTRODUCTION

Acute variceal bleeding represents a devastating decompensating episode and occurs at a rate of 4% per year in patients with cirrhosis, increasing to 15% per year in those with medium or large varices^[1].

Outcomes from a single episode of variceal bleeding have improved significantly in recent years. Better endoscopic therapy exists in the form of endoscopic variceal ligation and tissue adhesive glue^[2,3] and more effective pharmacotherapy including potent vasoactive drugs^[4,5] and prophylactic antibiotics^[6]. However, the mortality rates of 16%-20% are still significant and medium term outcome has not improved in the last 25 years^[7-10].

Failure to control bleeding, as defined by the Baveno V criteria, is estimated at approximately 17% in the modern era^[11]. Traditional factors associated with failure to control bleeding at 5 d and mortality at one month were active bleeding at endoscopy, severity of liver disease and an hepatic venous pressure gradient of > 20 mmHg^[12,13]. More recently the model for end-stage liver disease (MELD) score has been shown to be useful in predicting outcome, with a MELD score < 11 being associated with < 5% mortality and a MELD score > 19 with > 20% mortality^[14].

CURRENT OPTIONS FOR FAILURE OF STANDARD THERAPY

Failure to control bleeding requires salvage therapy such as balloon tamponade (BT) or insertion of transjugular intrahepatic portosystemic shunts (TIPS). These methods are effective at control of bleeding, but have important limitations. BT is a temporary therapy which most experts suggest can be used for a maximum duration of 24 h as a bridge to more definitive therapy^[15]. The success of BT in controlling haemorrhage is reported to be between 88%-91% in the first 24 h^[16]. BT is associated with the risks of oesophageal tear, mucosal ischaemia and aspiration pneumonia. TIPS carries a risk of worsening liver function and encephalopathy and is associated with a 30 d mortality of 30% when used as a

rescue therapy^[17]. In addition TIPS is not readily available in many centres that manage upper gastrointestinal haemorrhage.

The importance of early haemostasis was demonstrated in a randomised controlled trial of early TIPS insertion. Participants were randomised to either TIPS insertion within 72 h or standard medical therapy, which could include rescue TIPS. It demonstrated a reduction in uncontrolled bleeding or re-bleeding in the early TIPS group (3% vs 45%), a reduction in average intensive care unit stay (3.6 d vs 8.6 d) and a significant reduction in 1 year mortality (14% vs 39%, $P = 0.001$)^[18]. Patients over 75 years of age, those with a Childs Pugh score > 13 and those with advanced hepatocellular carcinoma were excluded from this study. Similar results have been shown using early TIPS in high-risk patients selected for a hepatic venous pressure gradient > 20 mmHg^[19].

Attempts to replicate these results outside of clinical trials have been encouraging, but show that patient selection is vital and TIPS can be associated with significant complications. A United Kingdom centre began implementing an early TIPS protocol in 2010 for high-risk patients with acute variceal haemorrhage (Childs Pugh C or Childs Pugh B with active bleeding at endoscopy). The median time to TIPS was 12 h and the same exclusion criteria as reported in the above early TIPS study applied. Overall 30-d mortality was 8.6% and at 6 mo it was 14.7%. The re-bleeding rate was 11.4% and all re-bleeding occurred within the first 7 d^[20]. A series from France proved similar efficacy with regards to haemostasis, with failure to control bleeding in 1/23 (4%). However, in this series there was a significant deterioration in liver function in 10/23 with 5 patients dying and 5 requiring transplantation. In addition 5/23 patients developed acute heart failure and 3 of these required mechanical ventilation^[21].

Based on this data it would seem reasonable to promote TIPS as an initial treatment for high-risk patients with portal hypertensive bleeding. However, TIPS requires specialist equipment and expertise, and the logistics of providing this to all high-risk patients would be difficult for many healthcare systems internationally. There is, therefore, a need for a treatment which can be applied easily and effectively to patients at high risk of re-bleeding that could reduce early re-bleeding and promote a bridge to effective secondary prophylaxis or TIPS.

SELF-EXPANDING MESH-METAL STENT FOR VARICEAL HAEMORRHAGE

The SX-ELLA Danis stent (Ella CS, Hradec Kralove, Czech Republic) is a removable, covered, self-expanding mesh-metal stent (SEMS) that was designed for the emergency treatment of oesophageal variceal bleeding. It is 135 mm long and 25 mm in diameter giving it the ability to tamponade bleeding varices in the distal oesophagus. It is supplied with a unique insertion

system, where by a gastric balloon is inflated to anchor the distal end of the stent at the gastro-oesophageal junction when traction is applied. The Danis stent can be deployed without direct endoscopic or fluoroscopic guidance, and its' position should be confirmed by chest radiograph after insertion. Stents can be left in place for up to 14 d and can be removed endoscopically using the accompanying stent removal device. The stent provides immediate haemostasis and prevents re-bleeding for the time it is *in situ*. This allows recovery of liver function, consideration of definitive therapy and institution of secondary prophylaxis in addition to maintaining an oral route for fluids and nutrition. SEMs have also be useful in the management of BT related oesophageal rupture and for broncho-oesophageal fistula.

CURRENT EVIDENCE FOR SEMS

To date there have been 4 large case series, with ≥ 10 patients, a number of smaller case series and reports and one randomised controlled trial assessing the safety and efficacy of SEMs in the control of variceal haemorrhage^[22-24].

The first series was reported by Hubmann *et al*^[25] in 20 patients with Child-Pugh B or C cirrhosis and massive ongoing bleeding. Two patients received Choo stents (140 mm \times 18 mm) and three patients received a Boubela-Danis stent (95 mm \times 20 mm). The next 15 patients received the purpose designed SX-ELLA Danis stent as described above. The first five were placed *via* an endoscopic guide wire and fluoroscopic control, the remainder were placed using the insertion device without a guide-wire or fluoroscopy. The stents were able to successfully control haemorrhage in all cases with no reported re-bleeding during 30 d of follow-up. In one case there was mild ulceration in the distal oesophagus after removal, no other complications were reported. Following stent extraction at a median of 5 d (1-14 d), 18 patients went on to have a definitive procedure to prevent re-bleeding (TIPS, azygoportal disconnection, liver transplant, radiological embolization or endoscopic intervention (variceal ligation or sclerotherapy)). Mortality was 10% within 30 d (one at day three from hepatic failure and one at day five from multi-organ failure) and 20% at 60 d (Figure 1).

The same group of investigators published a further series of the SX-ELLA Danis stent including 15 patients previously described, with an additional 19 patients all of whom had failure to control bleeding following standard endoscopic techniques^[26]. Haemostasis was achieved in all 34 cases using the SX-ELLA Danis stent without complications. All stents were deployed successfully, for a mean of 6 d (range 1-14 d). There were a total of 7 instances of stent migration, which was attributed to low stent position at insertion. Mortality was 26.5% at 30 d and 29.4% at 60 d and there was no re-bleeding reported during follow-up.

A tertiary United Kingdom centre reported SEMs use in 10 patients with on-going variceal bleeding

despite standard endoscopic therapy^[27]. Two patients had the added complication of BT induced oesophageal rupture. Stents were successfully deployed in 9 cases, in once case the gastric balloon failed to inflate and the procedure was abandoned. Nine/ten patients had active bleeding at the time of endoscopy and haemostasis was achieved in 7/9 (78%). The patients with continued haemorrhage were subsequently shown to be bleeding from gastric varices. The mortality rate at 6 wk was 50%.

Fierz *et al*^[28] described a combined case series of 9 patients from Swiss Hospitals. They reported a total of 9 bleeding episodes in 7 cirrhotic patients (two patients had two separate bleeds). In three cases SEMs was used as first line endoscopic therapy, and in the remaining 6 cases there had been inadequate control of haemorrhage with band ligation or sclerotherapy. The majority of patients were Child-Pugh class C and the mean MELD score was 34. All stents were placed with endoscopic assistance and two cases of distal stent migration were noticed, no other complications were reported. Control of haemorrhage was achieved in all cases, except one where the stent was not deployed correctly. The reported 6 wk mortality rate of 78% is high and reflects the severity of underlying liver disease in this cohort^[28].

Zakaria *et al*^[29] have reported a series of 16 patients where SEMs was used for the primary therapy of variceal haemorrhage. Patients with hepatitis C related cirrhosis and evidence of on-going bleeding from varices, cherry red spots, or fresh blood in the oesophagus or stomach received a stent for between 2 and 4 d. Successful control of haemorrhage with the SEMs was reported in 14/16 patients. Of the two treatment failures one was caused by the rupture of the gastric balloon and sclerotherapy was applied to the varix and in the second the SEMs failed to control bleeding from a GOV-1 varix which required cyanoacrylate glue.

The results of the first randomised controlled trial comparing SEMs to BT were published in abstract form in 2013^[30]. This was a multicentre trial of 8 hospitals in Spain.

The study included consenting adult patients with cirrhosis and acute variceal bleeding (as defined by the Baveno II consensus) who met either of the following inclusion criteria: (1) Failure to control bleeding (as defined by Baveno IV criteria) despite pharmacological (somatostatin 3 or 6 mg/12 h *iv* or terlipressin, 2 mg/4 h *iv*) AND endoscopic therapy (oesophageal banding ligation preferably or sclerotherapy); and (2) Massive bleeding, uncontrolled despite pharmacological therapy started at any moment, with no need of previous endoscopic therapy. Uncontrolled bleeding was defined as an upper digestive bleeding in which no hemodynamic stability (systolic arterial pressure > 70 mmHg and heart rate < 100 bpm) could be achieved.

The exclusion criteria were oesophageal rupture; oesophageal, gastric or upper respiratory tract tumor; oesophageal stenosis; recent oesophageal surgery;

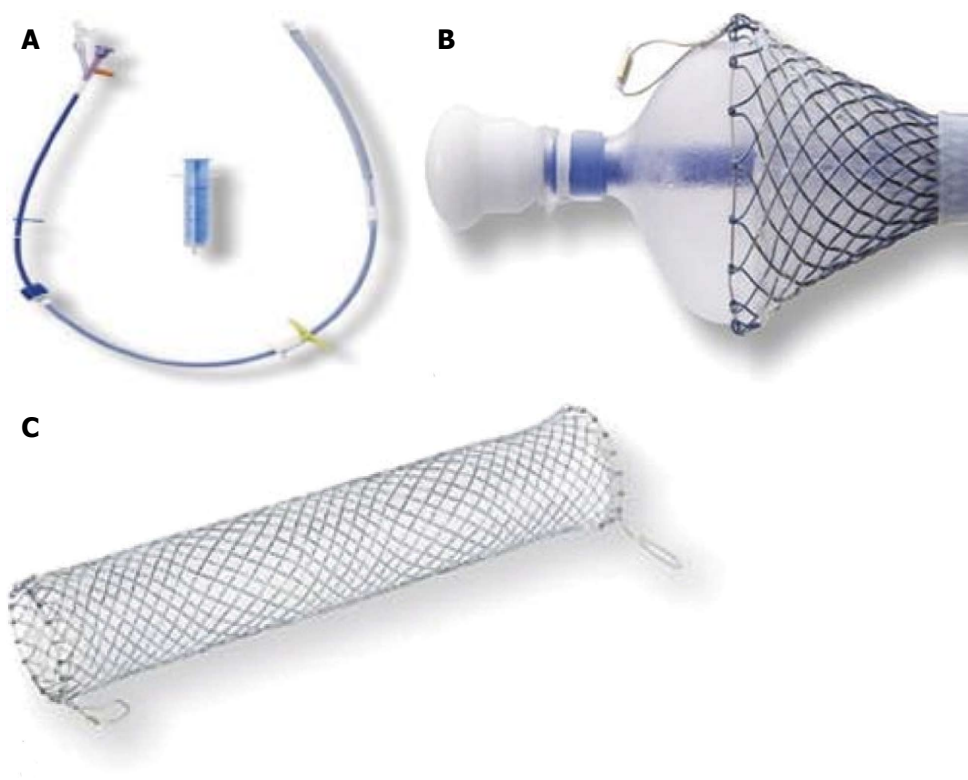


Figure 1 The Danis Stent with delivery system. A: The SX-ELLA Danis stent is supplied preloaded in an insertion device that has a 26F diameter and is 60 cm long; B: A balloon at the distal end of the insertion device (shown partially inflated) allows anchoring of the distal end of the stent at the cardia during deployment; C: The fully deployed stent is 135 mm long and 25 mm wide.

previous oesophageal tamponade to treat the index bleed; a big hiatal hernia precluding the correct placement of the oesophageal device; known hepatocellular carcinoma surpassing Milan criteria and terminal disease.

Twenty-eight patients were randomized to BT ($n = 15$) or SEMS (SX-Ella Danis; $n = 13$).

Both groups were matched for the aetiology and severity of liver disease, presence of active bleeding at endoscopy and for the initial therapy received. SEMS were placed without endoscopic or fluoroscopic guidance, but under sedation, and their position confirmed by chest radiograph. Stents remained *in situ* for a maximum of 7 d and during that time patients could undergo a TIPS. The median time to TIPS was reported as 3.5 (0-7) d in the SEMS group and 0.8 (0-1) d in the BT group. The number of patients who underwent successful TIPS placement was not reported. Unfortunately, due to difficulties with participant recruitment the study was under powered. The initial power calculation suggested that 23 patients would be required in each group (Table 1).

One patient in the SEMS group received a BT due to technical difficulties deploying the stent, however the analysis was performed using an intention to treat basis. Haemostasis was achieved in 77% of the SEMS group and 43% of the BT group ($P = 0.1$). The incidence of serious adverse events was lower in the SEMS group, particularly the incidence of aspiration pneumonia 2/13 vs 8/15 in the BT group. Survival at 15 d was 61% and

47% in the SEMS and BT groups respectively ($P = 0.4$).

LIMITATIONS OF SEMS IN VARICEAL HAEMORRHAGE

There have been reports of minor oesophageal ulceration several case series describing SEMS placement. However, this resolved spontaneously on removal of the stent and neither mortality nor oesophageal perforation have been observed.

Stent migration is the main issue encountered after deployment and, if occurs, impedes effective haemostasis. If adequate traction is not applied to the delivery device at the time of stent deployment, migration is more likely to occur.

There have been a number of reports of failed deployment due to balloon rupture. The insertion device is designed with a safety feature where by the balloon will rupture if more than 100 mL of air is insufflated. This is designed to prevent the complication of an over distended balloon causing an oesophageal tear, should it have been misplaced in the oesophagus (rather than the stomach) prior to inflation. Rupture of the balloon can be avoided if only 100 mL of air is insufflated.

In one case report a patient developed respiratory failure 6 d following successful control of bleeding using an SX-ELLA Danis stent^[22]. Bronchoscopy revealed narrowing of the bronchus due to external compression from the proximal portion of the stent. The stent was

Table 1 Summary of case series reporting self-expanding mesh-metal stent use in the control of oesophageal variceal haemorrhage

Ref.	Stent used	n	Indications/severity of liver disease	Length of Insertion (d)	Initial Haemostasis with SEMS	Mortality (d)	Complications/notes
Hubmann <i>et al</i> ^[25] , 2006	Choo in 2 Elle-Boubela in 3 SX-ELLA Danis in 15	20	FTCB in 19 FTCB and Oesophageal perforation in 1 CP A 0%/B 40%/C 60%	6 (2-14)	100%	10% 30 d 20% 60 d	Minor ulceration in 1 patient Migration in 2 patients
¹ Zehetner <i>et al</i> ^[26] , 2008	SX-ELLA Danis	34	FTCB CP A 0%/B 38%/C 62%	5 (1-14)	97%	26.5% 30 d 29.4% 60 d	1 patient continued to bleed from a gastric ulcer Migration in 7 patients
Dechene <i>et al</i> ^[22] , 2009	SX-ELLA Danis	1	FTCB	6	100%		Stent extracted at day 6 due to tracheal compression patient died on day 13 of hepatic failure Outcomes after 10 d not reported
Mishin <i>et al</i> ^[24] , 2010	SX-ELLA Danis	1	FTCB (EBL ulcer)	8	100%	0% 10 d	
Wright <i>et al</i> ^[27] , 2010	SX-ELLA Danis	10	FTCB in 8 BT induced oesophageal tear in 2 Median MELD 26 (14-39)	6 (6-14)	70%	50% 42 d	Uncontrolled bleeding from gastric varices after insertion in 2 patients Failure to place stent in 1 patient
² Dechêne <i>et al</i> ^[23] , 2012	SX-ELLA Danis	9	FTCB Median MELD 32 (16-40)	11 (7-14)	100%	56% 30 d 67% 60 d	1 patient died within 5 d from liver failure (technically FTCB)
Fierz <i>et al</i> ^[28] , 2013	SX-ELLA Danis	9	FTCB Median MELD 27 (11-37)	0.5-5	89%	78% 42 d	1 failure due to incorrect deployment
Holster <i>et al</i> ^[32] , 2013	SX-ELLA Danis	5	FTCB Median MELD 21 (11-28)	6-214	100%	Not reported	1 re-bleed at 7 d from the GOJ
Zakaria <i>et al</i> ^[29] , 2013	SX-ELLA Danis	16	Primary therapy in acute variceal bleed CP A 13%/B 50%/C 37%	2-4	94%	25%	Uncontrolled bleeding from GOV-1 varix after insertion in 1 patient Failure to place stent in 1 patients

¹20 patients included in this trial were also included in the first trial by Hubmann *et al*^[25]; ²Dechene *et al*^[22] previously reported 1 patient from this series in 2009. FTCB: Failure to control bleeding; BT: Balloon tamponade; EBL: Endoscopic band ligation; CP: Child-Pugh score; MELD: Model for end-stage liver disease score; GOV-1: Gastro-oesophageal varices type 1.

removed and bronchial obstruction resolved. In this case varices were secondary to hilar cholangiocarcinoma and the patient died from liver failure 7 d after the stent was removed.

CONCLUSION

Despite the recent advances in treatment of variceal bleeding there are still significant rates of treatment failure and mortality and there is still considerable variation in patient outcomes.

Current guidelines for the management of variceal haemorrhage suggest that a TIPS should be considered for high risk cases and in patients with bleeding refractory to standard medical and endoscopic therapies^[15,31]. However, TIPS is not suitable for all patients and the complications of liver failure and hepatic encephalopathy limit the use of TIPS in some patients. There is, therefore, an unmet need where standard endoscopic therapy is ineffective and TIPS is not a suitable treatment.

SEMS are very effective in the control of oesophageal variceal haemorrhage, and in all of the series reported to date the only "stent failures" have either been where the stent was not deployed correctly or

where the bleeding was from concomitant gastric varices. The mortality rates reported in the case series are very variable, and the main determinant is whether they are used as definitive therapy, or as a bridge to another therapy, mortality being improved with the latter.

It is not yet clear whether SEMS have a defined place in the algorithm for the management of variceal haemorrhage. The data from Escorsell *et al*^[30] has not confirmed that SEMS perform better than BT in refractory bleeding, but there was a trend towards fewer complications and more effective haemostasis. This has led to a recommendation from the BAVENO VI committee for SEMS to be considered as an alternative to BT in their most recent consensus report^[15]. Further data from randomised controlled trials are required to guide clinicians in their use of these devices, however they are an attractive alternative to BT and may be an effective bridge to definitive therapy.

REFERENCES

- 1 Poca M, Puente A, Graupera I, Villanueva C. Prognostic markers in patients with cirrhosis and portal hypertension who have not

- bled. *Dis Markers* 2011; **31**: 147-154 [PMID: 22045400 DOI: 10.3233/DMA-2011-0837]
- 2 **Salerno F**, Cazzaniga M. Prevention of early variceal rebleeding adding banding to terlipressin therapy. *Gut* 2009; **58**: 1182-1183 [PMID: 19671551 DOI: 10.1136/gut.2009.182006]
- 3 **Cipolletta L**, Zambelli A, Bianco MA, De Grazia F, Meucci C, Lupinacci G, Salerno R, Piscopo R, Marmo R, Orsini L, Rotondano G. Acrylate glue injection for acutely bleeding oesophageal varices: A prospective cohort study. *Dig Liver Dis* 2009; **41**: 729-734 [PMID: 19362522 DOI: 10.1016/j.dld.2009.02.006]
- 4 **Ioannou G**, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev* 2003; **(1)**: CD002147 [PMID: 12535432 DOI: 10.1002/14651858.CD002147]
- 5 **Gotsche PC**, Hróbjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. *Cochrane Database Syst Rev* 2008; **(3)**: CD000193 [PMID: 18677774 DOI: 10.1002/14651858.CD000193.pub3]
- 6 **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; **(9)**: CD002907 [PMID: 20824832 DOI: 10.1002/14651858.CD002907.pub2]
- 7 **D'Amico G**, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003; **38**: 599-612 [PMID: 12939586 DOI: 10.1053/jhep.2003.50385]
- 8 **Carbonell N**, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004; **40**: 652-659 [PMID: 15349904 DOI: 10.1002/hep.20339]
- 9 **Augustin S**, Altamirano J, González A, Dot J, Abu-Suboh M, Armengol JR, Azpiroz F, Esteban R, Guardia J, Genescà J. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. *Am J Gastroenterol* 2011; **106**: 1787-1795 [PMID: 21625271 DOI: 10.1038/ajg.2011.173]
- 10 **Hobolth L**, Krag A, Bendtsen F. The recent reduction in mortality from bleeding oesophageal varices is primarily observed from Days 1 to 5. *Liver Int* 2010; **30**: 455-462 [PMID: 19968778 DOI: 10.1111/j.1478-3231.2009.02169.x]
- 11 **Puente A**, Hernández-Gea V, Graupera I, Roque M, Colomo A, Poca M, Aracil C, Gich I, Guarnier C, Villanueva C. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. *Liver Int* 2014; **34**: 823-833 [PMID: 24373180 DOI: 10.1111/liv.12452]
- 12 **Ben-Ari Z**, Cardin F, McCormick AP, Wannamethee G, Burroughs AK. A predictive model for failure to control bleeding during acute variceal haemorrhage. *J Hepatol* 1999; **31**: 443-450 [PMID: 10488702]
- 13 **Moitinho E**, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999; **117**: 626-631 [PMID: 10464138]
- 14 **Reverter E**, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, Keough A, Llop E, González A, Seijo S, Berzigotti A, Ma M, Genescà J, Bosch J, García-Pagán JC, Abraldes JG. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. *Gastroenterology* 2014; **146**: 412-419.e3 [PMID: 24148622 DOI: 10.1053/j.gastro.2013.10.018]
- 15 **de Franchis R**. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]
- 16 **Panés J**, Terés J, Bosch J, Rodés J. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. *Dig Dis Sci* 1988; **33**: 454-459 [PMID: 3280273]
- 17 **Riggio O**, Ridola L, Lucidi C, Angeloni S. Emerging issues in the use of transjugular intrahepatic portosystemic shunt (TIPS) for management of portal hypertension: time to update the guidelines? *Dig Liver Dis* 2010; **42**: 462-467 [PMID: 20036625 DOI: 10.1016/j.dld.2009.11.007]
- 18 **García-Pagán JC**, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, Abraldes JG, Nevens F, Vinel JP, Mössner J, Bosch J. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med* 2010; **362**: 2370-2379 [PMID: 20573925 DOI: 10.1056/NEJMoa0910102]
- 19 **Monescillo A**, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, Marrero JM, Buceta E, Sánchez J, Castellot A, Peñate M, Cruz A, Peña E. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology* 2004; **40**: 793-801 [PMID: 15382120 DOI: 10.1002/hep.20386]
- 20 **Britton E**, Mahoney S, Powell S, McWilliams R, Shaikh U, Healy A, Evans J, Rowlands P, Richardson P. Early TIPS in patients with acute variceal bleeding and the effect on thirty and six month mortality rates - A single centre experience. *J Hepatol* 2013; **58**: S250 [DOI: 10.1016/S0168-8278(13)60614-5]
- 21 **Rudler MCP**, Saque V, Le Corvec T, Benosman H, Poynard T, Thabut D. Early TIPS in patients with acute variceal bleeding: an external validation. The 63rd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting; 2012 November 9-13; Boston, USA. USA: Wiley, 2012: 274A
- 22 **Dechene A**, Adamzik M, Gerken G, Canbay A. Acute bronchial obstruction following esophageal stent implantation for variceal bleeding. *Endoscopy* 2009; **41** Suppl 2: E146-E147 [PMID: 19544272 DOI: 10.1055/s-0028-1119725]
- 23 **Dechène A**, El Fouly AH, Bechmann LP, Jochum C, Saner FH, Gerken G, Canbay A. Acute management of refractory variceal bleeding in liver cirrhosis by self-expanding metal stents. *Digestion* 2012; **85**: 185-191 [PMID: 22269340 DOI: 10.1159/000335081]
- 24 **Mishin I**, Ghidirim G, Dolghii A, Bunic G, Zastavitsky G. Implantation of self-expanding metal stent in the treatment of severe bleeding from esophageal ulcer after endoscopic band ligation. *Dis Esophagus* 2010; **23**: E35-E38 [PMID: 20731698 DOI: 10.1111/j.1442-2050.2010.01090.x]
- 25 **Hubmann R**, Bodlaj G, Czompo M, Benkő L, Pichler P, Al-Kathib S, Kiblböck P, Shamiyeh A, Biesenbach G. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. *Endoscopy* 2006; **38**: 896-901 [PMID: 16981106 DOI: 10.1055/s-2006-944662]
- 26 **Zehetner J**, Shamiyeh A, Wayand W, Hubmann R. Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. *Surg Endosc* 2008; **22**: 2149-2152 [PMID: 18622540 DOI: 10.1007/s00464-008-0009-7]
- 27 **Wright G**, Lewis H, Hogan B, Burroughs A, Patch D, O'Beirne J. A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. *Gastrointest Endosc* 2010; **71**: 71-78 [PMID: 19879564 DOI: 10.1016/j.gie.2009.07.028]
- 28 **Fierz FC**, Kistler W, Stenz V, Gubler C. Treatment of esophageal variceal hemorrhage with self-expanding metal stents as a rescue maneuver in a swiss multicentric cohort. *Case Rep Gastroenterol* 2013; **7**: 97-105 [PMID: 23626509 DOI: 10.1159/000350192]
- 29 **Zakaria MS**, Hamza IM, Mohey MA, Hubmann RG. The first Egyptian experience using new self-expandable metal stents in acute esophageal variceal bleeding: pilot study. *Saudi J Gastroenterol* 2013; **19**: 177-181 [PMID: 23828748 DOI: 10.4103/1319-3767.114516]
- 30 **Escorsell A**, Cardenas A, Morillas R, Albillos A, de la Pena J, Villanueva C, Garcia-Pagan JC, Bosch J. Self-Expandable Esophageal Metal Stent vs Balloon Tamponade in Esophageal Variceal Bleeding Refractory to Medical and Endoscopic Treatment: A Multicenter Randomized Controlled Trial. *Hepatology* 2013; **58**: 36A-91A [DOI: 10.1002/hep.26725]
- 31 **de Franchis R**. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53**: 762-768 [PMID: 20638742 DOI: 10.1016/j.jhep.2010.06.004]
- 32 **Holster IL**, Kuipers EJ, van Buuren HR, Spaander MC, Tjwa ET. Self-expandable metal stents as definitive treatment for esophageal

variceal bleeding. *Endoscopy* 2013; **45**: 485-488 [PMID: 23468191]

DOI: 10.1055/s-0032-1326227]

P- Reviewer: Deipolyi AR, Ruiz-Margain A, Siramolpiwat S,
Stephenn X **S- Editor:** Ji FF **L- Editor:** A **E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 January 25; 8(2): 30-121





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Izuru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Rajiman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

EDITORIAL

- 30 Endoscopic treatment of esophageal achalasia
Esposito D, Maione F, D'Alessandro A, Sarnelli G, De Palma GD

THERAPEUTICS ADVANCES

- 40 Colorectal endoscopic submucosal dissection from a Western perspective: Today's promises and future challenges
Marín-Gabriel JC, Fernández-Esparrach G, Díaz-Tasende J, Herreros de Tejada A

TOPIC HIGHLIGHT

- 56 Laparoscopic esophagomyotomy for achalasia in children: A review
Pandian TK, Naik ND, Fahy AS, Arghami A, Farley DR, Ishitani MB, Moir CR
- 67 Endoscopic ultrasound in the diagnosis and management of carcinoma pancreas
Puri R, Manrai M, Thandassery RB, Alfadda AA

REVIEW

- 77 Drug eluting biliary stents to decrease stent failure rates: A review of the literature
Shatzel J, Kim J, Sampath K, Syed S, Saad J, Hussain ZH, Mody K, Pipas JM, Gordon S, Gardner T, Rothstein RI
- 86 Submucosal tunnel endoscopy: Peroral endoscopic myotomy and peroral endoscopic tumor resection
Eleftheriadis N, Inoue H, Ikeda H, Onimaru M, Maselli R, Santi G
- 104 Endoscopic ultrasound-guided interventions in special situations
Prachayakul V, Aswakul P

ORIGINAL ARTICLE

Retrospective Study

- 113 Evidence to suggest adoption of water exchange deserves broader consideration: Its pain alleviating impact occurs in 90% of investigators
Cadoni S, Liggi M, Falt P, Sanna S, Argiolas M, Fanari V, Gallittu P, Mura D, Porcedda ML, Smajstrla V, Erriu M, Leung FW

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 2 January 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Lucian Negreanu, MD, PhD, Assistant Pharmacist, Assistant Professor, Doctor, Head, Internal Medicine II Department, Internal Medicine II Gastroenterology, University Hospital Bucharest, 050098 Bucharest, Romania

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE
January 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/1948-5190/g_info_20100316080002.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Endoscopic treatment of esophageal achalasia

Dario Esposito, Francesco Maione, Alessandra D'Alessandro, Giovanni Sarnelli, Giovanni D De Palma

Dario Esposito, Francesco Maione, Alessandra D'Alessandro, Giovanni Sarnelli, Giovanni D De Palma, Department of Clinical Medicine and Surgery, University of Naples Federico II, School of Medicine, 80131 Naples, Italy

Giovanni D De Palma, Center of Excellence for Technical Innovation in Surgery, University of Naples Federico II, School of Medicine, 80131 Naples, Italy

Author contributions: Esposito D, Maione F, D'Alessandro A, Sarnelli G and De Palma GD were all equally responsible for the design, conception, drafting, and final approval of this paper.

Conflict-of-interest statement: Dario Esposito, Francesco Maione, Alessandra D'Alessandro, Giovanni Sarnelli and Giovanni D De Palma have nothing to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Giovanni D De Palma, MD, Director of Center of Excellence for Technical Innovation in Surgery, Department of Clinical Medicine and Surgery, University of Naples Federico II, School of Medicine, via Pansini 5, 80131 Napoli, Italy. giovanni.depalma@unina.it
Telephone: +39-81-7462773
Fax: +39-81-7462752

Received: June 27, 2015
Peer-review started: June 29, 2015
First decision: August 16, 2015
Revised: November 26, 2015
Accepted: December 13, 2015
Article in press: December 15, 2015
Published online: January 25, 2016

Abstract

Achalasia is a motility disorder of the esophagus

characterized by dysphagia, regurgitation of undigested food, chest pain, weight loss and respiratory symptoms. The most common form of achalasia is the idiopathic one. Diagnosis largely relies upon endoscopy, barium swallow study, and high resolution esophageal manometry (HRM). Barium swallow and manometry after treatment are also good predictors of success of treatment as it is the residue symptomatology. Short term improvement in the symptomatology of achalasia can be achieved with medical therapy with calcium channel blockers or endoscopic botulin toxin injection. Even though few patients can be cured with only one treatment and repeat procedure might be needed, long term relief from dysphagia can be obtained in about 90% of cases with either surgical interventions such as laparoscopic Heller myotomy or with endoscopic techniques such pneumatic dilatation or, more recently, with per-oral endoscopic myotomy. Age, sex, and manometric type by HRM are also predictors of responsiveness to treatment. Older patients, females and type II achalasia are better after treatment compared to younger patients, males and type III achalasia. Self-expandable metallic stents are an alternative in patients non responding to conventional therapies.

Key words: Achalasia; High resolution manometry subtypes; Eckardt score; Per-oral endoscopic myotomy; Pneumatic dilatation; Botulin toxin; Myotomy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Achalasia is characterized by dysphagia, regurgitation, chest pain, weight loss and respiratory symptoms. Diagnosis and post-treatment assessment largely rely upon endoscopy, barium swallow study and high resolution esophageal manometry (HRM). Short term improvement in the symptomatology can be achieved with medical therapy or endoscopic botulin toxin injection. Long term relief from dysphagia can be obtained with either laparoscopic Heller myotomy, pneumatic dilatation or per-oral endoscopic myotomy. Age, sex, and manometric subtype by HRM are also predictors of responsiveness to treatment. Self-expandable metallic stents are an

alternative in patients non responding to conventional therapies.

Esposito D, Maione F, D'Alessandro A, Samelli G, De Palma GD. Endoscopic treatment of esophageal achalasia. *World J Gastrointest Endosc* 2016; 8(2): 30-39 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/30.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.30>

INTRODUCTION

Achalasia is a motility disorder of the esophagus characterized by dysphagia, regurgitation of undigested food, chest pain, weight loss and respiratory symptoms^[1,2].

Achalasia is a relatively rare condition with incidence ranging from 0.3 to 1.63 cases per 100000 people per year in adults^[3-6]. There seems to be no difference in sex and racial distribution. Incidence rates of this pathology seems to be rising, it remains unclear if this reflects a true rise in the incidence or an improved diagnosis^[3,6,7-16].

Most studies found the median age at the diagnosis to be over 50 years^[3,4,17] whereas other authors have suggested a bimodal distribution of incidence by age with peaks around 30 and 60 years of age^[7-9].

Although the etiology remains unknown, it has been established that achalasia results from the disappearance of the myenteric neurons leading to loss of peristalsis and failure of relaxation of the lower esophageal sphincter, particularly during swallowing^[18].

Antibodies against myenteric neurons have been found in serum samples obtained from patients affected with achalasia^[19-21]. Genetic^[22-27], autoimmune^[28,29], and viral^[30-33] conditions may play a role in the development of the condition.

Since symptoms of achalasia are not specific, the diagnosis of the disease can be delayed for as long as 5 years^[34,35]. Dysphagia for solids and liquids occurs in > 90% of patients affected with achalasia, other symptoms include weight loss (35%-91%), food regurgitation (76%-91%), respiratory complications such as chest pain (25%-64%) and heartburn (18%-52%) nocturnal cough (30%) and aspiration (8%)^[1,36-38].

In a patient presenting with dysphagia, it is mandatory to rule out malignancies but also pseudoachalasia or any other anatomical lesions with radiology or endoscopy. Old age, weight loss and rapidly progressing dysphagia are particularly suspected for pseudo-achalasia and thus should be investigated by the mean of and endoscopic ultrasound or computer tomography (CT)-scan^[39,40]. These imaging techniques will reveal thickening of the esophageal wall, mass or lesions.

However, both endoscopy and radiology only identify about half of patients with achalasia, especially in early

stage. Endoscopy may reveal a dilated esophagus with retained food and a difficult access to gastric cavity due to increased resistance of the gastro-esophageal junction in advanced stages of the disease.

In addition, a timed barium swallow esophagram (TBA) can be done to assess emptying of the esophagus; the height of the barium column 5 min after the ingestion is a measure of emptying^[41,42] (Figure 1). A TBA has proven itself useful also in the post-operative assessment of the disease.

Manometry is the mainstay of the assessment in achalasia both before and after treatment. Manometric features of achalasia are absence of peristalsis, incomplete relaxation of LOS on deglutition (residual pressure > 10 mmHg) with increased resting tone of LOS and, sometimes, increased intra-esophageal pressure^[2].

High resolution manometry (HRM) is now regarded as the gold standard for the diagnosis of achalasia^[43,44], this diagnostic technique is performed by mean of catheters incorporating 36 or more pressure sensors spaced 1 cm apart.

Thanks to the greater accuracy of HRM, three clinically relevant sub-classifications of achalasia have been distinguished on the basis of the pattern of contractility in the esophagus^[45].

Type I (classical achalasia; no pressurisation to over 30 mmHg in distal esophagus and failed relaxation on swallow), type II (achalasia with compression or compartmentalisation in the distal esophagus > 30 mmHg), and type III (two or more spastic contractions) (Figure 2).

TREATMENT

Since the underlying defect cannot be reversed, the treatment of achalasia remains palliative. Current therapeutic options include pharmacologic therapy, endoscopic treatment and surgery. The primary goal of all therapies is the improvement of the esophageal food passage by reducing the distal esophageal obstruction.

Pharmacological treatment

Nitrates and Calcium-channel blockers are the most widely used drugs for the treatment of achalasia^[46-49]. Nifedipine is administered 15-60 min before meals in sublingual doses of 10-20 mg. It inhibits the cellular calcium uptake resulting in inhibition of LOS muscle contractions and lowering of the LOS resting pressure by 30%-60%^[46-48]. Side effects are seen in up to 30% of patients and include hypotension, headache, and dizziness even if tolerance develops over time.

Only two poorly designed randomized controlled trials have been identified in a Cochrane review by Wen *et al*^[50] about the use of nitrates in achalasia so no solid recommendations can be given at present about this treatment.

Botulin toxin A is a neurotoxin blocking the release of acetylcholine from the synapsis terminals. It can be

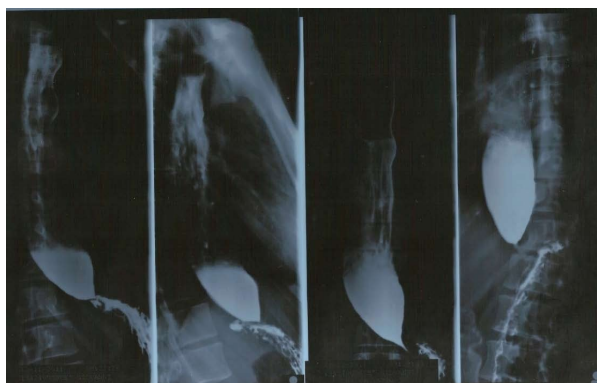


Figure 1 Barium swallow esophagograms showing typical bird-beak appearance of the distal esophagus.

injected during upper endoscopy through an injection needle directly in four or eight quadrants into the LOS at the dose of 80-100 units^[51,52].

This combined endoscopic/pharmacological treatment has proven itself safe and effective. More than 80% of patients have clinical response by one month even if response fades quickly and only about 60% of patients are still in remission at 1-year follow-up^[53].

Botulinum toxin compared with pneumodilatation^[54-58] and laparoscopic myotomy^[59] shows initial comparable relief from dysphagia but a rapid relapse of symptoms after 6-12 mo. So, botulinum toxin, as calcium-channel blockers or nitrates use, should be used as a temporary option before a more durable treatment or in high risk patients who are poor candidates for surgery or pneumodilatation.

Pneumatic dilatation

Pneumatic dilatation stretches and tears the LOS fibers with air-filled balloons, the most widely used ones are Rigidflex Balloon System (Boston Scientific, Marlborough, MA, United States). The balloons are available in three sizes (30, 35 and 40 mm) made of non-compliant polyethylene; they are placed over a guide-wire at endoscopy, positioned across the LOS and inflated under fluoroscopic guidance, a graded dilation protocol starting with a 30 mm balloon is usually preferred^[60] (Figure 3).

An esophageal lavage with large-bore tubes might be needed in patients with mega-esophagus before the procedure. In patients with previous pneumodilatation failure, younger than 40 years or after a previous Heller myotomy it is possible to begin with a 35 mm balloon. The balloon positioning is checked with fluoroscopy or, sometimes, endoscopy; the waist caused by the non-relaxing LOS should impinge on the middle portion of the balloon. After careful positioning, the balloon is inflated until the waist is flattened; the pressure needed in the balloon is 7-15 psi of air and is held for 15-60 s.

Patients must be on a liquid diet for several days and fast for 12 h prior to procedure. The procedure is usually performed as an outpatient surgery under conscious

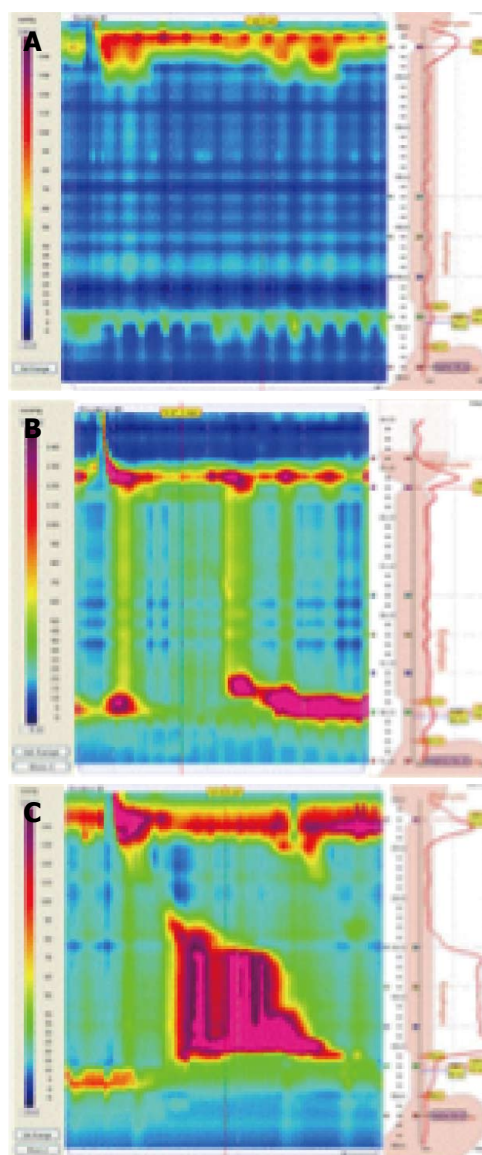


Figure 2 High-resolution manometric types of achalasia according to the Chicago Classification: Type 1, characterized by the absence of peristalsis (A); type 2, defined by the presence of esophageal compression, named panesophageal pressurization (B); type 3, characterized by the presence of peristaltic fragments or spastic waves (C).

sedation in the morning, the patient is then kept under observation for 2-6 h and can return to normal activities the subsequent day. During observation, patients should be assessed for chest pain and fever. A Gastrografin swallowing assessment should be performed in patients complaining with significant pain in order to exclude esophageal perforation.

Subsequent dilatations can be performed after a 2 to 4 wk interval if needed on the basis of symptom relief, LOS pressure measurements or improvement in esophageal emptying^[36,61-63].

Pneumatic dilatation with 30, 35 and 40 mm Rigidflex Balloons results in good to excellent symptom relief in 74%, 86% and 90% of patients respectively at 3-year follow-up but nearly two thirds of patients have

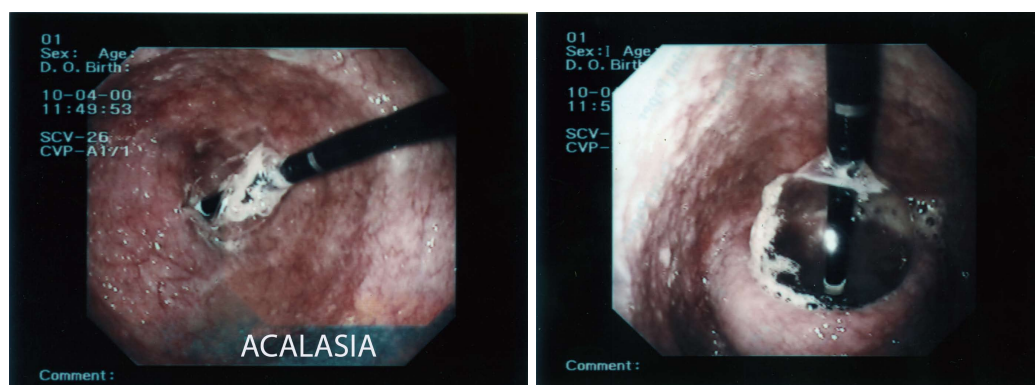


Figure 3 Pneumatic dilation with a Rigidflex balloon under endoscopic control.

symptom relapse over a 4-6 years^[38,63,64].

Long term relapses can be managed to obtain long-term remission by a repeat dilatation strategy. Best outcomes are seen in patients with type II pattern by HRM, women and in those older than 40 years^[1,38,41,65,66].

Patients with type III seem to have better results if treated with Heller myotomy compared to pneumatic dilatation, no significant differences are seen in type I and II. The different response in type III patients seems to be due to the fact that Heller myotomy results in a more extensive and proximal disruption of oesophageal muscle fibers^[67].

At present, pneumatic dilatation has proven itself to be the most cost-effective treatment for achalasia over a 5-10 year period^[68,69]. Up to one third of patients have complications after pneumatic dilatation, most of them are minor such as bleeding, fever, chest pain, mucosal esophageal hematoma and mucosal tear without perforation. Even though severe gastro-esophageal reflux disease is rare after pneumatic dilatation, 15-35 of patients experiences heartburn which can be treated with proton pump-inhibitors^[70]. Perforation is, by far, the most serious complication occurring in about 2.0% of patients^[71] (reported rate of 0%-16%), about 50% of perforated patients require surgery thus, poor surgical candidates are poor candidates to pneumatic dilatation as well. In a recent series, 16 consecutive transmural perforations were managed conservatively^[72]. Small perforations are usually treated with total parenteral nutrition and antibiotics for days to weeks. Large perforations will require surgical repair by thoracotomy. Difficulty in keeping the balloon in place is a reported risk factor for perforation^[73]. Also, performing the initial dilatation with a 35 mm balloon seems to put the patient at risk for perforation, compared to an initial dilatation performed with a 30 mm balloon^[66].

Per-oral endoscopic myotomy

Ortega first described a series of 17 patients affected with achalasia and treated with a direct trans-mucosal lower esophageal sphincter myotomy and good clinical, radiologic and manometric results in 1981. No confirmatory work was published, perhaps due to complications such as

perforation and mediastinitis^[74]. Natural orifice transluminal endoscopic surgery made its appearance in 2004 and there has been a tendency towards the development of less invasive alternative to transcutaneous surgical interventions since then. To obtain an access to the mediastinum or the peritoneum, a technique consisting in the creation of a submucosal tunnel closed by a mucosal flap was developed^[75].

Per-oral endoscopic myotomy (POEM) was developed from this technique and features the creation of a submucosal tunnel enabling the LES myotomy to be performed away from the mucosal entry site which is closed at the end of the procedure.

In 2007, the first LES myotomy was performed in a porcine survival model^[76] and in 2008, Inoue *et al.*^[77] used the technique of submucosal tunneling to perform the first endoscopic LES myotomy on humans and coined the term POEM for *per oral endoscopic myotomy*. Even though, POEM is mainly performed for achalasia, it can be successfully applied in diffuse esophageal spasm, nutcracker and jackhammer esophagus^[78,79]. POEM can be also used in patients with prior Heller myotomy and previous endoscopic pneumatic dilatation^[80,81].

POEM contraindications include severe pulmonary disease, bleeding disorders esophageal irradiation or esophageal malignancy and endoscopic intervention including endoscopic mucosal resection and^[82] endoscopic submucosal dissection (ESD). POEM requires general anesthesia with the patient in supine position. It is recommended to use anesthesia with positive pressure ventilation to prevent severe mediastinal emphysema^[83]. A traditional forward-viewing endoscope and equipment employed in ESD are used. Carbon dioxide is used for insufflation. The esophageal submucosal space is expanded with injection of indigo carmine-saline mixture (typically, 0.3% indigo carmine). The submucosal tunnel is initiated 10-15 cm above the gastroesophageal junction (GEJ). The recommended mucosal entry site is, generally, on the anterior wall between 11 and 2 o'clock^[83,84]. In case POEM is performed in patients in which a balloon dilatation has been performed with poor results, since the anterior route can be seriously scarred, the incision is usually performed at the 7 o'clock position^[85]. After a

2 cm mucosal incision is made, the submucosal tunnel is extended downward by using a technique similar to ESD to reach the gastric cardia 2-3 cm distal to the GEJ.

Accurate identification of EGJ is essential. Delineation of the GEJ is done in a variety of ways like monitoring the endoscope insertion length, identification of the longitudinal palisade vessels in the submucosal layer, change in the submucosal vascular pattern (from palisade to reticular) at EGJ, stenotic segment of the submucosal tunnel, tattooing at the gastric cardia using indocyanine green (ICG) and even transillumination viewed by a second endoscope^[86]. The myotomy is performed starting at 2-3 cm distal to the mucosal entry, thus, more than 10 cm above the GEJ and carried up to, at least, 2 cm distally to the GEJ.

At the beginning of the procedure, the circular muscle is dissected and the longitudinal muscle layer is identified; the inter-muscular space is the correct dissection plane. Some authors favor the dissection of the sole circular muscle fiber, since these are regarded as having the major function in muscle contraction and the risk of surrounding structures injury is reduced by keeping the outer muscle intact^[87]. The outer longitudinal muscle layer can be extremely thin, the injury to this muscle fibers and the exposure of the mediastinal structures does not cause any sequelae if the mucosa is still intact, thus an inadvertent mucosal flap injury must always be repaired promptly with clip placement, endoscopic suturing or fibrin spray glue^[88].

The incision at 2 o'clock position leads to the lesser curvature of the stomach, in contrast, the hiss angle is located at 8 o'clock. Anterior myotomy potentially avoids damage to the sling muscle, and especially His angle so that no anti-reflux procedure is needed. The 2 o'clock approach might be less efficacious at the LES disruption which is the main goal of the achalasia surgery leading to less relieve of dysphagia but may be useful in avoiding symptomatic GERD after the procedure. In contrast, the 5 o'clock position for the myotomy may lead to less dysphagia but could theoretically have more GERD which can be treated with PPI^[83].

Using CO₂ for insufflation and positive-pressure ventilation prevents severe pneumomediastinum should a perforation occur. The muscle layer cutting is continued for at least 2 cm distal to the GEJ; closure of the mucosal entry site can be performed with either hemostatic clips or endoscopic suturing (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas), no statistically significant difference in mean closure time, complications or mean cost have been noted^[83].

Closure might also be performed with over-the-scope clip and fibrin glue^[89,90]. Whatever closure technique is used, Gentamicin infusion within the submucosal tunnel is reported. After the procedure, patients should have a radiographic study (either plain or contrast enhanced chest and abdominal X-ray) to exclude perforations leading to pneumomediastinum or pneumoperitoneum. Antibiotics are usually given during the procedure and for

several days after the discharge^[83,87].

Some authors perform an EGDS and a timed barium esophagogram (TBE) on the 1st post-operative day to confirm mucosal integrity. If mucosal integrity is confirmed by these studies, the patient may be allowed to drink on day 1, soft diet is started on day 2 and normal diet can be restarted on day 3^[87]. Post-operative TBE can also be used to confront the Vaezi score before and after the procedure. Reported results of POEM are excellent with dysphagia efficacy using Eckardt score in > 90% of subjects, no mortality is reported this far^[82,91-100]. On the subject of POEM complications, pneumoperitoneum and pneumomediastinum are usually managed with either paracentesis and by inserting a small caliber of intercostal drainage for a couple of days^[87].

Acute intraoperative bleeding can be managed, if the bleeding point can be identified, by mean of normal coagulation techniques used in ESD (Coaggrasper, APC, etc.). In case of an unidentified bleeding point, applying pressure with the tip of the endoscope in the submucosal space or from the natural lumen is suggested. A post-operative hematoma may occur; conservative treatment, keeping the patient fasting with intravenous antibiotics is suggested. The hematoma, usually, resolves spontaneously within 1 to 2 wk.

Post-operative hematemesis, melena, hypotension, retrosternal pain may be the hallmark of a delayed bleeding. CT-scan and emergency upper GI endoscopy are mandatory to confirm the diagnosis. The bleeding point is usually located at the edge of the sectioned muscle; in case the bleeding point cannot be identified, placing a Sengstaken-Blakemore tube is an adequate treatment^[101].

GERD is the most frequent adverse event after POEM, prevalence varies considerably^[82,90-92,95,96,100,101] and can be as high as 40%.

Self-expanding metallic stent

Early reports regarding the use of self-expanding metallic stent (SEMS) in the treatment of achalasia unresponsive to conventional treatments were published in 1998^[102]. SEMS permanently disrupt the muscular fibers of the cardia and represents a safe and effective measure for patients not fit for more invasive therapeutic options; Nitinol coil (InStent Inc., Eden, Paire, United States), Ultraflex (Microvasive, Boston Scientific, Natick, MA, United States) or specially designed (Z-stent, Sigma, Huaian, China) stents have been tested, keeping them in place for 3-7 d^[103,104] or 30 d^[105].

All the trials regarding the use of metal stents in achalasia reported a technical success of 100% and early clinical success of 87%-100%^[102,104-107].

Success rates largely depend on the stent diameter, being higher for 30 mm stents compared with either 25 and 20 mm (87% vs 73% vs 43% clinical remission rate respectively)^[107].

Complications reported were migration (5.3% to 37.5%) and chest pain (17% to 40%)^[102,104-107], one single case series of 4 patients reported the occurrence of

dysphagia recurrence secondary to food bolus impaction or inflammatory stricture (100%)^[108], one patient died secondary to aorto-enteric fistula. Even complication rate depends on the diameter, the wider the stent, the lower the migration rate (6.6% vs 13.3% vs 26.7%) and the higher the chest pain rate (40% vs 33% vs 17%, respectively)^[107]. All the authors concluded that temporary stent placement is an effective treatment for achalasia and could be used for treating carefully selected cases.

DECISION MAKING IN THE TREATMENT OF ACHALASIA

About 90% of patients treated for achalasia can return to good quality of life and normal swallowing function^[109]. On the other hand, few can be cured with only one treatment, repeat procedure might be needed as many patients relapse over time.

Success rates for Heller myotomy and dilatation defined as relieve from dysphagia or regurgitation are quite similar as shown in a study from the Cleveland Clinic^[63]. Moreover, a large retrospective longitudinal study from Canada shows that the cumulative risk for any subsequent treatment (dilatation, myotomy, or oesophagectomy) after 1, 5, and 10 years was slightly higher for pneumatic dilatation compared to HLM (36.8%, 56.2%, and 63.5% after initial pneumatic dilatation vs 16.4%, 30.3%, and 37.5% after initial myotomy (HR 2.37; 95%CI: 1.86-3.02) but this risk difference only occurred when repeat was recorded as an adverse event^[110].

Physiological studies can predict long-term success of therapeutic maneuvers. Eckardt *et al.*^[61] reported that remission rates at 2-year follow-up largely depended on post-procedural LOS pressure being 100% for LOS pressure less than 10 mmHg, 71% for post-procedural LOS pressure between 10 and 20 mmHg and 23% for pressure over 20 mmHg.

The timed barium oesophagram is also a better predictor of success than LOS pressure is; patients with complete symptom relief and improvement in oesophageal emptying were likely to fare better than those with symptom relief but poor oesophageal emptying (82% vs 10%) at 3-year follow-up as Vaezi *et al.*^[41] reported.

Age, sex, and manometric type by HRM are also predictors of responsiveness to treatment. Success rates for pneumatic dilatation are higher for type II achalasia than for type I and type III (96% vs 56% vs 29% respectively) as Pandolfino *et al.*^[45] reported. Type III achalasia might be best treated by laparoscopic Heller myotomy (LHM). It is still unclear whether the fact that a patient had been previously treated endoscopically may hamper the results of a LHM.

Some studies suggest that previous treatments could negatively impact the results of the laparoscopic operation^[111-114] whereas other authors reported that

only patients who had been previously treated with both botulin toxin injection and pneumatic dilatation had worst results.

With reference to the age factor, patients younger than 40 years need repeat pneumatic dilatations more often than those older than 40 years usually do; also, male respond less well than women do to pneumatic dilatation^[1,61,63,66,115]. Similarly, women younger than 35 years do not respond well to pneumatic dilatation^[63]. These findings are probably due to stronger LOS tone in younger patients. Myotomy is, then, the best treatment for adolescents and young adults. Also, pseudoachalasia is best treated by LHM.

Botulinum toxin injection should be considered as a first line therapy for elderly patients or those in which severe comorbidities make them poor surgical candidates since it is safe, effective and might need to be repeated no more than once a year.

The role of POEM as a substitute for myotomy will have to be defined over time with longer follow-up studies, at present, Inoue highlights its usefulness as a re-do procedure in case of LHM failure.

Due to the difficulty to resect adhesions in redo surgery and high morbidity of esophagectomy, POEM is a better choice for treatment recurrence achalasia. Also, a POEM can be useful in these cases as it allows to perform another myotomy in a different location from the prior surgery^[87].

REFERENCES

- 1 **Vantrappen G**, Hellemans J, Deloof W, Valembois P, Vandenbroucke J. Treatment of achalasia with pneumatic dilatations. *Gut* 1971; **12**: 268-275 [PMID: 5574797]
- 2 **Richter JE**, Boeckxstaens GE. Management of achalasia: surgery or pneumatic dilation. *Gut* 2011; **60**: 869-876 [PMID: 21303915 DOI: 10.1136/gut.2010.212423]
- 3 **Farrukh A**, DeCaestecker J, Mayberry JF. An epidemiological study of achalasia among the South Asian population of Leicester, 1986-2005. *Dysphagia* 2008; **23**: 161-164 [PMID: 18027026]
- 4 **Sadowski DC**, Ackah F, Jiang B, Svenson LW. Achalasia: incidence, prevalence and survival. A population-based study. *Neurogastroenterol Motil* 2010; **22**: e256-e261 [PMID: 20465592 DOI: 10.1111/j.1365-2982.2010.01511.x]
- 5 **Birgisson S**, Richter JE. Achalasia in Iceland, 1952-2002: an epidemiologic study. *Dig Dis Sci* 2007; **52**: 1855-1860 [PMID: 17420933]
- 6 **Gennaro N**, Portale G, Gallo C, Rocchietto S, Caruso V, Costantini M, Salvador R, Ruol A, Zaninotto G. Esophageal achalasia in the Veneto region: epidemiology and treatment. Epidemiology and treatment of achalasia. *J Gastrointest Surg* 2011; **15**: 423-428 [PMID: 21116729 DOI: 10.1007/s11605-010-1392-7]
- 7 **Howard PJ**, Maher L, Pryde A, Cameron EW, Heading RC. Five year prospective study of the incidence, clinical features, and diagnosis of achalasia in Edinburgh. *Gut* 1992; **33**: 1011-1015 [PMID: 1398223]
- 8 **Arber N**, Grossman A, Lurie B, Hoffman M, Rubinstein A, Lilos P, Rozen P, Gilat T. Epidemiology of achalasia in central Israel. Rarity of esophageal cancer. *Dig Dis Sci* 1993; **38**: 1920-1925 [PMID: 8404415]
- 9 **Ho KY**, Tay HH, Kang JY. A prospective study of the clinical features, manometric findings, incidence and prevalence of achalasia in Singapore. *J Gastroenterol Hepatol* 1999; **14**: 791-795 [PMID: 10482430]

- 10 **Mayberry JF**, Atkinson M. Variations in the prevalence of achalasia in Great Britain and Ireland: an epidemiological study based on hospital admissions. *Q J Med* 1987; **62**: 67-74 [PMID: 3423207]
- 11 **Mayberry JF**, Rhodes J. Achalasia in the city of Cardiff from 1926 to 1977. *Digestion* 1980; **20**: 248-252 [PMID: 6967027]
- 12 **Mayberry JF**, Atkinson M. Studies of incidence and prevalence of achalasia in the Nottingham area. *Q J Med* 1985; **56**: 451-456 [PMID: 4048387]
- 13 **Earlam RJ**, Ellis FH, Nobrega FT. Achalasia of the esophagus in a small urban community. *Mayo Clin Proc* 1969; **44**: 478-483 [PMID: 5788257]
- 14 **Galen EA**, Switz DM, Zfass AM. Achalasia: incidence and treatment in Virginia. *Va Med* 1982; **109**: 183-186 [PMID: 7080659]
- 15 **Mayberry JF**, Newcombe RG, Atkinson M. An international study of mortality from achalasia. *Hepatogastroenterology* 1988; **35**: 80-82 [PMID: 3259530]
- 16 **Stein CM**, Gelfand M, Taylor HG. Achalasia in Zimbabwean blacks. *S Afr Med J* 1985; **67**: 261-262 [PMID: 3983775]
- 17 **Enestvedt BK**, Williams JL, Sonnenberg A. Epidemiology and practice patterns of achalasia in a large multi-centre database. *Aliment Pharmacol Ther* 2011; **33**: 1209-1214 [PMID: 21480936 DOI: 10.1111/j.1365-2036.2011.04655.x]
- 18 **Cotran RS**, Kumar V, Collins T. Robbins Pathologic basis of disease. 6th ed. Philadelphia: WB Saunders, 1999: 778-779
- 19 **Storch WB**, Eckardt VF, Wienbeck M, Eberl T, Auer PG, Hecker A, Junginger T, Bosseckert H. Autoantibodies to Auerbach's plexus in achalasia. *Cell Mol Biol (Noisy-le-grand)* 1995; **41**: 1033-1038 [PMID: 8747084]
- 20 **Moses PL**, Ellis LM, Anees MR, Ho W, Rothstein RI, Meddings JB, Sharkey KA, Mawe GM. Antineuronal antibodies in idiopathic achalasia and gastro-oesophageal reflux disease. *Gut* 2003; **52**: 629-636 [PMID: 12692044]
- 21 **Ruiz-de-León A**, Mendoza J, Sevilla-Mantilla C, Fernández AM, Pérez-de-la-Serna J, González VA, Rey E, Figueredo A, Díaz-Rubio M, De-la-Concha EG. Myenteric antiplexus antibodies and class II HLA in achalasia. *Dig Dis Sci* 2002; **47**: 15-19 [PMID: 11837716]
- 22 **Storch WB**, Eckardt VF, Junginger T. Complement components and terminal complement complex in oesophageal smooth muscle of patients with achalasia. *Cell Mol Biol (Noisy-le-grand)* 2002; **48**: 247-252 [PMID: 12030428]
- 23 **De la Concha EG**, Fernandez-Arquero M, Mendoza JL, Conejero L, Figueredo MA, Perez de la Serna J, Diaz-Rubio M, Ruiz de Leon A. Contribution of HLA class II genes to susceptibility in achalasia. *Tissue Antigens* 1998; **52**: 381-384 [PMID: 9820602]
- 24 **Verne GN**, Hahn AB, Pineau BC, Hoffman BJ, Wojciechowski BW, Wu WC. Association of HLA-DR and -DQ alleles with idiopathic achalasia. *Gastroenterology* 1999; **117**: 26-31 [PMID: 10381906]
- 25 **de la Concha EG**, Fernandez-Arquero M, Conejero L, Lazaro F, Mendoza JL, Sevilla MC, Diaz-Rubio M, Ruiz de Leon A. Presence of a protective allele for achalasia on the central region of the major histocompatibility complex. *Tissue Antigens* 2000; **56**: 149-153 [PMID: 11019915]
- 26 **Núñez C**, García-González MA, Santiago JL, Benito MS, Mearin F, de la Concha EG, de la Serna JP, de León AR, Urcelay E, Vigo AG. Association of IL10 promoter polymorphisms with idiopathic achalasia. *Hum Immunol* 2011; **72**: 749-752 [PMID: 21641950 DOI: 10.1016/j.humimm.2011.05.017]
- 27 **de León AR**, de la Serna JP, Santiago JL, Sevilla C, Fernández-Arquero M, de la Concha EG, Núñez C, Urcelay E, Vigo AG. Association between idiopathic achalasia and IL23R gene. *Neurogastroenterol Motil* 2010; **22**: 734-738, e218 [PMID: 20367798 DOI: 10.1111/j.1365-2982.2010.01497.x]
- 28 **Gockel HR**, Schumacher J, Gockel I, Lang H, Haaf T, Nöthen MM. Achalasia: will genetic studies provide insights? *Hum Genet* 2010; **128**: 353-364 [PMID: 20700745 DOI: 10.1007/s00439-010-0874-8]
- 29 **Booy JD**, Takata J, Tomlinson G, Urbach DR. The prevalence of autoimmune disease in patients with esophageal achalasia. *Dis Esophagus* 2012; **25**: 209-213 [PMID: 21899655 DOI: 10.1111/j.1442-2050.2011.01249.x]
- 30 **Facco M**, Brun P, Baesso I, Costantini M, Rizzetto C, Berto A, Baldan N, Palù G, Semenzato G, Castagliuolo I, Zaninotto G. T cells in the myenteric plexus of achalasia patients show a skewed TCR repertoire and react to HSV-1 antigens. *Am J Gastroenterol* 2008; **103**: 1598-1609 [PMID: 18557707 DOI: 10.1111/j.1572-0241.2008.01956.x]
- 31 **Villanacci V**, Annese V, Cuttitta A, Fisogni S, Scaramuzzi G, De Santo E, Corazzi N, Bassotti G. An immunohistochemical study of the myenteric plexus in idiopathic achalasia. *J Clin Gastroenterol* 2010; **44**: 407-410 [PMID: 19834336 DOI: 10.1097/MCG.0b013e3181bc9ebf]
- 32 **Birgisson S**, Galinski MS, Goldblum JR, Rice TW, Richter JE. Achalasia is not associated with measles or known herpes and human papilloma viruses. *Dig Dis Sci* 1997; **42**: 300-306 [PMID: 9052510]
- 33 **Niwamoto H**, Okamoto E, Fujimoto J, Takeuchi M, Furuyama J, Yamamoto Y. Are human herpes viruses or measles virus associated with esophageal achalasia? *Dig Dis Sci* 1995; **40**: 859-864 [PMID: 7720482]
- 34 **Eckardt VF**. Clinical presentations and complications of achalasia. *Gastrointest Endosc Clin N Am* 2001; **11**: 281-292, vi [PMID: 11319062]
- 35 **Eckardt VF**, Köhne U, Junginger T, Westermeier T. Risk factors for diagnostic delay in achalasia. *Dig Dis Sci* 1997; **42**: 580-585 [PMID: 9073142]
- 36 **Hulselmans M**, Vanuytsel T, Degreef T, Sifrim D, Coosemans W, Lerut T, Tack J. Long-term outcome of pneumatic dilation in the treatment of achalasia. *Clin Gastroenterol Hepatol* 2010; **8**: 30-35 [PMID: 19782766 DOI: 10.1016/j.cgh.2009.09.020]
- 37 **Eckardt VF**, Stauf B, Bernhard G. Chest pain in achalasia: patient characteristics and clinical course. *Gastroenterology* 1999; **116**: 1300-1304 [PMID: 10348812]
- 38 **Fisichella PM**, Raz D, Palazzo F, Niponmick I, Patti MG. Clinical, radiological, and manometric profile in 145 patients with untreated achalasia. *World J Surg* 2008; **32**: 1974-1979 [PMID: 18575930 DOI: 10.1007/s00268-008-9656-z]
- 39 **Tracey JP**, Traube M. Difficulties in the diagnosis of pseudo-achalasia. *Am J Gastroenterol* 1994; **89**: 2014-2018 [PMID: 7942729]
- 40 **de Borst JM**, Wagtmans MJ, Fockens P, van Lanschot JJ, West R, Boeckxstaens GE. Pseudoachalasia caused by pancreatic carcinoma. *Eur J Gastroenterol Hepatol* 2003; **15**: 825-828 [PMID: 12811315]
- 41 **Vaezi MF**, Baker ME, Achkar E, Richter JE. Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. *Gut* 2002; **50**: 765-770 [PMID: 12010876]
- 42 **de Oliveira JM**, Birgisson S, Doinoff C, Einstein D, Herts B, Davros W, Obuchowski N, Koehler RE, Richter J, Baker ME. Timed barium swallow: a simple technique for evaluating esophageal emptying in patients with achalasia. *AJR Am J Roentgenol* 1997; **169**: 473-479 [PMID: 9242756]
- 43 **Bredenoord AJ**, Fox M, Kahrilas PJ, Pandolfino JE, Schwizer W, Smout AJ. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. *Neurogastroenterol Motil* 2012; **24** Suppl 1: 57-65 [PMID: 22248109 DOI: 10.1111/j.1365-2982.2011.01834.x]
- 44 **Kahrilas PJ**. Esophageal motor disorders in terms of high-resolution esophageal pressure topography: what has changed? *Am J Gastroenterol* 2010; **105**: 981-987 [PMID: 20179690 DOI: 10.1038/ajg.2010.43]
- 45 **Pandolfino JE**, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008; **135**: 1526-1533 [PMID: 18722376 DOI: 10.1053/j.gastro.2008.07.022]
- 46 **Gelfond M**, Rozen P, Gilat T. Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide

- evaluation. *Gastroenterology* 1982; **83**: 963-969 [PMID: 6288509]
- 47 **Bortolotti M**, Labò G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. *Gastroenterology* 1981; **80**: 39-44 [PMID: 7450409]
 - 48 **Traube M**, Dubovik S, Lange RC, McCallum RW. The role of nifedipine therapy in achalasia: results of a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol* 1989; **84**: 1259-1262 [PMID: 2679048]
 - 49 **Triadafilopoulos G**, Aaronson M, Sackel S, Burakoff R. Medical treatment of esophageal achalasia. Double-blind crossover study with oral nifedipine, verapamil, and placebo. *Dig Dis Sci* 1991; **36**: 260-267 [PMID: 1995258]
 - 50 **Wen ZH**, Gardener E, Wang YP. Nitrates for achalasia. *Cochrane Database Syst Rev* 2004; **(1)**: CD002299 [PMID: 14973987]
 - 51 **Pasricha PJ**, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intraspincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; **332**: 774-778 [PMID: 7862180]
 - 52 **Annese V**, Bassotti G, Coccia G, Dinelli M, D'Onofrio V, Gatto G, Leandro G, Repici A, Testoni PA, Andriulli A. A multicentre randomised study of intraspincteric botulinum toxin in patients with oesophageal achalasia. GISMA Achalasia Study Group. *Gut* 2000; **46**: 597-600 [PMID: 10764700]
 - 53 **Leyden JE**, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev* 2006; **(4)**: CD005046 [PMID: 17054234]
 - 54 **Muehldorfer SM**, Schneider TH, Hochberger J, Martus P, Hahn EG, Ell C. Esophageal achalasia: intraspincteric injection of botulinum toxin A versus balloon dilation. *Endoscopy* 1999; **31**: 517-521 [PMID: 10533734]
 - 55 **Vaezi MF**, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL, Koehler RE, Baker ME. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999; **44**: 231-239 [PMID: 9895383]
 - 56 **Ghoshal UC**, Chaudhuri S, Pal BB, Dhar K, Ray G, Banerjee PK. Randomized controlled trial of intraspincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. *Dis Esophagus* 2001; **14**: 227-231 [PMID: 11869325]
 - 57 **Mikaeli J**, Fazel A, Montazeri G, Yaghoobi M, Malekzadeh R. Randomized controlled trial comparing botulinum toxin injection to pneumatic dilatation for the treatment of achalasia. *Aliment Pharmacol Ther* 2001; **15**: 1389-1396 [PMID: 11552910]
 - 58 **Zhu Q**, Liu J, Yang C. Clinical study on combined therapy of botulinum toxin injection and small balloon dilation in patients with esophageal achalasia. *Dig Surg* 2009; **26**: 493-498 [PMID: 20090338 DOI: 10.1159/000229784]
 - 59 **Zaninotto G**, Annese V, Costantini M, Del Genio A, Costantino M, Epifani M, Gatto G, D'Onofrio V, Benini L, Contini S, Molena D, Battaglia G, Tardio B, Andriulli A, Ancona E. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Ann Surg* 2004; **239**: 364-370 [PMID: 15075653]
 - 60 **Kadakia SC**, Wong RK. Graded pneumatic dilation using Rigidflex achalasia dilators in patients with primary esophageal achalasia. *Am J Gastroenterol* 1993; **88**: 34-38 [PMID: 8420271]
 - 61 **Eckardt VF**, Aigner C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. *Gastroenterology* 1992; **103**: 1732-1738 [PMID: 1451966]
 - 62 **Rohof WO**, Lei A, Boeckxstaens GE. Esophageal stasis on a timed barium esophagogram predicts recurrent symptoms in patients with long-standing achalasia. *Am J Gastroenterol* 2013; **108**: 49-55 [PMID: 23007004 DOI: 10.1038/ajg.2012.318]
 - 63 **Vela MF**, Richter JE, Khandwala F, Blackstone EH, Wachsberger D, Baker ME, Rice TW. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. *Clin Gastroenterol Hepatol* 2006; **4**: 580-587 [PMID: 16630776]
 - 64 **Zerbib F**, Thétiot V, Richey F, Benajah DA, Messager L, Lamouliatte H. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. *Am J Gastroenterol* 2006; **101**: 692-697 [PMID: 16635216]
 - 65 **Rohof WO**, Salvador R, Annese V, Bruley des Varannes S, Chaussade S, Costantini M, Elizalde JI, Gaudric M, Smout AJ, Tack J, Busch OR, Zaninotto G, Boeckxstaens GE. Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology* 2013; **144**: 718-725; quiz e13-4 [PMID: 23277105 DOI: 10.1053/j.gastro.2012.12.027]
 - 66 **Boeckxstaens GE**, Annese V, des Varannes SB, Chaussade S, Costantini M, Cuttitta A, Elizalde JI, Fumagalli U, Gaudric M, Rohof WO, Smout AJ, Tack J, Zwinderman AH, Zaninotto G, Busch OR. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011; **364**: 1807-1816 [PMID: 21561346 DOI: 10.1056/NEJMoa1010502]
 - 67 **Salvador R**, Costantini M, Zaninotto G, Morbin T, Rizzetto C, Zanatta L, Ceolin M, Finotti E, Nicoletti L, Da Dalt G, Cavallin F, Ancona E. The preoperative manometric pattern predicts the outcome of surgical treatment for esophageal achalasia. *J Gastrointest Surg* 2010; **14**: 1635-1645 [PMID: 20830530 DOI: 10.1007/s11605-010-1318-4]
 - 68 **O'Connor JB**, Singer ME, Imperiale TF, Vaezi MF, Richter JE. The cost-effectiveness of treatment strategies for achalasia. *Dig Dis Sci* 2002; **47**: 1516-1525 [PMID: 12141811]
 - 69 **Karanicolas PJ**, Smith SE, Inculet RI, Malthaner RA, Reynolds RP, Goeree R, Gafni A. The cost of laparoscopic myotomy versus pneumatic dilatation for esophageal achalasia. *Surg Endosc* 2007; **21**: 1198-1206 [PMID: 17479318]
 - 70 **Richter JE**. Update on the management of achalasia: balloons, surgery and drugs. *Expert Rev Gastroenterol Hepatol* 2008; **2**: 435-445 [PMID: 19072391 DOI: 10.1586/17474124.2.3.435]
 - 71 **Katzka DA**, Castell DO. Review article: an analysis of the efficacy, perforation rates and methods used in pneumatic dilation for achalasia. *Aliment Pharmacol Ther* 2011; **34**: 832-839 [PMID: 21848630 DOI: 10.1111/j.1365-2036.2011.04816.x]
 - 72 **Vanuytsel T**, Lerut T, Coosemans W, Vanbeekevoort D, Blondeau K, Boeckxstaens G, Tack J. Conservative management of esophageal perforations during pneumatic dilation for idiopathic esophageal achalasia. *Clin Gastroenterol Hepatol* 2012; **10**: 142-149 [PMID: 22064041 DOI: 10.1016/j.cgh.2011.10.032]
 - 73 **Metman EH**, Lagasse JP, d'Altoche L, Picon L, Scotto B, Barbieux JP. Risk factors for immediate complications after progressive pneumatic dilation for achalasia. *Am J Gastroenterol* 1999; **94**: 1179-1185 [PMID: 10235189]
 - 74 **Ortega JA**, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980; **26**: 8-10 [PMID: 7358270]
 - 75 **Sumiyama K**, Tajiri H, Gostout CJ. Submucosal endoscopy with mucosal flap safety valve (SEMF) technique: a safe access method into the peritoneal cavity and mediastinum. *Minim Invasive Ther Allied Technol* 2008; **17**: 365-369 [PMID: 18972253 DOI: 10.1080/13645700802528512]
 - 76 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382]
 - 77 **Inoue H**, Minami H, Satodate H, Kudo SE. First Clinical Experience of Submucosal Endoscopic esophageal myotomy for esophageal achalasia with no skin incision. *Gastrointest Endosc* 2009; **69**: AB122
 - 78 **Minami H**, Isomoto H, Yamaguchi N, Ohnita K, Takeshima F, Inoue H, Nakao K. Peroral endoscopic myotomy (POEM) for diffuse esophageal spasm. *Endoscopy* 2014; **46** Suppl 1 UCTN: E79-E81 [PMID: 24676826 DOI: 10.1055/s-0032-1309922]
 - 79 **Kandulski A**, Fuchs KH, Weigt J, Malfertheiner P. Jackhammer esophagus: high-resolution manometry and therapeutic approach using peroral endoscopic myotomy (POEM). *Dis Esophagus* 2014 Jan 27; Epub ahead of print [PMID: 24460870 DOI: 10.1111/dote.12182]
 - 80 **Zhou PH**, Li QL, Yao LQ, Xu MD, Chen WF, Cai MY, Hu JW, Li L, Zhang YQ, Zhong YS, Ma LL, Qin WZ, Cui Z. Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center

- study. *Endoscopy* 2013; **45**: 161-166 [PMID: 23389963 DOI: 10.1055/s-0032-1326203]
- 81 **Sharata A**, Kurian AA, Dunst CM, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. *J Gastrointest Surg* 2013; **17**: 1188-1192 [PMID: 23609138 DOI: 10.1007/s11605-013-2193-6]
 - 82 **Stavropoulos SN**, Modayil RJ, Friedel D, Savides T. The Inter-25 national Per Oral Endoscopic Myotomy Survey (IPOEMS): a snapshot of the global POEM experience. *Surg Endosc* 2013; **27**: 3322-3338 [PMID: 23549760 DOI: 10.1007/s00464-013-2913-8]
 - 83 **Friedel D**, Modayil R, Stavropoulos SN. Per-oral endoscopic myotomy: major advance in achalasia treatment and in endoscopic surgery. *World J Gastroenterol* 2014; **20**: 17746-17755 [PMID: 25548473 DOI: 10.3748/wjg.v20.i47.17746]
 - 84 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
 - 85 **Minami H**, Inoue H, Haji A, Isomoto H, Urabe S, Hashiguchi K, Matsushima K, Akazawa Y, Yamaguchi N, Ohnita K, Takeshima F, Nakao K. Per-oral endoscopic myotomy: emerging indications and evolving techniques. *Dig Endosc* 2015; **27**: 175-181 [PMID: 25040806 DOI: 10.1111/den.12328]
 - 86 **Baldaque-Silva F**, Marques M, Vilas-Boas F, Maia JD, Sá F, Macedo G. New transillumination auxiliary technique for peroral endoscopic myotomy. *Gastrointest Endosc* 2014; **79**: 544-545 [PMID: 24268533 DOI: 10.1016/j.gie.2013.10.023]
 - 87 **Kravtsov IU**, Antonov IV. [Surgical treatment of umbilical hernia in children]. *Khirurgiia (Mosk)* 1989; **11**: 125-128 [PMID: 2533300]
 - 88 **Modayil R**, Friedel D, Stavropoulos SN. Endoscopic suture repair of a large mucosal perforation during peroral endoscopic myotomy for treatment of achalasia. *Gastrointest Endosc* 2014; **80**: 1169-1170 [PMID: 24830579 DOI: 10.1016/j.gie.2014.03.035]
 - 89 **Saxena P**, Chavez YH, Kord Valeshabad A, Kalloo AN, Khashab MA. An alternative method for mucosal flap closure during peroral endoscopic myotomy using an over-the-scope clipping device. *Endoscopy* 2013; **45**: 579-581 [PMID: 23592391 DOI: 10.1055/s-0032-1326398]
 - 90 **Li H**, Linghu E, Wang X. Fibrin sealant for closure of mucosal penetration at the cardia during peroral endoscopic myotomy (POEM). *Endoscopy* 2012; **44** Suppl 2 UCTN: E215-E216 [PMID: 22622752 DOI: 10.1055/s-0032-1309358]
 - 91 **Swanstrom LL**, Kurian A, Dunst CM, Sharata A, Bhayani N, Rieder E. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. *Ann Surg* 2012; **256**: 659-667 [PMID: 22982946 DOI: 10.1097/SLA.0b013e31826b5212]
 - 92 **Stavropoulos SN**, Modayil R, Brathwaite CE, Halwan B, Taylor SI, Coppola T, Long D, Friedel D, Grendell JH. Per Oral Endoscopic Myotomy (POEM) for Achalasia: Large Single-Center 4-Year Series by a Gastroenterologist With Emphasis on Objective Assessment of Emptying, GERD, LES Distensibility and Post-Procedural Pain. *Gastrointest Endosc* 2014; **79** (Supplement 5): AB365
 - 93 **Zhou PH**, Cai MY, Yao LQ, Zhong YS, Ren Z, Xu MD, Chen WF, Qin XY. [Peroral endoscopic myotomy for esophageal achalasia: report of 42 cases]. *Zhonghua Weichang Waikes Zazhi* 2011; **14**: 705-708 [PMID: 21948538]
 - 94 **Costamagna G**, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis* 2012; **44**: 827-832 [PMID: 22609465]
 - 95 **Chiu PW**, Wu JC, Teoh AY, Chan Y, Wong SK, Liu SY, Yung MY, Lam CC, Sung JJ, Chan FK, Lau JY, Ng EK. Peroral endoscopic myotomy for treatment of achalasia: from bench to bedside (with video). *Gastrointest Endosc* 2013; **77**: 29-38 [PMID: 23043852 DOI: 10.1016/j.gie.2012.08.018]
 - 96 **Hungness ES**, Teitelbaum EN, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, Soper NJ. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *J Gastrointest Surg* 2013; **17**: 228-235 [PMID: 23054897 DOI: 10.1007/s11605-012-2030-3]
 - 97 **Minami H**, Isomoto H, Yamaguchi N, Matsushima K, Akazawa Y, Ohnita K, Takeshima F, Inoue H, Nakao K. Peroral endoscopic myotomy for esophageal achalasia: clinical impact of 28 cases. *Dig Endosc* 2014; **26**: 43-51 [PMID: 23581563 DOI: 10.1111/den.12086]
 - 98 **Von Renteln D**, Fuchs KH, Fockens P, Bauerfeind P, Vassiliou MC, Werner YB, Fried G, Breithaupt W, Heinrich H, Bredenoord AJ, Kersten JF, Verlaan T, Trevisonno M, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology* 2013; **145**: 309-311.e1-3 [PMID: 23665071 DOI: 10.1053/j.gastro.2013.04.057]
 - 99 **Onimaru M**, Inoue H, Ikeda H, Yoshida A, Santi EG, Sato H, Ito H, Maselli R, Kudo SE. Peroral endoscopic myotomy is a viable option for failed surgical esophagocardiomyotomy instead of redo surgical Heller myotomy: a single center prospective study. *J Am Coll Surg* 2013; **217**: 598-605 [PMID: 23891071 DOI: 10.1016/j.jamcollsurg.2013.05.025]
 - 100 **Verlaan T**, Rohof WO, Bredenoord AJ, Eberl S, Rösch T, Fockens P. Effect of peroral endoscopic myotomy on esophagogastric junction physiology in patients with achalasia. *Gastrointest Endosc* 2013; **78**: 39-44 [PMID: 23453184 DOI: 10.1016/j.gie.2013.01.006]
 - 101 **Cai MY**, Zhou PH, Yao LQ, Xu MD, Zhong YS, Li QL, Chen WF, Hu JW, Cui Z, Zhu BQ. Peroral endoscopic myotomy for idiopathic achalasia: randomized comparison of water-jet assisted versus conventional dissection technique. *Surg Endosc* 2014; **28**: 1158-1165 [PMID: 24232052]
 - 102 **De Palma GD**, Catanzano C. Removable self-expanding metal stents: a pilot study for treatment of achalasia of the esophagus. *Endoscopy* 1998; **30**: S95-S96 [PMID: 9865580]
 - 103 **Coppola F**, Gaia S, Rolle E, Recchia S. Temporary endoscopic metallic stent for idiopathic esophageal achalasia. *Surg Innov* 2014; **21**: 11-14 [PMID: 23793575 DOI: 10.1177/155335061349]
 - 104 **Zhao JG**, Li YD, Cheng YS, Li MH, Chen NW, Chen WX, Shang KZ. Long-term safety and outcome of a temporary self-expanding metallic stent for achalasia: a prospective study with a 13-year single-center experience. *Eur Radiol* 2009; **19**: 1973-1980 [PMID: 19296113 DOI: 10.1007/s00330-009-1373-y]
 - 105 **Zeng Y**, Dai YM, Wan XJ. Clinical remission following endoscopic placement of retrievable, fully covered metal stents in patients with esophageal achalasia. *Dis Esophagus* 2014; **27**: 103-108 [PMID: 23796127 DOI: 10.1111/dote.12083]
 - 106 **Mukherjee S**, Kaplan DS, Parasher G, Sipple MS. Expandable metal stents in achalasia--is there a role? *Am J Gastroenterol* 2000; **95**: 2185-2188 [PMID: 11007215 DOI: 10.1111/j.1572]
 - 107 **Cheng YS**, Ma F, Li YD, Chen NW, Chen WX, Zhao JG, Wu CG. Temporary self-expanding metallic stents for achalasia: a prospective study with a long-term follow-up. *World J Gastroenterol* 2010; **16**: 5111-5117 [PMID: 20976849]
 - 108 **De Palma GD**, Iovino P, Masone S, Persico M, Persico G. Self-expanding metal stents for endoscopic treatment of esophageal achalasia unresponsive to conventional treatments. Long-term results in eight patients. *Endoscopy* 2001; **33**: 1027-1030 [PMID: 11740645 DOI: 10.1055/s-2001-18933]
 - 109 **Vela MF**, Richter JE, Wachsberger D, Connor J, Rice TW. Complexities of managing achalasia at a tertiary referral center: use of pneumatic dilatation, Heller myotomy, and botulinum toxin injection. *Am J Gastroenterol* 2004; **99**: 1029-1036 [PMID: 15180721]
 - 110 **Lopushinsky SR**, Urbach DR. Pneumatic dilatation and surgical myotomy for achalasia. *JAMA* 2006; **296**: 2227-2233 [PMID: 17090769]
 - 111 **Snyder CW**, Burton RC, Brown LE, Kakade MS, Finan KR, Hawn MT. Multiple preoperative endoscopic interventions are associated with worse outcomes after laparoscopic Heller myotomy for achalasia. *J Gastrointest Surg* 2009; **13**: 2095-2103 [PMID: 19789928 DOI: 10.1007/s11605-009-1049-6]
 - 112 **Finley CJ**, Kondra J, Clifton J, Yee J, Finley R. Factors associated with postoperative symptoms after laparoscopic Heller myotomy.

- Ann Thorac Surg* 2010; **89**: 392-396 [PMID: 20103306 DOI: 10.1016/j.athoracsur.2009.10.046]
- 113 **Rosemurgy AS**, Morton CA, Rosas M, Albrink M, Ross SB. A single institution's experience with more than 500 laparoscopic Heller myotomies for achalasia. *J Am Coll Surg* 2010; **210**: 637-645, 645-647 [PMID: 20421021 DOI: 10.1016/j.jamcollsurg.2010.01.035]
- 114 **Portale G**, Costantini M, Rizzetto C, Guirrolì E, Ceolin M, Salvador R, Ancona E, Zaninotto G. Long-term outcome of laparoscopic Heller-Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. *J Gastrointest Surg* 2005; **9**: 1332-1339 [PMID: 16332491]
- 115 **Ghoshal UC**, Kumar S, Saraswat VA, Aggarwal R, Misra A, Choudhuri G. Long-term follow-up after pneumatic dilation for achalasia cardia: factors associated with treatment failure and recurrence. *Am J Gastroenterol* 2004; **99**: 2304-2310 [PMID: 15571574]

P- Reviewer: Fuchs HF, Samiullah S **S- Editor:** Song XX
L- Editor: A **E- Editor:** Lu YJ



Colorectal endoscopic submucosal dissection from a Western perspective: Today's promises and future challenges

José Carlos Marín-Gabriel, Gloria Fernández-Esparrach, José Díaz-Tasende, Alberto Herreros de Tejada

José Carlos Marín-Gabriel, José Díaz-Tasende, Department of Gastroenterology, Endoscopy Unit, High Risk GI Cancer Clinic, i+12, Hospital Universitario "12 de Octubre", 28041 Madrid, Spain

Gloria Fernández-Esparrach, Department of Gastroenterology, Endoscopy Unit, CIBEREHD, IDIBAPS, Hospital Clínic, Universidad de Barcelona, 08036 Barcelona, Spain

Alberto Herreros de Tejada, Department of Gastroenterology, IDIPHIM, Hospital Universitario Puerta de Hierro, Majadahonda, 28222 Madrid, Spain

Author contributions: Marín-Gabriel JC and Fernández-Esparrach G designed and coordinated this review; Marín-Gabriel JC, Díaz-Tasende J and Herreros de Tejada A contributed to the writing of the manuscript and revised it before submission; Fernández-Esparrach G gave final approval of the version to be submitted and the revised version.

Conflict-of-interest statement: The authors report no conflicts of interest regarding the content of this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: José Carlos Marín-Gabriel, MD, PhD, Department of Gastroenterology, Endoscopy Unit, High Risk GI Cancer Clinic, i+12, Hospital Universitario "12 de Octubre", Avda. Andalucía s/n, 28041 Madrid, Spain. josecarlos.marin@salud.madrid.org
Telephone: +34-91-7792827
Fax: +34-91-7792957

Received: June 29, 2015
Peer-review started: June 30, 2015
First decision: August 25, 2015
Revised: November 1, 2015

Accepted: November 24, 2015
Article in press: November 25, 2015
Published online: January 25, 2016

Abstract

Over the last few years, endoscopic submucosal dissection (ESD) has shown to be effective in the management of early colorectal neoplasms, particularly in Asian countries where the technique was born. In the Western world, its implementation has been slow and laborious. In this paper, the indications for ESD, its learning model, the available methods to predict the presence of deep submucosal invasion before the procedure and the published outcomes from Asia and Europe will be reviewed. Since ESD has several limitations in terms of learning achievement in the West, and completion of the procedure for the first cases is difficult in our part of the world, a short review on colorectal assisted ESD has been included. Finally, other endoscopic and surgical treatment modalities that are in competition with colorectal ESD will be summarized.

Key words: Endoscopic submucosal dissection; Endoscopic full-thickness resection; Endoscopic mucosal resection; Hybrid endoscopic submucosal dissection; Early colorectal cancer; Assisted endoscopic submucosal dissection; Magnification chromoendoscopy; Colorectal surgery; Colorectal neoplasm; Submucosal invasion; Predictive factors; Training; Learning curve

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In the Western world, endoscopic submucosal dissection (ESD) implementation is slow and laborious. In this paper, the indications for ESD, its learning model, the available methods to predict the presence of deep submucosal invasion before the procedure and the published outcomes from Asia and Europe will be reviewed. Additionally, a short review on colorectal assisted

ESD has been included. Finally, other endoscopic and surgical treatment modalities that are in competition with colorectal ESD will be summarized.

Marín-Gabriel JC, Fernández-Esparrach G, Díaz-Tasende J, Herreros de Tejada A. Colorectal endoscopic submucosal dissection from a Western perspective: Today's promises and future challenges. *World J Gastrointest Endosc* 2016; 8(2): 40-55 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/40.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.40>

INTRODUCTION

Current colorectal cancer (CRC) screening population-based programs^[1,2] will increase the detection of early neoplastic lesions suitable for endoscopic resection^[3]. Although endoscopic mucosal resection (EMR) is appropriate to resect large flat or sessile colorectal lesions^[4-8], recurrence after piecemeal resection is still a limitation^[9,10]. In recent years, endoscopic submucosal dissection (ESD) has been endorsed as an ideal technique for *en bloc* resection of large colorectal neoplasms with high risk of focal adenocarcinoma or submucosal fibrosis^[11]. Nevertheless, the optimal outcomes of colorectal ESD (CR-ESD) achieved in Japanese series^[12,13] are constrained by the long learning curve and high complication rate when trying to introduce it in Western countries^[14-16]. Thus, there is some controversy regarding the best approach to the management of large early neoplastic lesions in the colon^[17]. Some authors advocate for the refinement of piecemeal EMR or a hybrid method of combined submucosal incision and EMR as a more realistic option for Western endoscopists^[7,10,18], whereas others support progressive embracement of CR-ESD through a well-defined training strategy^[19-21]. Different topics related to CR-ESD, including training, indications, outcomes, adjunctive devices to simplify the procedure and results when ESD is compared to alternative techniques, will be reviewed.

TRAINING: JAPANESE VS WESTERN MODEL

ESD is a complex procedure and the mastery of technical skills by new trainees has been based on a traditional mentor-pupil close teaching relationship in Japan since the introduction of the technique^[22,23]. However, recent expansion of ESD in Western countries has been led by a small group of experienced endoscopists that have usually performed a self-learning process based on observation and animal model training^[24-27]. Obvious reasons for this different approach are the lack of ESD experts in Western countries and the low detection rate of early gastric cancer as the ideal setting for beginners.

Japanese training model for ESD

In Japan, the traditional model of teaching ESD has

consisted of senior experts in large referral centers directly supervising new trainees in a step-by-step scheme^[28-30]. Firstly, there is a selection of potential candidates based on prior achievement of good skills on endoscopic diagnosis of early gastrointestinal cancer and therapeutic maneuvers^[28]. Secondly, the apprentice has to observe a certain number of ESD procedures performed by the mentor, occasionally participating as an assistant to become familiar with the special devices used. If possible, the trainee should complete this initial training period with some hands-on exposure to animal models^[31]. The trainee is then invited to perform some partial phase of the ESD (marking, initial circumferential cutting, final dissection, preventive coagulation...) under close supervision by the mentor^[32]. The ideal setting that has been suggested to begin with is performing ESD in selected lesions at an easily accessible gastric location^[30]. When considered ready, the trainee is finally encouraged to perform a complete gastric ESD. Increasing number of cases completed eventually grant enough skills to move on to more difficult locations in the stomach. Several Japanese authors have suggested a number ranging from 20 to 80 cases to be considered proficient in gastric ESD^[29,30,32]. Afterwards, the trainee may continue with other areas of the GI tract: esophagus, rectum and colon. Difficult colonic cases are generally restricted to experts with outstanding skills and extensive experience^[33].

CR-ESD training in Japan

CR-ESD represents the last step in the natural evolution of ESD training. Colonic lesions are commonly located in difficult areas, where positioning of the endoscope may be extremely challenging, and there is general agreement that prior experience with gastric ESD is needed^[34,35]. Several studies have investigated the appropriate number of CR-ESD to achieve proficiency. Some authors have proposed a minimum number of 20-30 cases under close supervision to achieve a certain level of competence^[36], and it is advisable to begin with rectal and smaller lesions^[37]. Nevertheless, the numbers needed to secure a high profile of successful R0 resection with few complications are closer to 80-100, according to some reports^[38].

Western training model for ESD

Small groups of endoscopists with particular interest in the technique have commonly promoted initiation of ESD in Western countries. The typical profile is that of an experienced attending gastroenterologist with extensive background in interventional endoscopy (EUS, ERCP, EMR...) ^[39]. Preliminaries could be either self-study based on articles and videos of procedures, attending ESD courses with hands-on training in animal models, etc. It is of particular interest to complete a visit to Japanese centers, where the trainee can benefit from first-hand experience observing experts performing ESD cases^[25,26]. This is a good opportunity to learn the basics of chromoendoscopy and magnification for lesion

assessment, different knives and ancillary devices used, steps of the ESD procedure including management of early and late complications, as well as specimen fixation and pathological assessment^[27]. Additional extensive hands-on training using animal models is essential for the next steps in skills acquirement, up to the point when main outcomes are good enough to encourage completion of the first human ESD cases^[19,24,25]. The fulfillment of the first human ESD cases should be based on a careful selection with preference for small gastric or rectal lesions. All these steps have been recommended in a European Society of Gastrointestinal Endoscopy position statement^[40], and a training algorithm comprising most of them has been recently proposed^[19].

Unfortunately, in many centers this training pathway must be self-teaching and is limited by the unfeasibility to obtain access to animal laboratory resources. Frustration from technical struggle or frequent complications may lead the process to a premature dead end. In addition, the bulk of potential candidates for ESD according to current recommendations are colorectal lesions^[11,39], which makes it ever more arduous and disheartening. There are some approaches to overcome these limitations: proposing a Japanese expert to come to your institution for direct supervision during the first ESD cases^[24,27,41] or attending hands-on courses in animal models in Japan to practice ESD under expert supervision have been suggested^[42].

Colorectal ESD training in Western countries

There are several studies in Europe focused on CR-ESD training. Initial reports showed suboptimal *en bloc* and R0 resection rates at the beginning^[15,43], but rapid progression was observed within a relatively a short time^[14,20,21,41]. The majority of endoscopists begin with selected small rectal lesions, to later move on to other colonic locations.

Some authors have proposed that a minimal intensive training may be sufficient for expert Western endoscopists to complete a sequential learning curve in rectal and colonic ESD, with a minimum of 20 untutored cases each after a short initial animal hands-on period (< 10 cases)^[41]. Nevertheless, such an approach should be carefully considered since reports from high volume Japanese centers recommend a minimum of 80 cases to obtain adequate skills, both in terms of speed (< 15 min/cm²), perforation (< 6%), *en bloc* (> 95%) and R0 (> 90%) resection rates^[38]. These numbers must be considered in light of the well-established scenario of close expert supervision in Japanese centers, which is frequently not the case in Europe^[16]. Some experts have recommended for inexperienced Western endoscopists to complete at least 40 cases before attempting large or fibrotic CR lesions^[44], two characteristics commonly present in the eligible population for CR-ESD^[11].

In summary, it has been shown that the ESD training process in Europe in a prevalence-based approach will be undoubtedly shaped by a significant number of

colonic and rectal cases^[39]. Untutored ESD training can achieve good outcomes in CR-ESD, but it is encouraged that initial cases are early neoplastic lesions with a low risk of invasion due to the fact that R1 resection is common in inexperienced endoscopists^[39]. Western reports have generally considered a resection rate > 80% acceptable; however, if Western endoscopists wish to pursue excellence in ESD, target outcome standards should probably not be less than those established in Japan, *i.e.*, *en bloc* and R0 resection rate > 90%.

HISTOLOGICAL PREDICTION AND INDICATIONS IN THE WEST

Intramucosal lesions and those well or moderately differentiated T1 adenocarcinomas with submucosal invasion less than 1000 µm and no lymphovascular infiltration, have little or no risk of metastasis^[45] and therefore constitute a typical indication for endoscopic treatment and especially for ESD. In a retrospective series of patients treated at the National Cancer Center Hospital (NCCH) in Tokyo, it was noted that the mucosal morphological pattern accurately predicted the risk of submucosal invasion. In this study, the laterally spreading tumor non granular (LST-NG) type lesions showed a higher risk of submucosal invasion compared with granular (LST-G) type lesions with a statistically significant difference (14% vs 7%; $P < 0.01$)^[46]. On the other hand, the presence of large nodules in LST-G type lesions, the finding of an invasive pit-pattern, "sclerotic" changes in the colorectal wall and a larger size in LST-NG type neoplasms, were also predictors of submucosal invasion. In this series, whereas submucosal invasion in LST-G most often occurs beneath the largest nodules and less frequently under depressed areas, 28% of LST-NG showed multifocal submucosal invasion in areas where there was no endoscopic warning signs. These findings were recognized as evidence of a different biological behaviour and drew attention to the need for an *en bloc* resection of these neoplasms.

The development of magnification chromoendoscopy (MCE) allowed Japanese endoscopists to describe different pit-patterns^[47] as well as microvascular structures^[48] in early CRC, increasing the accuracy of the histopathological prediction and improving the therapeutic decision-making process. When performed by Japanese expert endoscopists, MCE achieved a diagnostic accuracy of 98.8% in differentiating intramucosal or submucosal sm1 superficial invasion from sm2-sm3 deep submucosal invasion^[49]. In another seminal study, the identification of a type III A microvascular pattern by Narrow Band Imaging was predictive of intramucosal or sm1 neoplasia in 94.5% of cases, while a type III B pattern was associated with sm2-3 carcinomas in 72% of cases^[50].

We have fewer data from European or American centers, but a major Australian series of colorectal tumors treated by EMR^[7] found that LST-NG type with a Paris 0-II a +

Table 1 Indications for colorectal endoscopic submucosal dissection (Japan Gastroenterological Endoscopy Society)

Lesions for which endoscopic <i>en bloc</i> resection is required
(1) Lesions for which <i>en bloc</i> resection with snare EMR is difficult to apply
LST-NG, particularly LST-NG pseudo-depressed type
Lesions showing a Vi-type pit pattern
Carcinoma with shallow T1 submucosal invasion
Large depressed-type tumors
Large protruded-type lesions suspected to be carcinoma. Including LST-G, nodular mixed type
(2) Mucosal tumors with submucosal fibrosis as a result of a previous biopsy or prolapse caused by intestinal peristalsis
(3) Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis
(4) Local residual or recurrent early carcinomas after endoscopic resection

EMR: Endoscopic mucosal resection; LST-NG: Laterally spreading tumor non granular; LST-G: Laterally spreading tumor granular.

II c morphology and a Kudo crypt pattern V had a risk of submucosal invasion of 55.5%. On the other hand, LST-G homogeneous type tumors presented submucosal invasion in only 1.5% of cases. These figures reflect that superficial colorectal neoplasms behave similarly to those described in Japanese series and therefore morphological pattern and epithelial crypt analysis can be used for histological prediction and treatment decision-making in Western patients.

Many studies confirm the accuracy of Western endoscopists in differentiating between neoplastic and non-neoplastic polyps, but few reports have focused specifically on their ability to predict the presence of deep submucosal invasion prior to an endoscopic resection attempt. A study from the United Kingdom^[51] showed that Western endoscopists achieved a diagnostic accuracy of 78% in predicting deep submucosal invasion in Paris 0-II lesions by analyzing epithelial crypts and vascular patterns with MCE. In this study, high frequency miniprobe ultrasound examination improved the accuracy up to 94%.

Nevertheless, the limited data available from surgical series, including lesions deemed as endoscopically non-resectable, have demonstrated that between 10% and 20% of the specimens showed deep colonic wall invasion (stages T2-T4) or lymph node metastases that had not been suspected in the endoscopic assessment^[52-55], indicating a lower than expected accuracy in real life conditions.

The role of endoscopic ultrasonography (EUS) in the diagnosis of submucosal invasion or nodal involvement has been controversial. In one small study from Western Europe, endoscopic ultrasound with a 20 MHz probe was better than MCE in determining the depth of invasion and nodal staging^[56], but these results have not been consistently observed in other series of patients. In a study including more than 430 neoplasms treated in a single center in Japan, no significant differences were noted in the diagnostic accuracy between MCE and EUS^[57].

In general terms, ESD is indicated for the treatment of colorectal neoplasms that show no suspicion of deep submucosal invasion assessed by MCE and that cannot be resected *en bloc* by EMR. Given the technical

characteristics of ESD, the size of the lesion is not a limitation, although circumferential lesions are generally considered a contraindication given the high risk of stenosis.

In the absence of local evidence, most Western endoscopists performing ESD have traditionally followed Japanese guidelines. Table 1 shows ESD indications of the Japan Gastroenterological Endoscopy Society^[11]. In Europe, the Spanish Society of Digestive Endoscopy^[58] and the European Association of Endoscopic Surgery^[59] have adopted most of the Japanese indications for ESD as a standard treatment for superficial neoplasms larger than 20 mm in which *en bloc* EMR is difficult. These statements include mixed type LST-G, LST-NG, especially the pseudo-depressed type (Figure 1), large depressed lesions with a noninvasive pattern as assessed by MCE and neoplasia with fibrosis in the context of prior biopsy, attempts of resection or chronic inflammation.

Despite the gradual incorporation of Japanese knowledge about diagnosis and prediction of histological findings into European and American practices, major differences exist between Eastern and Western viewpoints on the endoscopic treatment of colorectal neoplasms. While ESD is widely accepted in Japan, and Japanese National Health Insurance has been covering its cost since 2012, in most Western hospitals a significant number of patients with endoscopically treatable lesions are still referred for surgery. In our part of the world, EMR is the preferred technique for the treatment of superficial neoplasms. As an alternative modality, ESD is still in the early steps of development, with a lack of a clear definition of its place in the treatment algorithms and significant uncertainties about the coverage of its costs.

These differences are clearly due to the greater experience of Japanese endoscopists, but also and significantly, because in Japan there has been little controversy about the importance of *en bloc* resection of tumors in which a risk of submucosal invasion is foreseeable. On the contrary, many Western endoscopists would contend that since most T1 adenocarcinomas with deep submucosal invasion can be identified in the histopathological study of piecemeal EMR, the benefits of *en bloc* resections are limited to a relatively small number

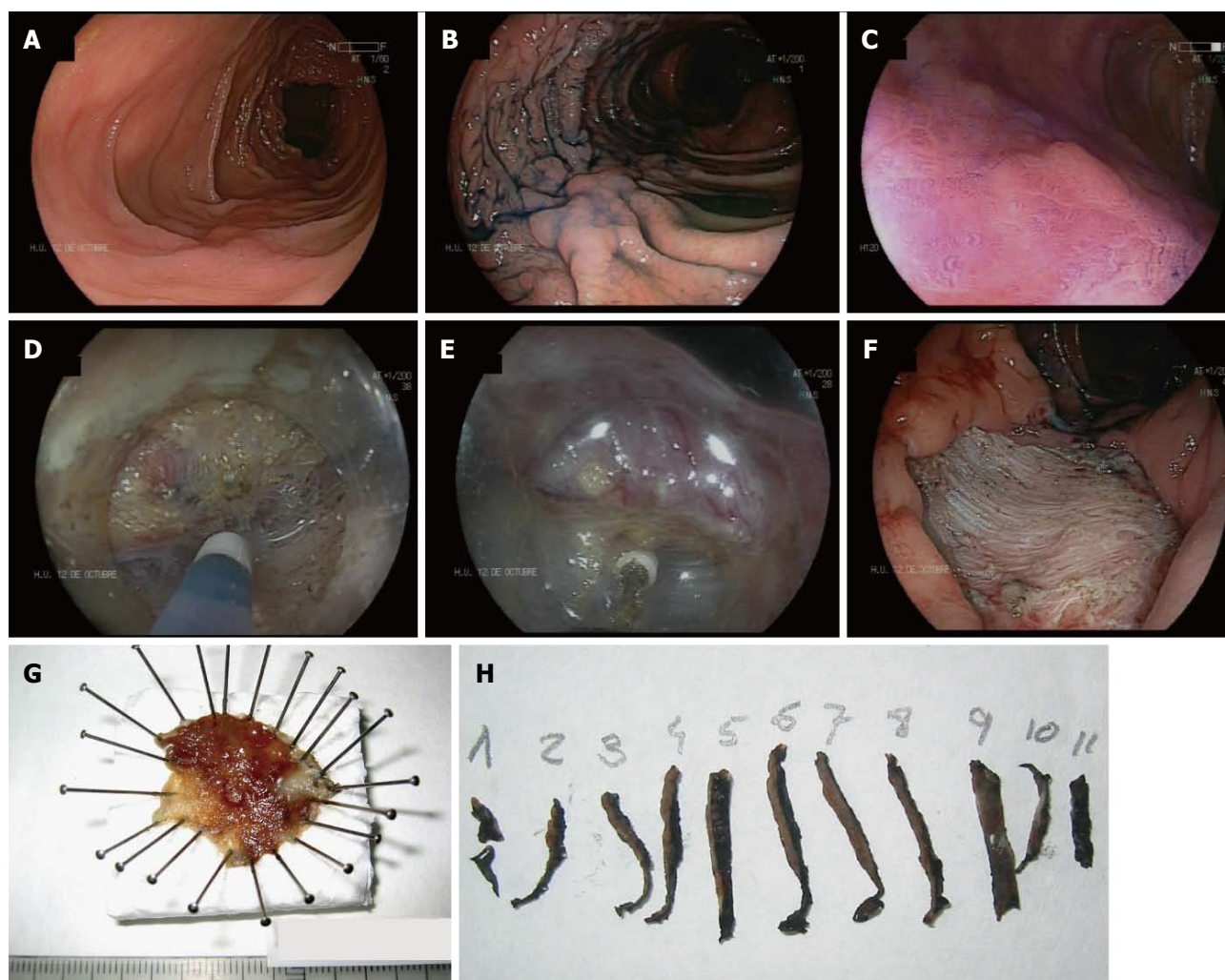


Figure 1 Endoscopic assessment and endoscopic submucosal dissection for a laterally spreading tumor non granular pseudodepressed type in the transverse colon. A: High resolution white light endoscopy; B: Targeted chromoendoscopy with indigo carmine (0.4%) highlights the border and characteristics of the lesion; C: Magnification chromoendoscopy with crystal violet (0.05%) shows a Kudo's Vi pit-pattern; D: Performing ESD with a 1.5 mm Flush-knife BT (Fujinon, Tokyo, Japan); E: Submucosal dissection of the lesion with an IT nano (Olympus, Tokyo, Japan); F: Residual scar after completion of the procedure; G: Resected specimen of CR-ESD stretched with pins on foam. Maximum diameter of the lesion was 32 mm; H: Specimen sectioned into pieces for histological assessment in the Department of Pathology. ESD: Endoscopic submucosal dissection; CR-ESD: Colorectal endoscopic submucosal dissection.

of lesions with sm1 infiltration which, in the case of R0 resections, could avoid surgery. Others would however argue that even intramucosal large LST-NG that can be difficult to resect by EMR because of partial non-lifting, could itself justify the implementation of the procedure.

OUTCOMES IN ASIAN AND IN EUROPEAN COUNTRIES

The tortuous morphology of the large intestine, a thinner wall when compared with the stomach, and the strong peristaltic motion of the colon, leads to a higher likelihood of complications during the procedure. It is very likely that the ESD learning curve is slower in the colon than in the stomach, and it has been overcome for many years in the experienced Asian centers.

As mentioned before, the experience with colorectal ESD out of the Asian countries is scarce. In European countries, our limited experience has shown less

favourable results than those coming from the East, with lower *en bloc* and R0 resection rates and higher perforation rates.

Tables 2 and 3 summarize the most relevant data of the published series. Many of them have methodological limitations and an intention-to-treat analysis is lacking. Although it is commonly reported that the cases are consecutively enrolled, other information is often not provided. In most cases, they are cross-sectional studies and when follow-up is included, this is usually for a period less than 3 years. More importantly, considering that we are talking about oncological outcomes, the 5-year survival rate has been assessed in only one study^[60].

The percentage of non-curative resections oscillates between 3.6%^[61] and 22.7%^[62]. Furthermore, it is noteworthy that the percentage of aborted procedures is scarcely reported. This is particularly striking when a complex procedure, with a prolonged learning curve, comes into focus. Reviewing the published series,

Table 2 Colorectal endoscopic submucosal dissection outcomes for epithelial neoplasms in Asian studies

Ref.	Patients, <i>n</i> (% rectal)	Study design	Enrollment period	Size (mm)	Time (min)	<i>En bloc</i> (%)	RO (%)	Perforation rate (%)	Delayed bleeding (%)	Hospital stay (d)	Follow-up
Fujishiro <i>et al</i> ^[63] , 2006	35 (100)	Prospective	Feb 2001 Feb 2005	32.8	NS	88.6	62.9	5.7	28.6	-	Missing rate: <i>n</i> = 0; 0% Mean: 36 mo (12-60) Recurrence rate at 2 mo: 2.8% 31/32 (96.8%) recurrence-free at 3 yr
Tamegai <i>et al</i> ^[64] , 2007	71 (23.9)	NS	Jan 2003 Dec 2005	32.7	61.1	98.6	95.6	NS	1.4	-	Missing rate: <i>n</i> = 7; 9.86% Mean: 12.2 mo (range 3-34) Recurrences: 0%
Hurlstone <i>et al</i> ^[70] , 2007	42 (33.3)	Prospective	Mar 2004 Aug 2006	31	48	78.6	73.8	2.4	2.4	22	Missing rate: <i>n</i> = 6; 14.3% Median: 6 mo (range: 3-18) Recurrences 4/36 (11%) Curative resections at 6 mo: 34/42 (81%)
Fujishiro <i>et al</i> ^[112] , 2007	200 (26)	NS	Jul 2000 Mar 2006	29.9	-	91.5	70.5	6	0.5	-	Median: 18 mo (range 12-60) Recurrences: 1.8%
Saito <i>et al</i> ^[65] , 2007	200 (30.5)	NS	Oct 2003 Jul 2006	35	90	84	70	5	2	5	Median: 7 mo Missing rate: 10% Recurrences: 0.5%
Tanaka <i>et al</i> ^[68] , 2007	70 (48.6)	NS	< Dec 2005	28	70.5	80	-	10	1.4	-	In curative resections, 0% recurrence rate Other information not provided
Zhou <i>et al</i> ^[113] , 2009	74 (56.7)	NS	Jul 2006 Dec 2007	32.6	110	93.2	89.2	8.1	1.4	-	Missing rate: <i>n</i> = 0; 0% Median: 14.3 mo (range 3-22) Recurrences: 0%
Isomoto <i>et al</i> ^[114] , 2009	292 (26.7)	NS	May 2001 Dec 2008	26.8	-	90.1	79.8	7.9	0.7	-	Missing rate: 24.6% Median: 33 mo in R0 36 mo in non-R0 resections R0: 0% recurrences 1 recurrence in non-R0 resections
Saito <i>et al</i> ^[115] , 2009	405 (27.4)	NS	NS	40	90	86.9	-	3.5	1	-	Mean \pm SD: 20 \pm 13 mo 2% recurrences
Iizuka <i>et al</i> ^[62] , 2009	44 (59)	Retrospective	Jan 2000 Dec 2004	39	110	61	58	8	-	-	-
Niimi <i>et al</i> ^[60] , 2010	310 (26.1)	Retrospective Monocentric	Jul 2000 Dec 2008	28.9	-	90.3	74.5	4.8	1.3	-	Median: 38.7 mo (12.8-104.2) 2% recurrences 3-yr overall/disease-specific survivals: 97.1%/100% 5-yr overall/disease-specific survivals: 95.3%/100% 8 died of other coexisting diseases 0 died of CRC
Yoshida <i>et al</i> ^[116] , 2010	250 (31.6)	NS	Apr 2005 Mar 2010	29.6	106	86.8	81.2	6	2.4	-	-
Saito <i>et al</i> ^[81] , 2010	145 (50.3)	Retrospective	Jan 2003 Dec 2006	37	108	84	-	6.2	1.4	-	Median: 20 mo 2.1% recurrences
Hotta <i>et al</i> ^[38] , 2010	120 (27.5)	NS	Jun 2003 Sep 2008	> 30	141	93.3	85	7.5	-	-	-
Saito <i>et al</i> ^[112] , 2010	1111 (30.3)	Multicentric Prospective	Jun 1998 Feb 2008	35	116	88	89	5.3	1.5	-	-
Toyonaga <i>et al</i> ^[117] , 2010	268 (25.7)	Retrospective	May 2002 May 2007	40.3	64.5	99.2	98.1	2.2	0.37	-	Median: 32.2 mo (6.5-85.2) Follow-up: 227 out of the 241 curative resections (94.2%) Missing rate: 5.8% Recurrences: 0%
Matsumoto <i>et al</i> ^[118] , 2010	203 (NS)	NS	Nov 2002 Jun 2009	33	-	85.7	-	6.9	-	-	-
Uraoka <i>et al</i> ^[119] , 2011	202 (32.7)	NS	Apr 2006 Mar 2010	40	-	91.6	87.1	2.4	0.5	-	Median: 11.4 mo Missing rate: 14% 0% disease specific mortality 1.5% overall mortality

Shono <i>et al</i> ^[61] , 2011	137 (26.2)	NS	Apr 2007 Oct 2010	29.2	79.2	89.1	85.4	3.6	3.6	-	0% recurrences No other information provided
Kim <i>et al</i> ^[120] , 2011	108 (44)	Retrospective	Mar 2007 Feb 2009	27.6	61.9	-	78.7	20.4	-	-	-
Lee <i>et al</i> ^[84] , 2012	314 (19.1)	Retrospective	Jan 2004 Nov 2009	28.9	54.7	92.7	87.6	8	0.64	3.6	-
Lee <i>et al</i> ^[121] , 2012	499 (18.1)	Retrospective	Oct 2006 Nov 2010	28.9	61.3	95	-	7.4	-	3.6	-
Hisabe <i>et al</i> ^[122] , 2012	200 (30)	NS	Jun 2003 Jun 2011	32.7	108.9	86	-	7	1	-	-
Saito <i>et al</i> ^[123] , 2012	1321 (25.6)	Multicentric	-	34.2	90	95.4	87.2	2.9	2.5	-	-
Okamoto <i>et al</i> ^[71] , 2013	30 (50)	NS	Dec 2010 Aug 2012	36	61	-	100	0	0	-	-
Lee <i>et al</i> ^[72] , 2013	874 (20.7)	Retrospective	> Oct 2006	26.5	53.8	97.1	90.5	6.1	0.5	3.5	-
Nakajima <i>et al</i> ^[80] , 2013	816 (36.3)	Prospective	Oct 2007	39.4	96	94.5	90.6	2	2.2	-	-
Nawata <i>et al</i> ^[124] , 2014	150 (20.6)	Multicentric Retrospective 2 groups: A < 50 mm/B ≥ 50 mm	Dec 2010 Apr 2010 Jul 2013	26/59	38/86	98.7	97.3	0	0	-	-
Sakamoto <i>et al</i> ^[66] , 2014	164 (38)	Retrospective	Apr 2005 Mar 2012	30	95	95	92	4	3	-	-
Saito <i>et al</i> ^[109] , 2014	900 (NS)	NS	NS	40	100	91	87	2.7	1.7	-	-
Lee <i>et al</i> ^[125] , 2015	173 (24.3)	Retrospective	Jan 2010 Dec 2013	25.95	-	88.4	81.5	11	3.4	-	-
Rahmi <i>et al</i> ^[67] , 2015	28 (25)	Retrospective 100% recurrences	Dec 2008 Jul 2013	17.5	63	96.4	92.9	3.5	0	7	Median: 22 mo Missing rate: 35.7% Recurrences: 0%

The given values for the size of the lesion and time spent on the procedure are shown as the measure of central tendency reported in the study (mean or median as appropriate). NS: Not specified. -: Information is not mentioned in the original paper.

aborted ESD procedures of between 3.6% and 15.9% have been described^[14,61,62].

Additionally, regarding complications, the perforation rate requiring surgery is seldom described, within a range of between 0%^[61-67] and 2.8%^[68]. Similarly, the need for transfusion or urgent endoscopic therapy due to severe gastrointestinal bleeding are, fortunately, rare, between 0%^[12,64,65,69-71] and 2.2%^[72].

Since ESD is accompanied by risk of delayed perforation and bleeding the postoperative course needs to be monitored carefully. However, no recommendations have been established for patient discharge after the procedure. Some Japanese authors have suggested a 5-d hospital stay for ESD^[73]. In South Korea and some European countries, duration of the hospital stay is 2-3 d unless complications develop^[16,72]. Recently, a Japanese group has published a clinical pathway to shorten hospital stays after the procedure. The authors concluded in the study that a three-day stay may be sufficient when no abnormalities occurred during ESD or on the first day after the endoscopic resection^[74]. In our center, a stay that lasts 3 d is typically the case when no complications are observed. No delayed perforations have been identified after those 3 d in our experience; indeed, this complication is more likely to happen during the first 24 h after the procedure.

COLORECTAL ASSISTED ESD

A good visualization of the submucosal layer is one of

the key factors for performing an effective and safe CR-ESD, and this can only be achieved by proper traction of the tissue.

Benefits of applying traction during ESD are the following: (1) It can provide better submucosal exposure and consequently decreases the risk of perforation; and (2) Traction decreases the contact area between the tissue and the endoknife, enabling a more effective cut^[75].

However, achieving good traction using only one knife through the scope is not easy. Unlike surgeons, who maintain tension and visibility by the hands of assistants, or by more than one device, the endoscopist who performs ESD can be considered as a one-armed person. In order to improve this disadvantage, a number of adjunctive devices have been designed.

Sinker-assisted ESD

A sinker-assisted ESD for colorectal neoplasms was reported by Saito *et al*^[76]. A 1 g sinker is attached to a metallic clip by a nylon thread. After the initial dissection of the submucosa, the clip is deployed to the edge of the mucosa. The sinker will then pull down the partly resected tumor. Finally, changing the position of the patient, will allow gravity to expose the submucosal layer in order to enhance visibility for the remaining dissection.

The Sakamoto and Osada clip

The S-O clip (Sakamoto and Osada clip) consists of

Table 3 Colorectal endoscopic submucosal dissection outcomes for epithelial neoplasms in European studies

Ref.	Patients, <i>n</i> (% rectal)	Study design	Enrollment period	Size (mm)	Time (min)	<i>En bloc</i> (%)	RO (%)	Perforation rate (%)	Delayed bleeding (%)	Hospital stay (d)	Follow-up
Farhat <i>et al</i> ^[16] , 2011	85 (84.7)	Prospective	Jan 2008 Aug 2010	-	-	67	62.3	-	-	-	-
Probst <i>et al</i> ^[14] , 2012	76 (86.6)	NS	Oct 2004 Sep 2011	45.8	176	81.6	69.7	6.6	10.5	-	Median: 23.6 mo (2-83) Included in follow-up: <i>n</i> = 65 9.2% residual neoplasms (5 piecemeal and 1 en bloc R1 lateral) Recurrences: 2.5%
Repici <i>et al</i> ^[20] , 2013	40 (100)	Prospective	Apr 2010 Jan 2011	46.8	86.1	90	80	5	2.5	-	Recurrences: 0% at 3-6 mo
Thorlacius <i>et al</i> ^[126] , 2013	29 (59)	NS	Jan 2012 Mar 2013	28	142	72	69	6.9	0	-	Missing rate: 82.7%
Spychalski <i>et al</i> ^[127] , 2015	70 (56)	NS	Jun 2013 Jun 2014	30	110	66	-	8	6	-	Missing rate: 14.6% Recurrences: 4.9%
Rahmi <i>et al</i> ^[128] , 2014	45 (100)	NS	Feb 2010 Jun 2012	35	110	64	53	18	13	3.4	Follow-up < 12 mo For curative resections at 12 mo: 88%
Bialek <i>et al</i> ^[129] , 2014	37 (67.6)	Prospective	2007 2013	37	70	86.5	81.1	0	5.7	-	At 1-yr follow-up: 1.7% recurrences

The given values for the size of the lesion and the time spent on the procedure are shown as the measure of central tendency reported in the study (mean or median as appropriate). NS: Not specified. -: Information is not mentioned in the original paper.

a metal clip attached to the end of a spring. A double nylon loop is connected at its other end. This system passes easily through the working channel of the endoscope. The device is attached to the mucosal flap and a second clip grasps the distal nylon loop to insert this end of the S-O clip to the wall opposite the lesion^[77].

Thin endoscope-assisted ESD

A double-scope method for large LSTs in the distal sigmoid colon or rectum has been reported by Uraoka *et al*^[78]. When partial dissection of the submucosa has been performed, a clip is attached to the edge of the mucosal flap. A thinner endoscope is then passed through the anus and the primary endoscope is removed. At that point, a snare grasps the clip and pulls the lesion away from the muscle layer. This maneuver allows retraction of the submucosa and improves visualization. The primary scope is inserted again to resume the dissection. A limitation of this method is that the thin endoscope is not stiff enough to achieve deep intubation and using it for proximal lesions is not possible.

"Clip-flap" method

Yamamoto *et al*^[79] reported recently a simple procedure requiring only common clips. After the mucosal flap has been created and the submucosal layer partially dissected, the edge of the mucosa is grasped with an endoclip. The cap attached to the tip of the endoscope is slipped under the clip and the dissection can be resumed as normal. One endoclip can be used for one region and other endoclips can be deployed in additional regions as needed. It is also possible to use two clips crossing one another. However, this method has several

limitations. When the colonic lumen narrows or the position of the endoscope becomes unstable, it may be difficult to grasp the mucosa with the clip and slip the cap under the device.

COLORECTAL ESD VS OTHER THERAPEUTIC STRATEGIES

EMR

Currently, ESD is the only technique that allows *en bloc* resection of colorectal mucosal or submucosal neoplasms of any size except for the full-thickness resection procedures. In the Western world, however, most lesions larger than 20 mm are still treated by piecemeal EMR.

In a prospective study of a large series of patients treated in 18 Japanese reference centers, it was observed that the rate of *en bloc* EMR was significantly reduced as the diameter of the lesion increased, reaching 66.5% in lesions of 20-29 mm, but was only 12.3% in lesions larger than 40 mm. Conversely, ESD *en bloc* resection rates remained above 90% regardless of the size of the lesion^[80].

The first study comparing retrospectively the results of colorectal EMR and ESD included 373 (145 ESD/228 EMR) resected tumors between 2003 and 2006 by expert endoscopists at the NCCH in Tokyo^[81]. As a result of differences in the indications of both procedures, the ESD group included larger lesions (37 ± 14 mm vs 28 ± 8 mm; *P* = 0.0006). However, the *en bloc* resection rate was significantly higher when performing ESD (84% vs 33%; *P* < 0.0001). An increased risk of tumor recurrence at follow-up colonoscopies was observed after EMR when compared with ESD (2% vs 14%;

$P < 0.0001$). It is worth noting that, in this study, all recurrences detected in the ESD group occurred after treatment of lesions previously treated by piecemeal EMR. The mean procedure time was nevertheless more than three times longer in patients treated with ESD (108 min vs 29 min; $P < 0.0001$) and perforations were almost five times higher (6.2% vs 1.3%), although differences were not statistically significant.

Some Japanese and South Korean studies^[73,82-85] have shown better outcomes for ESD in terms of *en bloc* and R0 resections and lower recurrence rates. In addition, higher perforation rates and an increased length of the procedure time have been also observed. Some of these studies, however, excluded patients who underwent surgery because of submucosal invasion, which could represent an overestimation of the clinical effectiveness of this procedure^[73,82]. Furthermore, it has been shown in both Eastern and Western series of ESD that its benefits on a lower rate of local recurrence rely on the ability of the procedure to achieve *en bloc* resections and only become evident in those procedures performed by endoscopists with a high proportion of R0 resections^[14].

The endoscopic resection of recurrent adenomas is another matter of concern. Although ESD may be used in endoscopic salvage procedures for recurrent lesions, performing this procedure is extremely difficult because of the presence of submucosal fibrosis attributable to previous resection. For this reason, in the Western world, the most commonly endoscopic procedure for treating recurrent adenomas after EMR is one additional EMR, although fibrosis after a previous resection often prevents lifting of the lesion after submucosal injection and causes the snare to slip off the tumor. There are very limited published data on the results for this strategy, with more than 10% of the patients needing surgery in this scenario^[7].

In a retrospective case series that included 67 cases of a second endoscopic resection for recurrent neoplasias, ESD achieved a 56% *en bloc* resection rate compared with 39% in the EMR group. Both of these results are lower than expected for primary colorectal tumors^[86]. In contrast, another study observed that 27 out of 28 patients were successfully treated using ESD for residual or recurrent colorectal tumors^[67].

More recently, underwater EMR (UEMR) has been evaluated for the treatment of these recurrences. When colon water distension is used instead of gas, the mucosa and submucosa involute, keeping the muscle layer in place, and there is no need for submucosal injection. Thus, the tumor can be snared easier than with conventional EMR. In a retrospective study, the *en bloc* resection and endoscopic complete removal rates were higher in the UEMR group when compared with the EMR group, and these differences were statistically significant. In addition, argon plasma coagulation ablation of residual tumor was lower in the UEMR group^[87]. Although the study had several limitations, UEMR appears to be useful for salvage endoscopic management of recurrent lesions

after a previous EMR.

Finally, some aspects remain to be clarified concerning the use of these endoscopic procedures for the treatment of defiant colorectal polyps. Thus, isolated cases of submucosal recurrences after piecemeal resection for intraepithelial or intramucosal neoplasms have been reported^[73,81]. This complication has been attributed to staging errors derived from the histopathological study of a piecemeal resection. Additionally, there is no data concerning the impact of perforations that occur during ESD on oncological prognosis.

ESD vs surgical procedures

The two main surgical options at present are laparoscopic-assisted colorectal surgery (LACS) and transanal endoscopic microsurgery (TEM). Several non-randomized controlled studies have compared ESD and surgical modalities for management of colorectal lesions, but good quality evidence is lacking to allow substantial recommendations. ESD has been shown to be a good option for early colorectal neoplastic lesion with absent or shallow submucosal invasion^[12,20,72], but diverse results have been reported when compared with alternative surgical modalities. Recent European guidelines for early rectal cancer do recommend either ESD or TEM, both with optimal curative resection rate, and discourage against conventional transanal excision unless both ESD and TEM are not feasible^[59].

LACS

LACS has widely succeeded as a less invasive technique compared with conventional open surgery^[88,89]. One retrospective study performed at the NCCH in Tokyo compared ESD with LACS for colorectal early carcinoma^[90]. The study population comprised T1m/T1sm1 in the ESD group and T1sm2 in the LACS group. Lesions were located from cecum to rectum, with double the proportion of rectal lesions in the ESD group (38% vs 17%). Results showed that ESD was associated with a shorter procedure time (106 min vs 206 min), shorter hospital stay (5 d vs 13 d) and lower complication rates (6.4% vs 13.6%). Nevertheless, *en bloc* and curative resection rates were lower in the ESD group (87.2% and 80.4%, respectively), compared to 100% for surgical patients. Similarly, a recent retrospective study comparing a series of 300 colorectal ESD to 190 LACS revealed high *en bloc* and curative resection rates for ESD (> 90%), with a shorter procedure time and hospital stay, and a lower complication rate compared with LACS (90 min vs 185 min; 5 d vs 10 d; 7% vs 15%, respectively)^[91]. It should be noted, however, that this report might be shaped by selection bias since a significant proportion of cases in the LACS group (35%) were post-EMR "lesions/scars" vs no cases in the ESD group, and apparently different from what was defined as local recurrence on ESD. Additionally, the ESD group included more than 75% of the lesions as LSTs vs only 10% in the LAC group.

In terms of hospital stay, five days or longer in LACS groups are common in Japanese studies. However,

other studies have reported shorter periods when an elective surgery has been performed, ranging from 3^[52] to 6 d^[92-94].

TEM

TEM is a technique for *en bloc* full-thickness rectal wall excision up to the level of the perirectal fat that can be applied for lesions located as far as 18-20 cm from the anal verge. The minimal distance from the anal verge is 5 cm due to the rigid structure of the rectoscope, making it troublesome to approach a lesion next to the anal verge^[95]. Developed more than 25 years ago as an alternative to standard transanal surgery^[96], TEM has become one of the gold standards for early rectal cancers, whenever available^[59]. There is increasing evidence that TEM is superior to conventional transanal resection (TAR) in terms of *en bloc* and R0 resection rates, and thus, lower recurrence, together with lower complication rates^[97-99]. Some of the limitations of TEM include the long learning curve^[100], similar to ESD, and the need for quite expensive special equipment.

Contradictory results have been obtained when comparing TEM with ESD. Whereas a recent meta-analysis showed better outcomes for TEM^[101], single center-based studies, either head-to-head between both techniques, or only limited to rectal location, showed better outcomes for ESD, with fewer complications or a shorter length of the hospital stay. In the aforementioned meta-analysis, TEM appeared more effective than ESD in terms of *en bloc* and R0 resection rates (98.7% vs 87.8% and 88.5% vs 74.6%, respectively), with a shorter procedure time (67 min vs 96 min) and with no significant differences in the complication rate or the need for additional surgery due to adverse events. Adenoma recurrence rate was, however, higher in the TEM group (5.2% vs 2.6%). Nevertheless, this study included small ESD series, most of them with less than 50 cases and published before 2010^[101]. A report with a small study population in both groups of ESD and TEM (< 20) showed comparable *en bloc* (91%-84%) and R0 (81%-84%) resection rates, with no differences in complications or length of hospital stay^[102]. A South Korean single center retrospective study included patients with flat lesions with suspected high grade dysplasia or submucosal invasive carcinoma who underwent ESD or TEM^[103]. *En bloc* and R0 resection rates were similar in both groups (ESD vs TEM: 96.7% vs 100% and 96.7% vs 97.0%, respectively), with no statistically significant differences in complication rate (3.3% vs 6.1%, respectively). Hospital stay was significantly lower after ESD (3.6 d vs 6.6 d). It should be noted that over 20% of patients in both groups required additional treatment, mostly due to histological risk factors for lymph node metastasis.

Regarding hospital stay with TEM, this outcome may vary significantly across centers. Thus, some authors have reported a median hospital stay of 2-3 d^[104-107], while other studies suggest even shorter stays and

have reported a 24 h discharging policy^[108]. To our knowledge, prospective direct comparisons between TEM and ESD that address the question of superiority in terms of length of hospital stay have yet to be published.

In summary, in an ideal scenario of a well-trained endoscopist, ESD might be the best option for early colorectal neoplasia as it combines a high rate of curative resection, similar to surgical procedures, while maintaining a low profile of invasiveness and less need for general anesthesia^[109]. But frequently this is not the case in most institutions in Western countries, and standard surgical techniques are commonly more accessible to physicians. Favorable results for ESD compared to surgical procedures published recently were only based in retrospective analysis studies, with significant risk of selection bias. There is a lack of randomized controlled trials to establish good quality evidence regarding both techniques. Nevertheless, it seems that if colorectal ESD expansion backed with encouraging outcomes continues, it might be difficult to complete such ideal head-to-head randomized studies since less invasive procedures with good results frequently gain spontaneous acceptance by patients and physicians.

Endoscopic full thickness resection

Since CR-ESD is a technically demanding procedure, with a long learning curve and requires more time for its completion when compared with other resection techniques, simpler and more standardized methods are required for the treatment of colorectal neoplasms. Furthermore, performing CR-ESD is challenging in the presence of technically difficult lesions with severe fibrosis, recurrent lesions, or difficult locations (at the bottom of the cecum, near the terminal ileum, and in the appendix). The advantage of the full thickness resection is the ability to easily and quickly resect the main lesion and quickly close the colon wall defect. However, large-sized lesions are difficult to resect when using only a device that depends on a snare to achieve the resection^[110]. To date, endoscopic treatment for this type of lesion requires additional devices to support closure and suturing. Unfortunately, most of them are not commercially available for widespread use.

Recently, a novel over-the-scope (OTSC) device has been developed for colorectal endoscopic full-thickness resection (eFTR). Although, colonic eFTR is not widely available in clinical practice, the initial results of this procedure have been published recently^[111].

The full-thickness resection device (FTRD) consists of an OTSC System cap with a preloaded clip and a snare integrated into cap's distal end. The lesion that has been previously marked with a marking probe included in the kit is then identified with the colonoscope. The tumor is then pulled into the cap using a grasping forceps. After ensuring that all the marked tissue is completely included into the cap, the OTSC is deployed. Finally,

the lesion is resected after closing the snare, applying electrosurgical current, and retrieved from the colon with the endoscope.

In the study mentioned above the main indication for eFTR was the presence of residual or recurrent neoplasm after a previous endoscopic resection. The median time to complete the procedure was 50 min. The mean diameter of the resection specimen was 24 mm within a range of 12 to 40 mm. The *en bloc* resection rate, R0 resection rate and the percentage of histologically confirmed full-thickness resection were 83.3%, 75.0% and 87.5%, respectively. There were no perforations or severe bleeding episodes. A postpolypectomy electrocoagulation syndrome was observed in 8% of the patients that was successfully treated with antibiotics.

The FTRD has, however, several limitations. The diameter of the outer cap does not allow the system to pass through the oral route. Consequently, it cannot be used for resection in the upper gastrointestinal tract. In the colon, the main limiting factors are the size of the lesion and the presence of submucosal fibrosis. Tumors over 25 millimeters in diameter might not easily fit into the cap and lack of elasticity of the colonic wall because of severe fibrosis often makes the resection difficult. Additionally, in the rectum, the perirectal tissue that fixes it prevents the achievement of a full-thickness resection.

CONCLUSION

CR-ESD is a major advance for the treatment of colorectal neoplasms: it has well-established indications, achieves higher *en bloc* resection rates when compared with EMR and is less invasive and costly than surgery.

Nevertheless, ESD also has several disadvantages: It has a long learning curve and the training process is not well established outside of Asian countries. These problems still have to be resolved in Europe. Additionally, complications in terms of bleeding and perforation rates are higher than those associated with EMR, a more established endoscopic procedure in Western countries.

Despite the many devices commercially available to perform the technique, standardization of CR-ESD still needs to be defined. Indeed, to date, the skill of the endoscopist seems to be the determining factor to achieve excellent outcomes.

Finally, simpler and more time-efficient methods for the treatment of colorectal tumors are required and new developments in this area are very likely to appear in the next few years. Probably, in the near future, methods such as FTRD will be competing treatments for CR-ESD in selected patients. More importantly, innovative methods and new devices for eFTR and suturing are evolving and may change the way the colorectal neoplasms are managed, blurring the boundaries between advanced endoscopy and surgery.

REFERENCES

- Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 2008; **103**: 1541-1549 [PMID: 18479499 DOI: 10.1111/j.1572-0241.2008.01875.x]
- Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, Church TR. Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013; **369**: 1106-1114 [PMID: 24047060 DOI: 10.1056/NEJMoa1300720]
- Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanás A, Andreu M, Carballo F, Morillas JD, Hernández C, Jover R, Montalvo I, Arenas J, Laredo E, Hernández V, Iglesias F, Cid E, Zubizarreta R, Sala T, Ponce M, Andrés M, Teruel G, Peris A, Roncales MP, Polo-Tomás M, Bessa X, Ferrer-Armengou O, Grau J, Serradesanferm A, Ono A, Cruzado J, Pérez-Riquelme F, Alonso-Abreu I, de la Vega-Prieto M, Reyes-Melian JM, Cacho G, Díaz-Tasende J, Herreros-de-Tejada A, Poves C, Santander C, González-Navarro A. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med* 2012; **366**: 697-706 [PMID: 22356323 DOI: 10.1056/NEJMoa1108895]
- Lim TR, Mahesh V, Singh S, Tan BH, Elsadig M, Radhakrishnan N, Conlong P, Babbs C, George R. Endoscopic mucosal resection of colorectal polyps in typical UK hospitals. *World J Gastroenterol* 2010; **16**: 5324-5328 [PMID: 21072895 DOI: 10.3748/wjg.v16.i42.5324]
- Heresbach D, Kornhauser R, Seyrig JA, Coumaros D, Claviere C, Bury A, Cottreau J, Canard JM, Chaussade S, Baudet A, Casteur A, Duval O, Ponchon T. A national survey of endoscopic mucosal resection for superficial gastrointestinal neoplasia. *Endoscopy* 2010; **42**: 806-813 [PMID: 20821362 DOI: 10.1055/s-0030-1255715]
- Luigiano C, Consolo P, Scaffidi MG, Strangio G, Giacobbe G, Alibrandi A, Pallio S, Tortora A, Melita G, Familiari L. Endoscopic mucosal resection for large and giant sessile and flat colorectal polyps: a single-center experience with long-term follow-up. *Endoscopy* 2009; **41**: 829-835 [PMID: 19750448 DOI: 10.1055/s-0029-1215091]
- Moss A, Bourke MJ, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, Zanati S, Chen RY, Byth K. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011; **140**: 1909-1918 [PMID: 21392504 DOI: 10.1053/j.gastro.2011.02.062]
- Conio M, Repici A, Demarquay JF, Bianchi S, Dumas R, Filiberti R. EMR of large sessile colorectal polyps. *Gastrointest Endosc* 2004; **60**: 234-241 [PMID: 15278051 DOI: 10.1016/S0016-5107(04)01567-6]
- Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. *Endoscopy* 2014; **46**: 388-402 [PMID: 24671869 DOI: 10.1055/s-0034-1364970]
- Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, Zanati S, Burgess NG, Sonson R, Byth K, Bourke MJ. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut* 2015; **64**: 57-65 [PMID: 24986245 DOI: 10.1136/gutjnl-2013-305516]
- Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Kudo SE, Tsuruta O, Sugihara K, Watanabe T, Saitoh Y, Igarashi M, Toyonaga T, Ajioka Y, Ichinose M, Matsui T, Sugita A, Sugano K, Fujimoto K, Tajiri H. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2015; **27**: 417-434 [PMID: 25652022 DOI: 10.1111/den.12456]
- Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D. A prospective, multicenter study of 1111 colorectal endoscopic submucosal

- dissections (with video). *Gastrointest Endosc* 2010; **72**: 1217-1225 [PMID: 21030017 DOI: 10.1016/j.gie.2010.08.004]
- 13 **Repici A**, Hassan C, De Paula Pessoa D, Pagano N, Arezzo A, Zullo A, Lorenzetti R, Marmo R. Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review. *Endoscopy* 2012; **44**: 137-150 [PMID: 22271024 DOI: 10.1055/s-0031-1291448]
 - 14 **Probst A**, Golger D, Anthuber M, Märkl B, Messmann H. Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. *Endoscopy* 2012; **44**: 660-667 [PMID: 22528673 DOI: 10.1055/s-0032-1309403]
 - 15 **Repici A**, Conio M, De Angelis C, Sapino A, Malesci A, Arezzo A, Hervoso C, Pellicano R, Comunale S, Rizzetto M. Insulated-tip knife endoscopic mucosal resection of large colorectal polyps unsuitable for standard polypectomy. *Am J Gastroenterol* 2007; **102**: 1617-1623 [PMID: 17403075 DOI: 10.1111/j.1572-0241.2007.01198.x]
 - 16 **Farhat S**, Chaussade S, Ponchon T, Coumaros D, Charachon A, Barrioz T, Koch S, Houcke P, Cellier C, Heresbach D, Lepilliez V, Napoleon B, Baret P, Coron E, Le Rhun M, Bichard P, Vaillant E, Calazel A, Bensoussan E, Bellon S, Mangialavori L, Robin F, Prat F. Endoscopic submucosal dissection in a European setting. A multi-institutional report of a technique in development. *Endoscopy* 2011; **43**: 664-670 [PMID: 21623560 DOI: 10.1055/s-0030-1256413]
 - 17 **Bourke M**. Current status of colonic endoscopic mucosal resection in the west and the interface with endoscopic submucosal dissection. *Dig Endosc* 2009; **21** Suppl 1: S22-S27 [PMID: 19691728 DOI: 10.1111/j.1443-1661.2009.00867.x]
 - 18 **Moss A**, Bourke MJ, Tran K, Godfrey C, McKay G, Chandra AP, Sharma S. Lesion isolation by circumferential submucosal incision prior to endoscopic mucosal resection (CSI-EMR) substantially improves en bloc resection rates for 40-mm colonic lesions. *Endoscopy* 2010; **42**: 400-404 [PMID: 20213591 DOI: 10.1055/s-0029-1243990]
 - 19 **Draganov PV**, Coman RM, Gotoda T. Training for complex endoscopic procedures: how to incorporate endoscopic submucosal dissection skills in the West? *Expert Rev Gastroenterol Hepatol* 2014; **8**: 119-121 [PMID: 24308749 DOI: 10.1586/17474124.2014.864552]
 - 20 **Repici A**, Hassan C, Pagano N, Rando G, Romeo F, Spaggiari P, Roncalli M, Ferrara E, Malesci A. High efficacy of endoscopic submucosal dissection for rectal laterally spreading tumors larger than 3 cm. *Gastrointest Endosc* 2013; **77**: 96-101 [PMID: 23261098 DOI: 10.1016/j.gie.2012.08.036]
 - 21 **Hülagü S**, Şentürk Ö, Korkmaz U, Şirin G, Duman AE, Dindar G, Çelebi A, Koç DÖ, Bozkurt N, Yılmaz H, Gürbüz Y, Duman D, Tarçın O. Endoscopic submucosal dissection for colorectal laterally spreading tumors. *Türk J Gastroenterol* 2013; **24**: 532-540 [PMID: 24623293]
 - 22 **Kakushima N**, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. *Endoscopy* 2006; **38**: 991-995 [PMID: 17058163 DOI: 10.1055/s-2006-944808]
 - 23 **Yamamoto S**, Uedo N, Ishihara R, Kajimoto N, Ogiyama H, Fukushima Y, Yamamoto S, Takeuchi Y, Higashino K, Iishi H, Tatsuta M. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* 2009; **41**: 923-928 [PMID: 19802773 DOI: 10.1055/s-0029-1215129]
 - 24 **Berr F**, Ponchon T, Neureiter D, Kiesslich T, Haringsma J, Kaehler GF, Schmoll F, Messmann H, Yahagi N, Oyama T. Experimental endoscopic submucosal dissection training in a porcine model: learning experience of skilled Western endoscopists. *Dig Endosc* 2011; **23**: 281-289 [PMID: 21951087 DOI: 10.1111/j.1443-1661.2011.01129.x]
 - 25 **Parra-Blanco A**, Gonzalez N, Arnau MR. Ex vivo and in vivo models for endoscopic submucosal dissection training. *Clin Endosc* 2012; **45**: 350-357 [PMID: 23251881 DOI: 10.5946/ce.2012.45.4.350]
 - 26 **Draganov PV**, Chang M, Coman RM, Wagh MS, An Q, Gotoda T. Role of observation of live cases done by Japanese experts in the acquisition of ESD skills by a western endoscopist. *World J Gastroenterol* 2014; **20**: 4675-4680 [PMID: 24782619 DOI: 10.3748/wjg.v20.i16.4675]
 - 27 **Herreros de Tejada A**. ESD training: A challenging path to excellence. *World J Gastrointest Endosc* 2014; **6**: 112-120 [PMID: 24748918 DOI: 10.4253/wjge.v6.i4.112]
 - 28 **Fujishiro M**, Jung HY, Goda K, Hirasawa K, Kakushima N, Lee IL, Morita Y, Oda I, Takeuchi M, Yamamoto Y, Zhou PH, Uedo N. Desirable training and roles of Japanese endoscopists towards the further penetration of endoscopic submucosal dissection in Asia. *Dig Endosc* 2012; **24** Suppl 1: 121-123 [PMID: 22533766 DOI: 10.1111/j.1443-1661.2012.01254.x]
 - 29 **Yamamoto Y**, Fujisaki J, Ishiyama A, Hirasawa T, Igarashi M. Current status of training for endoscopic submucosal dissection for gastric epithelial neoplasm at Cancer Institute Hospital, Japanese Foundation for Cancer Research, a famous Japanese hospital. *Dig Endosc* 2012; **24** Suppl 1: 148-153 [PMID: 22533772 DOI: 10.1111/j.1443-1661.2012.01278.x]
 - 30 **Oda I**, Odagaki T, Suzuki H, Nonaka S, Yoshinaga S. Learning curve for endoscopic submucosal dissection of early gastric cancer based on trainee experience. *Dig Endosc* 2012; **24** Suppl 1: 129-132 [PMID: 22533768 DOI: 10.1111/j.1443-1661.2012.01265.x]
 - 31 **Yoshida N**, Yagi N, Inada Y, Kugai M, Kamada K, Katada K, Uchiyama K, Ishikawa T, Takagi T, Handa O, Konishi H, Kokura S, Inoue K, Wakabayashi N, Abe Y, Yanagisawa A, Naito Y. Possibility of ex vivo animal training model for colorectal endoscopic submucosal dissection. *Int J Colorectal Dis* 2013; **28**: 49-56 [PMID: 22777001 DOI: 10.1007/s00384-012-1531-6]
 - 32 **Tsuji Y**, Ohata K, Sekiguchi M, Ito T, Chiba H, Gunji T, Yamamichi N, Fujishiro M, Matsuhashi N, Koike K. An effective training system for endoscopic submucosal dissection of gastric neoplasm. *Endoscopy* 2011; **43**: 1033-1038 [PMID: 22135195 DOI: 10.1055/s-0031-1291383]
 - 33 **Saito Y**, Otake Y, Sakamoto T, Nakajima T, Yamada M, Haruyama S, So E, Abe S, Matsuda T. Indications for and technical aspects of colorectal endoscopic submucosal dissection. *Gut Liver* 2013; **7**: 263-269 [PMID: 23710305 DOI: 10.5009/gnl.2013.7.3.263]
 - 34 **Uraoka T**, Kawahara Y, Kato J, Saito Y, Yamamoto K. Endoscopic submucosal dissection in the colorectum: present status and future prospects. *Dig Endosc* 2009; **21** Suppl 1: S13-S16 [PMID: 19691725 DOI: 10.1111/j.1443-1661.2009.00863.x]
 - 35 **Niimi K**, Fujishiro M, Goto O, Kodashima S, Koike K. Safety and efficacy of colorectal endoscopic submucosal dissection by the trainee endoscopists. *Dig Endosc* 2012; **24** Suppl 1: 154-158 [PMID: 22533773 DOI: 10.1111/j.1443-1661.2012.01251.x]
 - 36 **Sakamoto T**, Saito Y, Fukunaga S, Nakajima T, Matsuda T. Learning curve associated with colorectal endoscopic submucosal dissection for endoscopists experienced in gastric endoscopic submucosal dissection. *Dis Colon Rectum* 2011; **54**: 1307-1312 [PMID: 21904147 DOI: 10.1097/DCR.0b013e3182282ab0]
 - 37 **Shiga H**, Endo K, Kuroha M, Kakuta Y, Takahashi S, Kinouchi Y, Shimosegawa T. Endoscopic submucosal dissection for colorectal neoplasia during the clinical learning curve. *Surg Endosc* 2014; **28**: 2120-2128 [PMID: 24515262 DOI: 10.1007/s00464-014-3443-8]
 - 38 **Hotta K**, Oyama T, Shinohara T, Miyata Y, Takahashi A, Kitamura Y, Tomori A. Learning curve for endoscopic submucosal dissection of large colorectal tumors. *Dig Endosc* 2010; **22**: 302-306 [PMID: 21175483 DOI: 10.1111/j.1443-1661.2010.01005.x]
 - 39 **Berr F**, Wagner A, Kiesslich T, Friesenbichler P, Neureiter D. Untutored learning curve to establish endoscopic submucosal dissection on competence level. *Digestion* 2014; **89**: 184-193 [PMID: 24714421 DOI: 10.1159/000357805]
 - 40 **Deprez PH**, Bergman JJ, Meisner S, Ponchon T, Repici A, Dinis-Ribeiro M, Haringsma J. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. *Endoscopy* 2010; **42**: 853-858 [PMID: 20623442 DOI: 10.1055/s-0030-1255563]
 - 41 **Iacopini F**, Bella A, Costamagna G, Gotoda T, Saito Y, Elisei W, Grossi C, Rigato P, Scozzarro A. Stepwise training in rectal and

- colonic endoscopic submucosal dissection with differentiated learning curves. *Gastrointest Endosc* 2012; **76**: 1188-1196 [PMID: 23062760 DOI: 10.1016/j.gie.2012.08.024]
- 42 **Kaltenbach T**, Soetikno R, Kusano C, Gotoda T. Development of expertise in endoscopic mucosal resection and endoscopic submucosal dissection. *Tech Gastrointest Endosc* 2011; **13**: 100-104 [DOI: 10.1016/j.tgie.2011.01.013]
 - 43 **Hulagu S**, Senturk O, Aygun C, Kocaman O, Celebi A, Konduk T, Koc D, Sirin G, Korkmaz U, Duman AE, Bozkurt N, Dindar G, Attila T, Gurbuz Y, Tarcin O, Kalayci C. Endoscopic submucosal dissection for premalignant lesions and noninvasive early gastrointestinal cancers. *World J Gastroenterol* 2011; **17**: 1701-1709 [PMID: 21483630 DOI: 10.3748/wjg.v17.i13.1701]
 - 44 **Uraoka T**, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection: is it suitable in western countries? *J Gastroenterol Hepatol* 2013; **28**: 406-414 [PMID: 23278302 DOI: 10.1111/jgh.12099]
 - 45 **Kitajima K**, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004; **39**: 534-543 [PMID: 15235870 DOI: 10.1007/s00535-004-1339-4]
 - 46 **Uraoka T**, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592-1597 [PMID: 16682427 DOI: 10.1136/gut.2005.087452]
 - 47 **Kudo S**, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyu A. Colorectal tumours and pit pattern. *J Clin Pathol* 1994; **47**: 880-885 [PMID: 7962600]
 - 48 **Sano Y**, Ikematsu H, Fu KI, Emura F, Katagiri A, Horimatsu T, Kaneko K, Soetikno R, Yoshida S. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. *Gastrointest Endosc* 2009; **69**: 278-283 [PMID: 18951131 DOI: 10.1016/j.gie.2008.04.066]
 - 49 **Matsuda T**, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, Ikehara H, Ikematsu H, Fu KI, Emura F, Ono A, Sano Y, Shimoda T, Fujimori T. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. *Am J Gastroenterol* 2008; **103**: 2700-2706 [PMID: 18853968 DOI: 10.1111/j.1572-0241.2008.02190.x]
 - 50 **Ikematsu H**, Matsuda T, Emura F, Saito Y, Uraoka T, Fu KI, Kaneko K, Ochiai A, Fujimori T, Sano Y. Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. *BMC Gastroenterol* 2010; **10**: 33 [PMID: 20346170 DOI: 10.1186/1471-230X-10-33]
 - 51 **Hurlstone DP**, Hunter MD, Sanders DS, Thomson M, Cross SS. Olympus Lucera high-resolution vascular ectasia mapping in combination with the type V crypt pattern for the invasive depth estimation and nodal disease estimation in Paris type II colorectal cancers: a comparative prospective analysis to 20 MHz ultrasound. *J Clin Gastroenterol* 2007; **41**: 178-184 [PMID: 17245217 DOI: 10.1097/01.mcg.0000225679.06971.bb]
 - 52 **Pokala N**, Delaney CP, Kiran RP, Brady K, Senagore AJ. Outcome of laparoscopic colectomy for polyps not suitable for endoscopic resection. *Surg Endosc* 2007; **21**: 400-403 [PMID: 17180271 DOI: 10.1007/s00464-006-9069-8]
 - 53 **Brozovich M**, Read TE, Salgado J, Akbari RP, McCormick JT, Caushaj PF. Laparoscopic colectomy for apparently benign colorectal neoplasia: A word of caution. *Surg Endosc* 2008; **22**: 506-509 [PMID: 17704872 DOI: 10.1007/s00464-007-9497-0]
 - 54 **Dulskas A**, Samalavicius NE, Gupta RK, Zabulis V. Laparoscopic colorectal surgery for colorectal polyps: single institution experience. *Wideochir Inne Tech Maloinwazyjne* 2015; **10**: 73-78 [PMID: 25960797 DOI: 10.5114/wiitm.2015.49752]
 - 55 **Itah R**, Greenberg R, Nir S, Karin E, Skornick Y, Avital S. Laparoscopic surgery for colorectal polyps. *JSLS* 2009; **13**: 555-559 [PMID: 20202397 DOI: 10.4293/108680809X12589998404407]
 - 56 **Hurlstone DP**, Brown S, Cross SS, Shorthouse AJ, Sanders DS. High magnification chromoscopic colonoscopy or high frequency 20 MHz mini probe endoscopic ultrasound staging for early colorectal neoplasia: a comparative prospective analysis. *Gut* 2005; **54**: 1585-1589 [PMID: 15964906 DOI: 10.1136/gut.2005.069849]
 - 57 **Fu KI**, Kato S, Sano Y, Onuma EK, Saito Y, Matsuda T, Koba I, Yoshida S, Fujii T. Staging of early colorectal cancers: magnifying colonoscopy versus endoscopic ultrasonography for estimation of depth of invasion. *Dig Dis Sci* 2008; **53**: 1886-1892 [PMID: 18080834 DOI: 10.1007/s10620-007-0104-y]
 - 58 **Fernández-Esparrach G**, Calderón Á, De-la-Peña J, Díaz-Tasende JB, Esteban JM, Gimeno-García AZ, Herreros-de-Tejada A, Martínez-Ares D, Nicolás-Pérez D, Nogales Ó, Ono A, Orive-Calzada A, Parra-Blanco A, Rodríguez-Muñoz S, Sánchez-Hernández E, Sánchez-Yague A, Vázquez-Sequeiros E, Vila J, López-Rosés L. Endoscopic submucosal dissection. Sociedad Española de Endoscopia Digestiva (SEED) clinical guideline. *Rev Esp Enferm Dig* 2014; **106**: 120-132 [PMID: 24852737]
 - 59 **Morino M**, Risio M, Bach S, Beets-Tan R, Bujko K, Panis Y, Quirke P, Rembacken B, Rullier E, Saito Y, Young-Fadok T, Allaix ME. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. *Surg Endosc* 2015; **29**: 755-773 [PMID: 25609317 DOI: 10.1007/s00464-015-4067-3]
 - 60 **Niimi K**, Fujishiro M, Kodashima S, Goto O, Ono S, Hirano K, Minatsuki C, Yamamichi N, Koike K. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2010; **42**: 723-729 [PMID: 20806156 DOI: 10.1055/s-0030-1255675]
 - 61 **Shono T**, Ishikawa K, Ochiai Y, Nakao M, Togawa O, Nishimura M, Arai S, Nonaka K, Sasaki Y, Kita H. Feasibility of endoscopic submucosal dissection: a new technique for en bloc resection of a large superficial tumor in the colon and rectum. *Int J Surg Oncol* 2011; **2011**: 948293 [PMID: 22312533 DOI: 10.1155/2011/948293]
 - 62 **Iizuka H**, Okamura S, Onozato Y, Ishihara H, Kakizaki S, Mori M. Endoscopic submucosal dissection for colorectal tumors. *Gastroenterol Clin Biol* 2009; **33**: 1004-1011 [PMID: 19762190 DOI: 10.1016/j.gcb.2009.02.039]
 - 63 **Fujishiro M**, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Endoscopic submucosal dissection for rectal epithelial neoplasia. *Endoscopy* 2006; **38**: 493-497 [PMID: 16767585 DOI: 10.1055/s-2006-925398]
 - 64 **Tamegai Y**, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E, Liu Y, Uemura N, Saito K. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418-422 [PMID: 17516348 DOI: 10.1055/s-2007-966427]
 - 65 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973 [PMID: 17524403 DOI: 10.1016/j.gie.2007.02.053]
 - 66 **Sakamoto T**, Sato C, Makazu M, Sekiguchi M, Mori G, Yamada M, Kinjo Y, Turuki E, Abe S, Otake Y, Nakajima T, Matsuda T, Saito Y. Short-term outcomes of colorectal endoscopic submucosal dissection performed by trainees. *Digestion* 2014; **89**: 37-42 [PMID: 24458111 DOI: 10.1159/000356215]
 - 67 **Rahmi G**, Tanaka S, Ohara Y, Ishida T, Yoshizaki T, Morita Y, Toyonaga T, Azuma T. Efficacy of endoscopic submucosal dissection for residual or recurrent superficial colorectal tumors after endoscopic mucosal resection. *J Dig Dis* 2015; **16**: 14-21 [PMID: 25366265 DOI: 10.1111/1751-2980.12207]
 - 68 **Tanaka S**, Oka S, Kaneko I, Hirata M, Mouri R, Kanao H, Yoshida S, Chayama K. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc* 2007; **66**: 100-107 [PMID: 17591481 DOI: 10.1016/j.gie.2007.02.032]
 - 69 **Sakamoto T**, Takamaru H, Mori G, Yamada M, Kinjo Y, So E, Abe S, Otake Y, Nakajima T, Matsuda T, Saito Y. Endoscopic submucosal dissection for colorectal neoplasms. *Ann Transl Med*

- 2014; **2**: 26 [PMID: 25333002 DOI: 10.3978/j.issn.2305-5839.2014.03.02]
- 70 **Hurlstone DP**, Atkinson R, Sanders DS, Thomson M, Cross SS, Brown S. Achieving R0 resection in the colorectum using endoscopic submucosal dissection. *Br J Surg* 2007; **94**: 1536-1542 [PMID: 17948864 DOI: 10.1002/bjs.5720]
- 71 **Okamoto K**, Kitamura S, Muguruma N, Takaoka T, Fujino Y, Kawahara Y, Okahisa T, Takayama T. Mucosectomy2-short blade for safe and efficient endoscopic submucosal dissection of colorectal tumors. *Endoscopy* 2013; **45**: 928-930 [PMID: 24019129 DOI: 10.1055/s-0033-1344644]
- 72 **Lee EJ**, Lee JB, Lee SH, Kim do S, Lee DH, Lee DS, Youk EG. Endoscopic submucosal dissection for colorectal tumors--1,000 colorectal ESD cases: one specialized institute's experiences. *Surg Endosc* 2013; **27**: 31-39 [PMID: 22729707 DOI: 10.1007/s00464-012-2403-4]
- 73 **Kobayashi N**, Yoshitake N, Hirahara Y, Konishi J, Saito Y, Matsuda T, Ishikawa T, Sekiguchi R, Fujimori T. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. *J Gastroenterol Hepatol* 2012; **27**: 728-733 [PMID: 22004124 DOI: 10.1111/j.1440-1746.2011.06942.x]
- 74 **Tomiki Y**, Kawai M, Takehara K, Tashiro Y, Munakata S, Kure K, Ishiyama S, Sugimoto K, Kamiyama H, Takahashi M, Sakamoto K. Clinical pathway to discharge 3 days after colorectal endoscopic submucosal dissection. *Dig Endosc* 2015; **27**: 679-686 [PMID: 25756606 DOI: 10.1111/den.12468]
- 75 **Lee BI**. Debates on colorectal endoscopic submucosal dissection - traction for effective dissection: gravity is enough. *Clin Endosc* 2013; **46**: 467-471 [PMID: 24143304 DOI: 10.5946/ce.2013.46.5.467]
- 76 **Saito Y**, Emura F, Matsuda T, Uraoka T, Nakajima T, Ikematsu H, Gotoda T, Saito D, Fujii T. A new sinker-assisted endoscopic submucosal dissection for colorectal cancer. *Gastrointest Endosc* 2005; **62**: 297-301 [PMID: 16046999 DOI: 10.1016/S0016-5107(05)00546-8]
- 77 **Sakamoto N**, Osada T, Shibuya T, Beppu K, Matsumoto K, Mori H, Kawabe M, Nagahara A, Otaka M, Ogihara T, Watanabe S. Endoscopic submucosal dissection of large colorectal tumors by using a novel spring-action S-O clip for traction (with video). *Gastrointest Endosc* 2009; **69**: 1370-1374 [PMID: 19403131 DOI: 10.1016/j.gie.2008.12.245]
- 78 **Uraoka T**, Ishikawa S, Kato J, Higashi R, Suzuki H, Kaji E, Kuriyama M, Saito S, Akita M, Hori K, Harada K, Ishiyama S, Shiode J, Kawahara Y, Yamamoto K. Advantages of using thin endoscope-assisted endoscopic submucosal dissection technique for large colorectal tumors. *Dig Endosc* 2010; **22**: 186-191 [PMID: 20642607 DOI: 10.1111/j.1443-1661.2010.00992.x]
- 79 **Yamamoto K**, Hayashi S, Saiki H, Indo N, Nakabori T, Yamamoto M, Shibuya M, Nishida T, Ichiba M, Inada M. Endoscopic submucosal dissection for large superficial colorectal tumors using the "clip-flap method". *Endoscopy* 2015; **47**: 262-265 [PMID: 25412089 DOI: 10.1055/s-0034-1390739]
- 80 **Nakajima T**, Saito Y, Tanaka S, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisasbe T, Matsuda T, Ishikawa H, Sugihara K. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. *Surg Endosc* 2013; **27**: 3262-3270 [PMID: 23508817 DOI: 10.1007/s00464-013-2903-x]
- 81 **Saito Y**, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg Endosc* 2010; **24**: 343-352 [PMID: 19517168 DOI: 10.1007/s00464-009-0562-8]
- 82 **Tajika M**, Niwa Y, Bhatia V, Kondo S, Tanaka T, Mizuno N, Hara K, Hijioka S, Imaoka H, Ogura T, Haba S, Yamao K. Comparison of endoscopic submucosal dissection and endoscopic mucosal resection for large colorectal tumors. *Eur J Gastroenterol Hepatol* 2011; **23**: 1042-1049 [PMID: 21869682 DOI: 10.1097/MEG.0b013e32834aa47b]
- 83 **Terasaki M**, Tanaka S, Oka S, Nakadoi K, Takata S, Kanao H, Yoshida S, Chayama K. Clinical outcomes of endoscopic submucosal dissection and endoscopic mucosal resection for laterally spreading tumors larger than 20 mm. *J Gastroenterol Hepatol* 2012; **27**: 734-740 [PMID: 22098630 DOI: 10.1111/j.1440-1746.2011.06977.x]
- 84 **Lee EJ**, Lee JB, Lee SH, Youk EG. Endoscopic treatment of large colorectal tumors: comparison of endoscopic mucosal resection, endoscopic mucosal resection-precutting, and endoscopic submucosal dissection. *Surg Endosc* 2012; **26**: 2220-2230 [PMID: 22278105 DOI: 10.1007/s00464-012-2164-0]
- 85 **Kim YJ**, Kim ES, Cho KB, Park KS, Jang BK, Chung WJ, Hwang JS. Comparison of clinical outcomes among different endoscopic resection methods for treating colorectal neoplasia. *Dig Dis Sci* 2013; **58**: 1727-1736 [PMID: 23385636 DOI: 10.1007/s10620-013-2560-x]
- 86 **Sakamoto T**, Saito Y, Matsuda T, Fukunaga S, Nakajima T, Fujii T. Treatment strategy for recurrent or residual colorectal tumors after endoscopic resection. *Surg Endosc* 2011; **25**: 255-260 [PMID: 20559661 DOI: 10.1007/s00464-010-1169-9]
- 87 **Kim HG**, Thosani N, Banerjee S, Chen A, Friedland S. Underwater endoscopic mucosal resection for recurrences after previous piecemeal resection of colorectal polyps (with video). *Gastrointest Endosc* 2014; **80**: 1094-1102 [PMID: 25012560 DOI: 10.1016/j.gie.2014.05.318]
- 88 **Spanjersberg WR**, van Sambeek JD, Bremers A, Rosman C, van Laarhoven CJ. Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme. *Surg Endosc* 2015; **29**: 3443-3453 [PMID: 25801106 DOI: 10.1007/s00464-015-4148-3]
- 89 **Kennedy RH**, Francis A, Dutton S, Love S, Pearson S, Blazeby JM, Quirke P, Franks PJ, Kerr DJ. EnROL: a multicentre randomised trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme. *BMC Cancer* 2012; **12**: 181 [PMID: 22591460 DOI: 10.1186/1471-2407-12-181]
- 90 **Kiriya S**, Saito Y, Yamamoto S, Soetikno R, Matsuda T, Nakajima T, Kuwano H. Comparison of endoscopic submucosal dissection with laparoscopic-assisted colorectal surgery for early-stage colorectal cancer: a retrospective analysis. *Endoscopy* 2012; **44**: 1024-1030 [PMID: 23012216 DOI: 10.1055/s-0032-1310259]
- 91 **Nakamura F**, Saito Y, Sakamoto T, Otake Y, Nakajima T, Yamamoto S, Murakami Y, Ishikawa H, Matsuda T. Potential perioperative advantage of colorectal endoscopic submucosal dissection versus laparoscopy-assisted colectomy. *Surg Endosc* 2015; **29**: 596-606 [PMID: 25037724 DOI: 10.1007/s00464-014-3705-5]
- 92 **Wilson MZ**, Hollenbeak CS, Stewart DB. Laparoscopic colectomy is associated with a lower incidence of postoperative complications than open colectomy: a propensity score-matched cohort analysis. *Colorectal Dis* 2014; **16**: 382-389 [PMID: 24373345 DOI: 10.1111/codi.12537]
- 93 **Iroautalam AJ**, Chen HH, Potenti FM, Parameswaran S, Wexner SD. Laparoscopic colectomy yields similar morbidity and disability regardless of patient age. *Int J Colorectal Dis* 1999; **14**: 155-157 [PMID: 10460906]
- 94 **Chen HH**, Wexner SD, Weiss EG, Nogueras JJ, Alabaz O, Iroautalam AJ, Nessim A, Joo JS. Laparoscopic colectomy for benign colorectal disease is associated with a significant reduction in disability as compared with laparotomy. *Surg Endosc* 1998; **12**: 1397-1400 [PMID: 9822465]
- 95 **Demartines N**, von Flüe MO, Harder FH. Transanal endoscopic microsurgical excision of rectal tumors: indications and results. *World J Surg* 2001; **25**: 870-875 [PMID: 11572026]
- 96 **Buess G**, Kipfmüller K, Hack D, Grüssner R, Heintz A, Junginger T. Technique of transanal endoscopic microsurgery. *Surg Endosc* 1988; **2**: 71-75 [PMID: 3413659]
- 97 **Moore JS**, Cataldo PA, Osler T, Hyman NH. Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. *Dis Colon Rectum* 2008; **51**: 1026-1030 [PMID: 18481147 DOI: 10.1007/s10350-008-9337-x]
- 98 **Allaix ME**, Arezzo A, Cassoni P, Famiglietti F, Morino M. Recurrence after transanal endoscopic microsurgery for large rectal

- adenomas. *Surg Endosc* 2012; **26**: 2594-2600 [PMID: 22476837 DOI: 10.1007/s00464-012-2238-z]
- 99 **Middleton PF**, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. *Dis Colon Rectum* 2005; **48**: 270-284 [PMID: 15711865 DOI: 10.1007/s10350-004-0804-8]
 - 100 **Koebrugge B**, Bosscha K, Ernst MF. Transanal endoscopic microsurgery for local excision of rectal lesions: is there a learning curve? *Dig Surg* 2009; **26**: 372-377 [PMID: 19923824 DOI: 10.1159/000257228]
 - 101 **Arezzo A**, Passera R, Saito Y, Sakamoto T, Kobayashi N, Sakamoto N, Yoshida N, Naito Y, Fujishiro M, Niimi K, Ohya T, Ohata K, Okamura S, Iizuka S, Takeuchi Y, Uedo N, Fusaroli P, Bonino MA, Verra M, Morino M. Systematic review and meta-analysis of endoscopic submucosal dissection versus transanal endoscopic microsurgery for large noninvasive rectal lesions. *Surg Endosc* 2014; **28**: 427-438 [PMID: 24149849 DOI: 10.1007/s00464-013-3238-3]
 - 102 **Kawaguti FS**, Nahas CS, Marques CF, Martins BC, Retes FA, Medeiros RS, Hayashi T, Wada Y, de Lima MS, Uemura RS, Nahas SC, Kudo SE, Maluf-Filho F. Endoscopic submucosal dissection versus transanal endoscopic microsurgery for the treatment of early rectal cancer. *Surg Endosc* 2014; **28**: 1173-1179 [PMID: 24232053 DOI: 10.1007/s00464-013-3302-z]
 - 103 **Park SU**, Min YW, Shin JU, Choi JH, Kim YH, Kim JJ, Cho YB, Kim HC, Yun SH, Lee WY, Chun HK, Chang DK. Endoscopic submucosal dissection or transanal endoscopic microsurgery for nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer. *Endoscopy* 2012; **44**: 1031-1036 [PMID: 23012217 DOI: 10.1055/s-0032-1310015]
 - 104 **Barendse RM**, van den Broek FJ, van Schooten J, Bemelman WA, Fockens P, de Graaf EJ, Dekker E. Endoscopic mucosal resection vs transanal endoscopic microsurgery for the treatment of large rectal adenomas. *Colorectal Dis* 2012; **14**: e191-e196 [PMID: 22023493 DOI: 10.1111/j.1463-1318.2011.02863.x]
 - 105 **Darwood RJ**, Wheeler JM, Borley NR. Transanal endoscopic microsurgery is a safe and reliable technique even for complex rectal lesions. *Br J Surg* 2008; **95**: 915-918 [PMID: 18496889 DOI: 10.1002/bjs.6018]
 - 106 **Mihai R**, Borley N. Transanal endoscopic microsurgery--impact on the practice of a colorectal surgeon in a district general hospital. *Ann R Coll Surg Engl* 2005; **87**: 432-436 [PMID: 16263010 DOI: 10.1308/003588405x51083]
 - 107 **Maglio R**, Muzi GM, Massimo MM, Masoni L. Transanal minimally invasive surgery (TAMIS): new treatment for early rectal cancer and large rectal polyps-experience of an Italian center. *Am Surg* 2015; **81**: 273-277 [PMID: 25760203]
 - 108 **Wright CJ**, Tutton M. Early discharge following transanal endoscopic microsurgery is safe. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 399-402 [PMID: 24720502 DOI: 10.1089/lap.2013.0258]
 - 109 **Saito Y**, Yamada M, So E, Abe S, Sakamoto T, Nakajima T, Otake Y, Ono A, Matsuda T. Colorectal endoscopic submucosal dissection: Technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. *Dig Endosc* 2014; **26** Suppl 1: 52-61 [PMID: 24191896 DOI: 10.1111/den.12196]
 - 110 **Fujihara S**, Mori H, Kobara H, Nishiyama N, Matsunaga T, Ayaki M, Yachida T, Morishita A, Izuishi K, Masaki T. Current innovations in endoscopic therapy for the management of colorectal cancer: from endoscopic submucosal dissection to endoscopic full-thickness resection. *Biomed Res Int* 2014; **2014**: 925058 [PMID: 24877148 DOI: 10.1155/2014/925058]
 - 111 **Schmidt A**, Bauerfeind P, Gubler C, Damm M, Bauder M, Caca K. Endoscopic full-thickness resection in the colorectum with a novel over-the-scope device: first experience. *Endoscopy* 2015; **47**: 719-725 [PMID: 25763833 DOI: 10.1055/s-0034-1391781]
 - 112 **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin Gastroenterol Hepatol* 2007; **5**: 678-683; quiz 645 [PMID: 17466600 DOI: 10.1016/j.cgh.2007.01.006]
 - 113 **Zhou PH**, Yao LQ, Qin XY. Endoscopic submucosal dissection for colorectal epithelial neoplasm. *Surg Endosc* 2009; **23**: 1546-1551 [PMID: 19263116 DOI: 10.1007/s00464-009-0395-5]
 - 114 **Isomoto H**, Nishiyama H, Yamaguchi N, Fukuda E, Ishii H, Ikeda K, Ohnita K, Nakao K, Kohno S, Shikuwa S. Clinicopathological factors associated with clinical outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2009; **41**: 679-683 [PMID: 19670135 DOI: 10.1055/s-0029-1214979]
 - 115 **Saito Y**, Sakamoto T, Fukunaga S, Nakajima T, Kiriya S, Matsuda T. Endoscopic submucosal dissection (ESD) for colorectal tumors. *Dig Endosc* 2009; **21** Suppl 1: S7-12 [PMID: 19691740 DOI: 10.1111/j.1443-1661.2009.00870.x]
 - 116 **Yoshida N**, Naito Y, Kugai M, Inoue K, Wakabayashi N, Yagi N, Yanagisawa A, Yoshikawa T. Efficient hemostatic method for endoscopic submucosal dissection of colorectal tumors. *World J Gastroenterol* 2010; **16**: 4180-4186 [PMID: 20806436 DOI: 10.3748/wjg.v16.i33.4180]
 - 117 **Toyonaga T**, Man-i M, Fujita T, East JE, Nishino E, Ono W, Morita Y, Sanuki T, Yoshida M, Kutsumi H, Inokuchi H, Azuma T. Retrospective study of technical aspects and complications of endoscopic submucosal dissection for laterally spreading tumors of the colorectum. *Endoscopy* 2010; **42**: 714-722 [PMID: 20806155 DOI: 10.1055/s-0030-1255654]
 - 118 **Matsumoto A**, Tanaka S, Oba S, Kanao H, Oka S, Yoshihara M, Chayama K. Outcome of endoscopic submucosal dissection for colorectal tumors accompanied by fibrosis. *Scand J Gastroenterol* 2010; **45**: 1329-1337 [PMID: 20626303 DOI: 10.3109/00365521.2010.495416]
 - 119 **Uraoka T**, Higashi R, Kato J, Kaji E, Suzuki H, Ishikawa S, Akita M, Hirakawa T, Saito S, Hori K, Kawahara Y, Mead RJ, Yamamoto K. Colorectal endoscopic submucosal dissection for elderly patients at least 80 years of age. *Surg Endosc* 2011; **25**: 3000-3007 [PMID: 21484532 DOI: 10.1007/s00464-011-1660-y]
 - 120 **Kim ES**, Cho KB, Park KS, Lee KI, Jang BK, Chung WJ, Hwang JS. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. *Endoscopy* 2011; **43**: 573-578 [PMID: 21448852 DOI: 10.1055/s-0030-1256339]
 - 121 **Lee EJ**, Lee JB, Choi YS, Lee SH, Lee DH, Kim do S, Youk EG. Clinical risk factors for perforation during endoscopic submucosal dissection (ESD) for large-sized, nonpedunculated colorectal tumors. *Surg Endosc* 2012; **26**: 1587-1594 [PMID: 22179462 DOI: 10.1007/s00464-011-2075-5]
 - 122 **Hisabe T**, Nagahama T, Hirai F, Matsui T, Iwashita A. Clinical outcomes of 200 colorectal endoscopic submucosal dissections. *Dig Endosc* 2012; **24** Suppl 1: 105-109 [PMID: 22533763 DOI: 10.1111/j.1443-1661.2012.01267.x]
 - 123 **Saito Y**, Kawano H, Takeuchi Y, Ohata K, Oka S, Hotta K, Okamoto K, Homma K, Uraoka T, Hisabe T, Chang DK, Zhou PH. Current status of colorectal endoscopic submucosal dissection in Japan and other Asian countries: progressing towards technical standardization. *Dig Endosc* 2012; **24** Suppl 1: 67-72 [PMID: 22533756 DOI: 10.1111/j.1443-1661.2012.01282.x]
 - 124 **Nawata Y**, Homma K, Suzuki Y. Retrospective study of technical aspects and complications of endoscopic submucosal dissection for large superficial colorectal tumors. *Dig Endosc* 2014; **26**: 552-555 [PMID: 24405078 DOI: 10.1111/den.12217]
 - 125 **Lee SP**, Kim JH, Sung IK, Lee SY, Park HS, Shim CS, Han HS. Effect of submucosal fibrosis on endoscopic submucosal dissection of colorectal tumors: pathologic review of 173 cases. *J Gastroenterol Hepatol* 2015; **30**: 872-878 [PMID: 25641510 DOI: 10.1111/jgh.12886]
 - 126 **Thorlacius H**, Uedo N, Toth E. Implementation of endoscopic submucosal dissection for early colorectal neoplasms in Sweden. *Gastroenterol Res Pract* 2013; **2013**: 758202 [PMID: 23935611 DOI: 10.1155/2013/758202]
 - 127 **Spychalski M**, Dziki A. Safe and efficient colorectal endoscopic submucosal dissection in European settings: is successful implementation of the procedure possible? *Dig Endosc* 2015; **27**: 368-373 [PMID: 25181427 DOI: 10.1111/den.12353]
 - 128 **Rahmi G**, Hotayt B, Chaussade S, Lepilliez V, Giovannini M,

Coumaros D, Charachon A, Cholet F, Laquière A, Samaha E, Prat F, Ponchon T, Bories E, Robaszkiewicz M, Boustière C, Cellier C. Endoscopic submucosal dissection for superficial rectal tumors: prospective evaluation in France. *Endoscopy* 2014; **46**: 670-676 [PMID: 24977400 DOI: 10.1055/s-0034-1365810]

129 **Bialek A**, Pertkiewicz J, Karpińska K, Marlicz W, Bielicki D, Starzyńska T. Treatment of large colorectal neoplasms by endoscopic submucosal dissection: a European single-center study. *Eur J Gastroenterol Hepatol* 2014; **26**: 607-615 [PMID: 24743502 DOI: 10.1097/MEG.0000000000000079]

P- Reviewer: Friedland S **S- Editor:** Ji FF **L- Editor:** A
E- Editor: Lu YJ



2016 Laparoscopic Surgery: Global view

Laparoscopic esophagomyotomy for achalasia in children: A review

T Kumar Pandian, Nimesh D Naik, Aodhnait S Fahy, Arman Arghami, David R Farley, Michael B Ishitani, Christopher R Moir

T Kumar Pandian, Nimesh D Naik, Aodhnait S Fahy, Arman Arghami, David R Farley, Division of Subspecialty General Surgery, Department of Surgery, Mayo Clinic, Rochester, MN 55905, United States

Arman Arghami, Division of Cardiothoracic Surgery, Department of Surgery, Mayo Clinic, Rochester, MN 55905, United States

Michael B Ishitani, Christopher R Moir, Division of Pediatric Surgery, Department of Surgery, Mayo Clinic, Rochester, MN 55905, United States

Author contributions: Pandian TK conceptualized the paper, conducted the literature search and content development; Naik ND, Fahy AS and Arghami A conducted the literature search and content development; Moir CR served as senior author and oversaw content development; all authors were involved in manuscript development and revision; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts-of-interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: David R Farley, MD, FACS, Division of Subspecialty General Surgery, Department of Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. farley.david@mayo.edu
Telephone: +1-507-2842644
Fax: +1-507-2845196

Received: April 28, 2015
Peer-review started: May 6, 2015
First decision: September 8, 2015

Revised: September 28, 2015

Accepted: November 13, 2015

Article in press: November 17, 2015

Published online: January 25, 2016

Abstract

Esophageal achalasia in children is rare but ultimately requires endoscopic or surgical treatment. Historically, Heller esophagomyotomy has been recommended as the treatment of choice. The refinement of minimally invasive techniques has shifted the trend of treatment toward laparoscopic Heller myotomy (LHM) in adults and children with achalasia. A review of the available literature on LHM performed in patients < 18 years of age was conducted. The pediatric LHM experience is limited to one multi-institutional and several single-institutional retrospective studies. Available data suggest that LHM is safe and effective. There is a paucity of evidence on the need for and superiority of concurrent antireflux procedures. In addition, a more complete portrayal of complications and long-term (> 5 years) outcomes is needed. Due to the infrequency of achalasia in children, these characteristics are unlikely to be defined without collaboration between multiple pediatric surgery centers. The introduction of peroral endoscopic myotomy and single-incision techniques, continue the trend of innovative approaches that may eventually become the standard of care.

Key words: Achalasia; Esophagomyotomy; Laparoscopy; Heller myotomy; Outcomes

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Laparoscopic Heller myotomy (LHM) is safe and effective in the pediatric achalasia population. Published studies are limited by their retrospective nature and small

sample sizes. Further information regarding the need for and type of concurrent fundoplication, a more complete description of complications, and long-term (> 5 years) outcomes is needed. Peroral endoscopic myotomy and the single-incision approach are innovative techniques that may eventually prove to be the standard of care. Herein, we review the available literature on LHM in children with achalasia.

Pandian TK, Naik ND, Fahy AS, Arghami A, Farley DR, Ishitani MB, Moir CR. Laparoscopic esophagomyotomy for achalasia in children: A review. *World J Gastrointest Endosc* 2016; 8(2): 56-66 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/56.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.56>

INTRODUCTION

Achalasia overview and diagnosis

Achalasia is a motility disorder characterized by abnormal esophageal peristalsis and partial or complete failure of the lower esophageal sphincter (LES) to relax during deglutition. The condition was first described in 1674 by physician and neuroanatomist Sir Thomas Willis of England^[1,2]. It is an uncommon diagnosis with an overall incidence of 1.6 per 100000 individuals^[3]. Less than 5% of patients present under the age of 15^[4,5]; the childhood incidence is only 0.11 per 100000^[6]. The etiology of achalasia is not fully understood but it may result from degeneration of neurons in the esophageal wall^[1,7]. Associations with Down syndrome and Chagas disease have been described^[8]. Between 0.5% and 7% of children with Down syndrome have been found to have achalasia^[8,9]. Children with the autosomal recessive Allgrove syndrome (triple A syndrome) suffer from alacrima, achalasia, ACTH-insufficiency, autonomic dysfunction, and neurodegeneration^[10]. These patients initially present with alacrima but achalasia is generally the first symptom which prompts pursuit of medical attention and diagnosis^[11].

Clinical suspicion for achalasia should be raised in children with dysphagia to solids and liquids and regurgitation of undigested food or saliva^[12]. Symptoms may progress to chest pain, emesis, aspiration, weight loss, and failure to thrive^[8]. Table 1 summarizes common symptoms and associated conditions of achalasia in children. Manometry is the most sensitive diagnostic tool^[13] characterizing incomplete or complete absence of LES relaxation with concurrent distal esophageal aperistalsis. For patients with equivocal motility testing, a barium esophagram will reveal a proximally dilated esophagus with distal tapering (Figure 1), the classic "bird-beak" appearance^[14]. An abnormal esophagram should be followed by upper endoscopy, to rule out a structural abnormality such as a Schatzki ring or congenital cartilaginous stricture^[15]. Newer methodologies for diagnosis include high-resolution manometry (HRM)

and multichannel intraluminal impedance pH monitoring (MII-pH); both of which can offer additional physiological details in diagnostic dilemmas^[16]. Specifically, HRM can plot the pressure generated by the esophagus, creating a topographical map which allows classification of achalasia into additional subtypes (I - III)^[16]. This information can then be used to provide tailored treatment. Using a series of electrodes, MII-pH can measure the intraluminal impedance of a food bolus^[16]. In general, HRM and MII-pH are not necessary if manometry is diagnostic.

Achalasia treatment overview

Treatment options for achalasia include pharmacological, endoscopic, or surgical methods. The primary goal is to decrease the pressure gradient across the LES. Calcium channel blockers are the most common pharmacological agents but their use in children is discouraged due to short-term effectiveness and concerning side effects^[16-19].

Few reports focus on the endoscopic injection of botulinum toxin for achalasia in the pediatric population; however available data suggest the duration of therapeutic effect is short-lived and may be beneficial as a bridge to more definitive treatment modalities^[16,20-22]. Randomized controlled trials (RCT) in adults confirm that laparoscopic surgical esophagomyotomy (Heller myotomy, LHM) is as safe, more durable^[23], and similar in cost long-term^[24], than injection of botulinum toxin.

Endoscopic pneumatic dilation (EPD) for achalasia in children has been described for many decades. Older reports identified favorable efficacy and durability^[4,25-29] as the reason for EPD as the initial procedure of choice^[4,27-30]. More recent literature with longer follow-up is mixed; some data suggest high rates of symptom recurrence necessitating repeat EPD^[17,31], while one study found an 87% overall 6-year success rate^[32] in children. In adults, a 2011 RCT reported equivalent therapeutic success of LHM and EPD at 2 years^[33]. Recent meta-analyses however, established that LHM results in few adverse events and higher rates of response compared to EPD^[34] and all other treatments^[35].

Based on the aforementioned literature, it is clear that randomized trials are needed to differentiate the effectiveness and resilience of EPD and LHM in children. Despite the lack of conclusive evidence, refinement of laparoscopic techniques in pediatrics, low complication rates associated with LHM, and high rates of success have shifted treatment preferences toward LHM^[17]. Herein, we aim to provide an overview of laparoscopic esophagomyotomy for achalasia in children and examine the current literature on this procedure.

PROCEDURE DETAILS

Evolution from open to laparoscopic esophagomyotomy

Heller *et al.*^[36] performed the first esophagomyotomy in 1913 via an open transabdominal approach and completed anterior and posterior myotomies on the distal esophagus (Figure 2A). The operation has undergone gradual modification including restriction to only an anterior

Table 1 Achalasia symptoms and associated conditions in children

Symptoms
Progressive dysphagia
Vomiting
Weight loss
Regurgitation
Aspiration
Chest pain
Failure to thrive
Associated conditions
Allgrove syndrome (triple A syndrome)
Down syndrome
Chagas disease

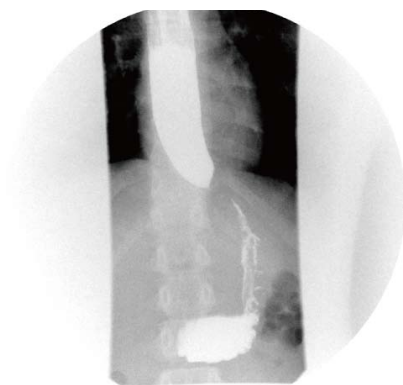


Figure 1 “Bird-beak” esophagram. Barium esophagram of a 16-year-old male demonstrating a dilated proximal esophagus with smooth tapering distally; findings consistent with achalasia.

myotomy^[37], either a transthoracic or transabdominal approach^[38], and the addition of antireflux procedures to the transabdominal method^[39]. However, the past three decades have witnessed the development of minimally invasive (MIS) approaches that have led to significant change in the management of achalasia in adult and pediatric patients. The first minimally invasive Heller myotomy (MIS-HM) was performed by Shimi *et al*^[40] via laparoscopy in 1991 on a 30-year-old female. This patient was discharged on postoperative day (POD) #3 and was symptom-free at 3 mo. Pellegrini *et al*^[41], then adapted the procedure for a thoracoscopic approach (THM) and this was well tolerated in 17 patients, with two conversions to open for mucosal lacerations. Dysphagia did not improve in the initial 3 patients however follow-up surgery extended the myotomies distally with favorable results. Originally, THM was the MIS procedure of choice and only patients with previous myotomies or thoracotomies underwent a laparoscopic operation^[42]. However, in the mid-1990s, groups began comparing THM and LHM and indicated that LHM with partial fundoplication led to reduced perioperative pain, shorter length of stays (LOS), less conversions to open procedures, improved relief of dysphagia and lower incidence of postoperative reflux^[43]. The risk of an incomplete myotomy with THM^[44], as well as the addition of an antireflux fundoplication by laparoscopy^[45,46] were

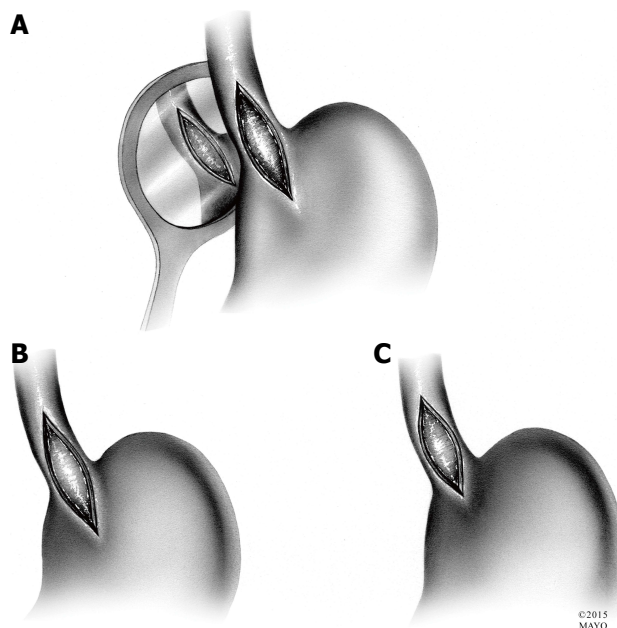


Figure 2 Esophageal myotomies. A: The original Heller myotomy, consisting of both anterior and posterior disruption of esophageal fibers; B: The most commonly performed Heller myotomy, with extension onto the stomach for 2-3 cm; C: Heller myotomy with minimal extension onto the stomach.

two key features that led to LHM gradually becoming the standard of care^[47].

Operative steps for esophagomyotomy

Some surgeons prefer that patients are limited to a liquid diet for 1-2 d preoperatively to minimize the amount of debris in the esophagus^[48]. After induction of general anesthesia, we perform esophageal suctioning prior to intubation to prevent the risk of aspiration. Patients are positioned in a modified lithotomy position and secured to the operating table such that there is low risk of slippage when placed in steep reverse Trendelenburg. An orogastric tube is placed and the surgeon stands between the legs of the patient (Figure 3). A total of 4-5 trocars are placed and similarly positioned as in an antireflux procedure (Figure 4). In adults, the port immediately cephalad to the umbilicus is typically used for the camera (30° laparoscope), whereas a transumbilical location is preferred in children. The remaining ports are utilized for retraction, dissection, and laparoscopic suturing. The size, location and role of each port is based on the child's size and body habitus as well as surgeon preference^[16,48-52].

Once pneumoperitoneum is established and all ports are placed, the operation is begun by cephalad retraction of the liver and incision of the gastro-hepatic ligament to identify the right crus of the diaphragm (Figure 5). The peritoneum and phrenoesophageal membrane are divided and dissection is carried across the anterior midline to identify the left diaphragmatic crus. Dissection is continued cephalad, staying anterior and lateral to expose 6-7 cm of the lower thoracic and abdominal esophagus. Care must be taken to identify and preserve the anterior and posterior vagus nerves.

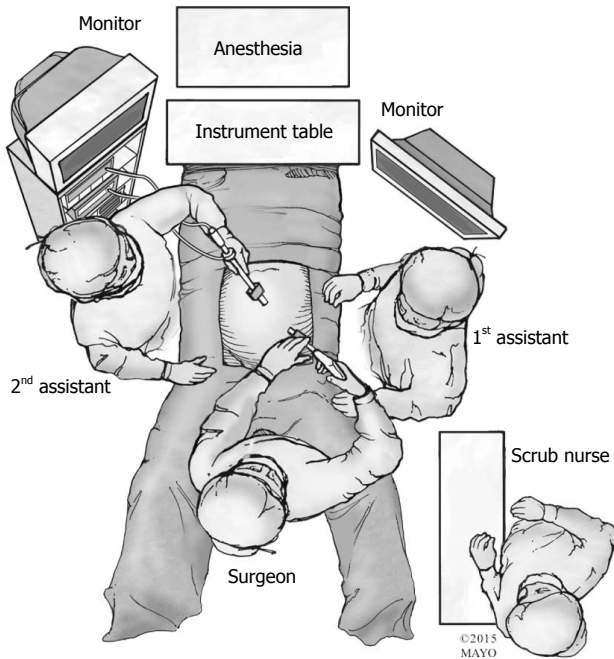


Figure 3 Patient positioning and operating room setup. The patient is placed in the modified lithotomy position and the surgeon stands between the patient's legs. First and second assistants are to the right and left of the patient.

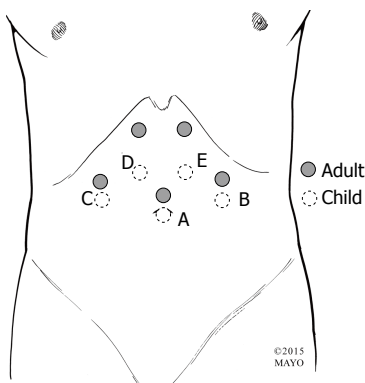


Figure 4 Trocar placement. Example trocar arrangements. A: Laparoscope; B: Babcock clamp or instrument to divide short gastrics; C: Liver retractor; D and E: Ports for dissecting and suturing; E: Electrocautery or ultrasonic shears for myotomy. The laparoscope is generally placed through a transumbilical port in children. The remaining ports are usually placed more caudad than in adults, with variable size (3 mm or 5 mm, rarely 10 mm), location, and function depending on patient body size/habitus and surgeon preference.

If an anterior (Dor) fundoplication is planned, further posterior dissection is not necessary. If a hiatal hernia is present, the crura are re-approximated posterior to the esophagus using interrupted sutures. For children undergoing fundoplication, the stomach is mobilized by dividing the short gastric vessels along the greater curvature from its midpoint to the angle of His.

To begin the myotomy, the esophageal fat pad is removed and the gastroesophageal junction (GEJ) is exposed. An esophageal dilator or bougie is placed transorally, to assist in splaying of the muscle fibers and to provide support during the myotomy. Traction is applied caudad and to the patient's left, to expose

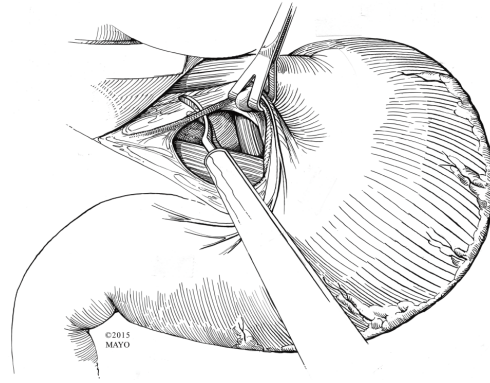


Figure 5 Incision of the gastrohepatic ligament. After retraction of the liver cephalad, the gastrohepatic ligament is incised and the lesser sac is entered. Blunt dissection is used to first identify the right crus of the diaphragm.

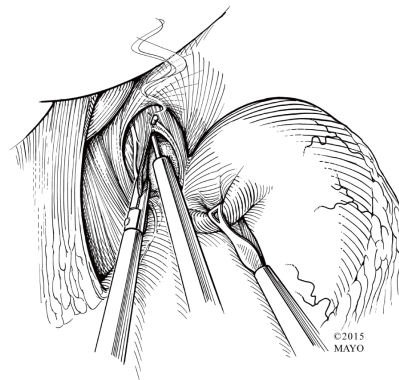


Figure 6 Myotomy with hook cautery. Electrocautery is used to begin the myotomy. It is performed at the 11 o'clock position on the anterior surface of the esophagus, taking care to avoid injury to the overlying vagus nerve. Once the submucosa is visible, blunt dissection is then typically employed to fully expose the mucosa.

the anterior surface of the esophagus. The myotomy is performed at the 11 o'clock position, typically using hook electrocautery (Figure 6). Many surgeons prefer to separate the longitudinal and circular muscle fibers of the esophagus bluntly after initial scoring sharply with electrocautery (Figure 7) or with other energy devices such as ultrasonic shears. The myotomy is then extended approximately 6 cm cephalad onto the esophagus, across the GEJ, and 2-3 cm onto the stomach (Figure 2B). Disruption and appropriate separation of muscle at the GEJ is often difficult due to decussation of the esophageal and gastric muscle fibers. The relationship between recurrence of dysphagia and length of myotomy extension onto the stomach is discussed in subsequent sections. While completing the myotomy, great care should be taken to avoid injury to the newly exposed mucosa. Previous Botox injections or EPD, prior to LHM may lead to scarring near the GEJ and portend a higher theoretical risk of perforation^[48,53,54]. Post-surgical data is mixed about this increased risk; at least one study suggests the risk is higher^[55] but others have shown there is no difference^[56,57]. If a perforation is suspected, it can be confirmed with endoscopy or esophageal water submersion and orogastric air insufflation. Mucosal

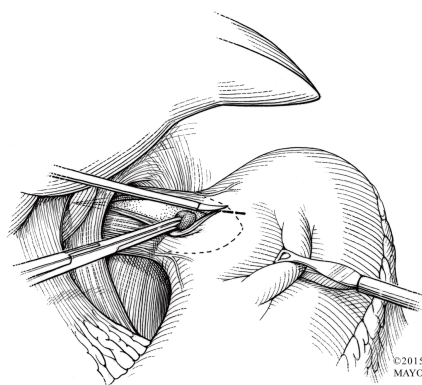


Figure 7 Myotomy with sharp and blunt dissection. Sharp and blunt dissection avoid the risk of thermal injury to the mucosa during myotomy.

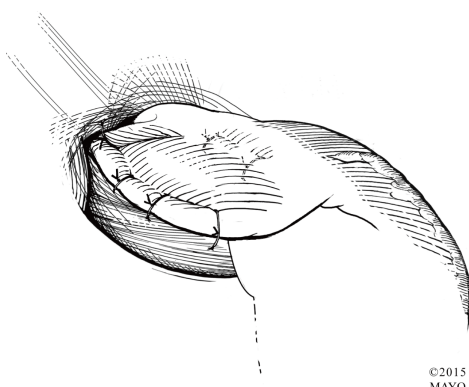


Figure 8 Anterior (Dor) fundoplication. The anterior (Dor) fundoplication is the most common fundoplication performed in children undergoing laparoscopic Heller myotomy. The fundus of the stomach is rolled over the myotomy and secured to the right and left edges of the cut esophageal muscle and crura. The myotomy is concealed. Additional stitches are placed from the anterior gastric fundus to the rim of the esophageal hiatus to relieve tension from the right-sided sutures.

disruptions are typically repaired in a primary fashion with interrupted absorbable suture.

Operative steps for partial fundoplication

The options for an antireflux procedure include a partial or complete fundoplication. Most surgeons favor a partial fundoplication due to the risk for high LES pressures and progression of esophageal dilation when a full 360° wrap is performed^[16,48-51,56-59].

If a 180° anterior (Dor) fundoplication (Figure 8) is planned, the short gastrics are divided and the gastric fundus is completely mobilized. In total, 2 rows of sutures between stomach and esophagus are used. The first row of 3 sutures is placed along the left esophageal wall. The cephalad-most stitch is triangular and incorporates the left diaphragmatic crus, the left side of the esophageal wall and the gastric fundus. The 2nd and 3rd stitches incorporate the fundus and left esophageal wall only. The more lateral portion of the fundus is then placed over the myotomy and is secured to the right esophageal wall in a similar fashion, utilizing a triangular stitch in the most cephalad position. The

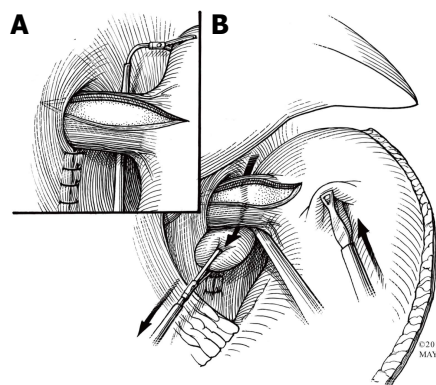


Figure 9 Passing gastric fundus posteriorly for Toupet fundoplication. A: Once the fundus is fully mobilized, it is handled by passing a grasper from right to left, posterior to the esophagus and gastroesophageal junction; B: The fundus is then pulled to the right and toward the right cut edge of the myotomy.

2nd and 3rd stitches incorporate the fundus and right esophageal wall only. An additional 2-3 stitches are then placed from the anterior gastric fundus to the rim of the esophageal hiatus to relieve tension from the right-sided sutures.

To complete a 270° posterior (Toupet) fundoplication, the gastric fundus is mobilized as above. The fundus is then passed posterior to the GEJ junction (Figure 9) to be secured to the right crus of the diaphragm (1-3 stitches) and the right edge of the myotomy (3 stitches). This is then repeated on the left esophageal wall (Figure 10).

Operative time, postoperative care, and cost

Published mean operative times for LHM with an antireflux procedure in children range from 120-190 min^[17,52,54,60-65]. Although there is some variation in hospital and surgeon postoperative LHM protocols, patients are often allowed to have sips of water or clear liquids on the day of surgery^[51,64,66] and an advancing diet beginning on POD #1^[48-51,66] or #3^[52,63,64]. Discharge often occurs on POD #3 or #4 (range POD 1.5-8)^[52,61-64,67]. At our institution, we begin an oral diet on the day of surgery and discharge children between POD #1-3 contingent on pain and dietary tolerance. Differences in institutional and surgeon experience with LHM likely explain the wide ranges reported in operative time and LOS.

To date, there is no description of associated hospital charges or cost of LHM for children in the literature. At our institution, the estimated average charge for LHM alone (without consideration of fundoplication or hospital stay) is \$5277. In the adult literature, a study by Shaligram *et al.*^[68] reported an average hospital cost of \$7441 for LHM with an antireflux procedure (exclusive of hospital stay) and that this cost was significantly lower than the open or robotic approach.

OUTCOMES

Overview

In general, outcomes of pediatric laparoscopic esophag-

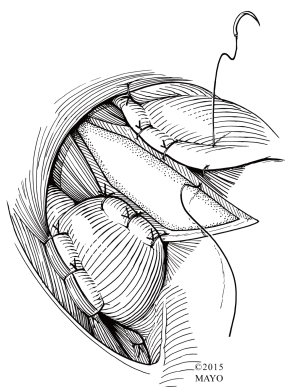


Figure 10 Posterior (Toupet) fundoplication. The stomach is secured to the right and left crura as well as the right and left cut edges of esophageal muscle, completing the posterior fundoplication. The myotomy remains exposed.

omyotomy to relieve dysphagia have been favorable. The majority of data is based on small, single-center experiences with published success rates ranging from 43%-100%^[6,17,52-54,60,62-64,66,67,69-72]. The adult literature suggests success rates in the 80% range^[16,73-75]. It is important to note however, that the definition of "success" has not been fully delineated. Some reports classify treatment as effective only if patients did not have any dysphagia recurrence at the longest available follow-up. Others believe success was achieved if reoperation was not necessary, even if other adjunctive treatments such as EPD were required postoperatively. Unfortunately, long-term outcome data (> 5 years) is sparse.

The two main postoperative complications available in the pediatric LHM literature are recurrence of dysphagia and symptoms of gastroesophageal reflux (GER). A summary of these and all intraoperative complications reported is provided in Table 2.

Effectiveness of LHM and adequate myotomy

The three largest pediatric LHM studies in the literature consist of 26^[67], 28^[53], and 31^[62] patients. We published our experience with this procedure in 2009. Seven (27%) of the 26 children who underwent LHM at our institution had symptom recurrence within 5 years^[67]. Among these 7 patients, 3 underwent a second LHM, 3 received EPD and/or injection of botulinum toxin^[67], and 1 patient had an unspecified procedure at a different institution. The 3 patients who underwent reoperation had extension of the myotomy proximally and/or distally. Similarly, in a United Kingdom based study by Pachl *et al.*^[53], 8 of 28 children required additional intervention within 3 years; 7 underwent EPD, of which 4 ultimately had a reoperation. The 8th patient proceeded directly to reoperation without EPD. Reoperative patients had revisions or extensions of the original myotomy^[53]. Esposito *et al.*^[62] published a 3-center experience in 2013 and found 5 of 31 children experienced recurrent dysphagia after LHM. Among these 5 patients, 2 had spontaneous resolution, 2 underwent EDP, and 1 underwent reoperation.

These results highlight the importance of performing an adequate myotomy. In a study by Tannuri *et al.*^[65],

15 children underwent LHM with a myotomy that extended 3-4 cm onto the stomach in contrast to the generally recommended 2-3 cm. Among these patients, 3 developed dysphagia; 2 cases resolved spontaneously and 1 patient required a single botulinum toxin injection. Traditionally, a longer myotomy in adults was thought to portend higher rates of GER (especially if done without an antireflux procedure)^[30,65,76] or formation of epiphrenic pseudodiverticula^[77]. This has not been definitively proven and continues to be debated with some authors claiming the contrary^[44,78]. What is known however, is that the esophageal muscular fibers need to be fully disrupted and the underlying mucosa exposed to prevent recurrence of dysphagia^[41]. The development of GER after LHM and data relating to an antireflux procedure are presented in subsequent sections.

Complications

Intraoperative complications during LHM in children include mucosal injury or perforation, aspiration, conversion to an open procedure, and hemorrhage. Mucosal injury and perforation appear to be the most common, with rates ranging from 0%-15% with the majority of studies reporting numbers < 10%^[6,17,52-54,62-67,69,71]. Almost all injuries were noted at the time of surgery, however a study by Rothenberg *et al.*^[72] did reveal a perforation that was discovered as late as POD #5. If discovered at the time of operation, a perforation should be closed primarily with interrupted absorbable suture^[48-50]. Children found to have perforation beyond the initial operative day, all underwent reoperation^[52,62,72]. Adult studies reveal similar rates of perforation and conversion to an open procedure^[73,74].

In general, rates of adverse events are low when children undergo laparoscopic esophagomyotomy. However, the available studies are nearly all single-center experiences and the largest experience consists of only 31 patients. Heterogeneity between and within studies makes it difficult to draw causal relationships and define etiologies for complications. As evidenced by Table 2, there is a significant amount of missing complication data. Only 2 of the 15 studies included in this review discuss other postoperative events and none report rates of infection. This may represent the relative safety of LHM or may be a reflection of the low numbers of patients. Due to the rarity of achalasia in children, prospective, multi-institutional studies are needed to provide a more comprehensive picture of LHM safety.

COMPARISONS

Laparoscopic vs thoracoscopic Heller myotomy

The available literature reveals a larger experience with LHM than THM as a form of MIS-HM in children. There are few studies which directly compare these two approaches in the pediatric population. Mehra *et al.*^[70] reported their experience with MIS-HM in 2001. In this study, 18 of 22 patients underwent LHM compared to 4 patients with THM. Mean duration of hospitalization

Table 2 Complications

Year	Ref.	LHM children (n)	Fundoplication (n)	Intraoperative complication (n)				Postoperative complication (n)		
				Mucosal injury or perforation	Aspiration Event	Conversion to open	Hemorrhage event	Recurrence of dysphagia	Symptoms of gastroesophageal reflux	Other
1996	Holcomb <i>et al</i> ^[69]	2	None	0	-/-	-/-	-/-	0	-/-	-/-
2001	Mehra <i>et al</i> ^[70]	18	8 Dor, 8 Toupet, 2 Nissen	2	-/-	2	-/-	a	a	-/-
2001	Patti <i>et al</i> ^[54]	13	12 Dor, 1 none	0	0	0	0	0	1	-/-
2001	Rothenberg <i>et al</i> ^[72]	5	4 Dor, 1 Toupet	1 (identified POD #5)	0	0	0	b	b	-/-
2003	Mattioli <i>et al</i> ^[64]	20	20 Dor	1	-/-	-/-	1	4	0	-/-
2007	Garzi <i>et al</i> ^[63]	12	6 Thal, 6 Dor	1	-/-	-/-	-/-	0	-/-	3 pts w/ odynophagia
2007	Paidas <i>et al</i> ^[71]	14	14 Dor	1	-/-	-/-	-/-	a	a	-/-
2009	Pastor <i>et al</i> ^[17]	14	11 Nissen, 3 unknown	2 (1 identified on unspecified POD)	-/-	2	-/-	b	b	-/-
2009	Askegard-Giesmann <i>et al</i> ^[67]	26	2 Dor, 23 Toupet, 1 none	2	1	0	0	7	1	-/-
2010	Corda <i>et al</i> ^[66]	20	None	3	-/-	4	1	5	0	-/-
2010	Lee <i>et al</i> ^[6]	7	4 Dor, 1 Nissen, 2 none	-/-	-/-	-/-	-/-	-/-	-/-	1 pt w/DVT
2010	Tannuri <i>et al</i> ^[65]	15	15 Dor	0	0	1	0	3	0	-/-
2000	Esposito <i>et al</i> ^[60]	31	31 Dor	3 (1 identified POD #2)	-/-	-/-	-/-	5	-/-	-/-
2014	Pachl <i>et al</i> ^[53]	28	9 Dor, 1 Nissen, 18 none	1	-/-	-/-	-/-	8	4	-/-
2015	Caldaro <i>et al</i> ^[52]	9	9 Dor	1 (identified POD #1)	-/-	-/-	-/-	2	1	-/-

-/-: Not explicitly stated in the study; a: Complication reported as average score or unclear description of number; b: Multiple myotomy approaches (laparoscopic, thoracoscopic, *etc.*) utilized in study cohort with unclear delineation of complications between groups; LHM: Laparoscopic Heller myotomy; DVT: Deep venous thrombosis.

and mean time to resumption of soft feeds were lower for those undergoing LHM^[70]. Similarly, Rothenberg *et al*^[72] found that THM resulted in slightly longer operative times and hospital stay in a study of 9 patients (4 THM, 5 LHM). In a 2011 review article assessing available adult meta-analyses, the authors conclude that LHM results in shorter hospital stays and reduced operative time, but that overall outcomes are similar to THM^[79].

The pediatric evidence comparing LHM and THM is not robust but extrapolation from adult studies suggests LHM is superior. Although not explicitly considered in the literature, postoperative pain and the necessity for tube thoracostomy are likely lower in children undergoing LHM.

The evidence for fundoplication

The need for a concomitant fundoplication during LHM to prevent postoperative GER continues to be debated both in the pediatric and adult populations^[17,53]. Among reported pediatric experiences, the study by Corda *et al*^[66] in 2010 included 20 patients, none of whom underwent an antireflux procedure. In this series, no patients suffered from postoperative GER^[66]. The

authors believe there is a higher chance for recurrent dysphagia when a fundoplication is performed and that it is easier to treat postoperative GER than dysphagia^[66]. Interestingly, another study by Pachl *et al*^[53] found that only 1 of 18 patients without an antireflux procedure had postoperative GER compared to 4 of 10 who suffered from symptoms in the fundoplication group. Of the remaining pediatric LHM studies which explicitly discuss this complication, most performed a Dor fundoplication with low rates of postoperative GER^[52,54,63-65,67].

The adult literature has higher level evidence and appears to favor performance of a partial fundoplication. In a 2004 RCT, Richards *et al*^[59] showed that the incidence of postoperative GER was significantly lower in patients who underwent a Dor fundoplication (9.1% vs 47.6%, $P < 0.05$). In addition, a recent review article assessing multiple prospective studies, meta-analyses, and RCTs in adults concluded that a partial fundoplication is indicated after Heller myotomy to reduce incidence of GER^[80].

Based on the available results, it is not clear whether all children should undergo a concomitant antireflux procedure during LHM. Multi-institutional randomized trials are needed to better answer this question. In the

interim, surgeons should treat each patient individually and base the decision to proceed with a fundoplication on preoperative existence of GER or presence of predisposing risk factors for GER.

Type of fundoplication

If the decision to proceed with an antireflux procedure is made, the surgeon must decide what type of fundoplication to perform. The main advantage of a fundoplication is to prevent reflux and disadvantages include possible postoperative dysphagia or formation of diverticula. As evidenced in Table 2, the majority of LHM procedures performed in children are anterior or Dor fundoplications and most have favorable results. There are no pediatric studies comparing the various types of fundoplications directly. In the Mayo Clinic experience published in 2009, we found that only 1 out of 23 patients undergoing Toupet fundoplication experienced postoperative GER^[67]. In other studies with multiple types of fundoplications^[17,63,70], it is not clear if patients suffered from postoperative GER and if they did, which fundoplication group performed better.

Katada *et al.*^[81] reported on 30 adults who underwent a Toupet fundoplication with concurrent LHM. The authors found that this combination helped to straighten the esophagus, reduced LES pressure, and relieved dysphagia^[81]. They did find however, that 2 patients developed esophageal diverticula postoperatively. A recent review article assessing multiple prospective studies and RCTs comparing LHM with various types of concomitant fundoplication in adults concluded that a partial fundoplication (Dor or Toupet) were superior based on higher rates of dysphagia and slightly lower rates of GER when a full (360° Nissen) fundoplication was performed^[80].

There is an obvious paucity of data to definitively recommend one type of antireflux procedure over another when performing LHM in children. Due to low rates of GER and complications found with various types of fundoplication, a multi-institutional RCT would be a valuable and feasible method to better understand this component of the LHM operation.

FUTURE DIRECTIONS

Peroral endoscopic myotomy

In the last decade, a new approach to performing esophageal myotomy has been gaining interest and attention. Peroral endoscopic myotomy (POEM) was developed as a multi-institutional endeavor and initially described in 2007 after performance on pigs^[82]. It is performed entirely endoscopically. A small incision is made in the esophageal mucosa and a balloon dilator is passed into the submucosal space and inflated^[82]. Following this, the esophageal muscular fibers are separated with electrocautery and once the myotomy is complete, the small incision in the mucosa is closed with endoscopic clips or suturing^[82]. The major advantage of this technique is that it is incision-free and performed

through a natural orifice. Since 2007, a number of small studies have been published on the human experience. A recent "white paper summary" found that therapeutic success was achieved in greater than 80% of these patients, self-limited adverse events occurred in < 10% of cases, and rates of post-procedure GER ranged from 20%-46%^[83].

To date, 3 studies have assessed peroral endoscopic myotomy in pediatric achalasia patients^[52,84,85]. The first published report was in a 3-year-old female with severe developmental issues in which total operative time was 198 min^[85]. There were no intraoperative or postoperative complications and the patient remained symptom-free at 1-year follow-up^[85]. A 2013 study completed the procedure on 3 patients with a mean age of 9.6 years in an average of 60 min^[84]. One patient had a small perforation of the mucosal flap and all 3 were discharged 4-7 d post-procedurally^[84]. One-year follow-up on 2 patients revealed that they remained symptom-free; the third patient was 1 mo post-procedure at the time of publication and also had no symptoms. The most recent and largest POEM study in children included a total of 9 patients and compared their outcomes directly with 9 patients undergoing LHM^[52]. The authors found that mean operative time was significantly lower (62 min vs 149 min, $P < 0.01$), myotomy length was longer (11 cm vs 7 cm, $P = 0.26$), postoperative oral intake occurred sooner (POD #2 vs POD #3, $P < 0.01$), and hospital stay was shorter (4.1 d vs 6 d, $P < 0.01$) in patients undergoing POEM^[52]. Operative and postoperative complications (mucosal perforation, GER) were similar, however, 2 patients in the LHM group had recurrence of dysphagia and 1 POEM patient required evacuation of a pneumoperitoneum during the procedure^[52].

Although the POEM experience for children with achalasia is limited, preliminary data suggests that it may be a viable and safe option when performed under experienced hands. Further studies are needed and ongoing.

Single incision LHM

Single-incision laparoscopic surgery for children has been gaining attention over the last 20 years^[86]. A number of procedures have been performed *via* 1 incision including appendectomy, cholecystectomy, colonic resections, pyloromyotomy, nephrectomy, and many others^[86]. In 2011, Kobayashi *et al.*^[87] reported their experience with single incision LHM (SI-LHM) in a 9-year-old boy. Operative time was 273 min, LOS was 8 d, and the patient had complete resolution of dysphagia with no symptoms of GER^[87]. Although further studies are necessary, this may be an additional operative approach to consider for children with achalasia.

CONCLUSION

Laparoscopic Heller myotomy has become the preferred treatment for pediatric patients with achalasia. Existing literature is limited to small retrospective studies. Available

data suggest that LHM is safe and effective in children. A number of related issues are yet to be definitively proven. The need for and type of concurrent fundoplication, a more comprehensive description of complications, and long-term (> 5 years) outcomes information are poorly defined and require additional evaluation. Due to the rarity of achalasia in children, these characteristics will require collaboration between multiple pediatric surgery centers and should be performed in a prospective randomized fashion when appropriate. Finally, the advent of POEM and SI-LHM techniques could ultimately change the approach chosen for esophagomyotomy and may become the standard of care in the future.

REFERENCES

- Hirano I.** Pathophysiology of achalasia and diffuse esophageal spasm. *GI Motility* (Online) 2006 [DOI: 10.1038/gimo22]
- Cash BD, Wong RK.** Historical perspective of achalasia. *Gastrointest Endosc Clin N Am* 2001; **11**: 221-234, v [PMID: 11319058]
- Sadowski DC, Ackah F, Jiang B, Svenson LW.** Achalasia: incidence, prevalence and survival. A population-based study. *Neurogastroenterol Motil* 2010; **22**: e256-e261 [PMID: 20465592 DOI: 10.1111/j.1365-2982.2010.01511.x]
- Babu R, Grier D, Cusick E, Spicer RD.** Pneumatic dilatation for childhood achalasia. *Pediatr Surg Int* 2001; **17**: 505-507 [PMID: 11666045 DOI: 10.1007/s003830000574]
- Franklin AL, Petrosyan M, Kane TD.** Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management. *World J Gastrointest Endosc* 2014; **6**: 105-111 [PMID: 24748917 DOI: 10.4253/wjge.v6.i4.105]
- Lee CW, Kays DW, Chen MK, Islam S.** Outcomes of treatment of childhood achalasia. *J Pediatr Surg* 2010; **45**: 1173-1177 [PMID: 20620315 DOI: 10.1016/j.jpedsurg.2010.02.086]
- Reynolds JC, Parkman HP.** Achalasia. *Gastroenterol Clin North Am* 1989; **18**: 223-255 [PMID: 2668168]
- Hallal C, Kieling CO, Nunes DL, Ferreira CT, Peterson G, Barros SG, Arruda CA, Fraga JC, Goldani HA.** Diagnosis, misdiagnosis, and associated diseases of achalasia in children and adolescents: a twelve-year single center experience. *Pediatr Surg Int* 2012; **28**: 1211-1217 [PMID: 23135808 DOI: 10.1007/s00383-012-3214-3]
- Preiksaitis HG, Miller L, Pearson FG, Diamant NE.** Achalasia in Down's syndrome. *J Clin Gastroenterol* 1994; **19**: 105-107 [PMID: 7963353 DOI: 10.1097/00004836-199409000-00005]
- Milenkovic T, Zdravkovic D, Savic N, Todorovic S, Mitrovic K, Koehler K, Huebner A.** Triple A syndrome: 32 years experience of a single centre (1977-2008). *Eur J Pediatr* 2010; **169**: 1323-1328 [PMID: 20499090 DOI: 10.1007/s00431-010-1222-7]
- Phillip M, Hershkovitz E, Schulman H.** Adrenal insufficiency after achalasia in the triple-A syndrome. *Clin Pediatr* (Phila) 1996; **35**: 99-100 [PMID: 8775483 DOI: 10.1177/000992289603500208]
- Fischella PM, Raz D, Palazzo F, Niponmick I, Patti MG.** Clinical, radiological, and manometric profile in 145 patients with untreated achalasia. *World J Surg* 2008; **32**: 1974-1979 [PMID: 18575930 DOI: 10.1007/s00268-008-9656-z]
- Hirano I, Tatum RP, Shi G, Sang Q, Joehl RJ, Kahrilas PJ.** Manometric heterogeneity in patients with idiopathic achalasia. *Gastroenterology* 2001; **120**: 789-798 [PMID: 11231931 DOI: 10.1053/gast.2001.22539]
- Vaezi MF, Pandolfino JE, Vela MF.** ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol* 2013; **108**: 1238-1249; quiz 1250 [PMID: 23877351 DOI: 10.1038/ajg.2013.196]
- Liacouras CA, Piccoli DA.** Achalasia. Pediatric gastroenterology: The requisites in pediatrics. 1st ed. Philadelphia: Mosby/Elsevier, 2008: 13-18
- Roll GR, Rabl C, Ciovia R, Peeva S, Campos GM.** A controversy that has been tough to swallow: is the treatment of achalasia now digested? *J Gastrointest Surg* 2010; **14** Suppl 1: S33-S45 [PMID: 19760373 DOI: 10.1007/s11605-009-1013-5]
- Pastor AC, Mills J, Marcon MA, Himidan S, Kim PC.** A single center 26-year experience with treatment of esophageal achalasia: is there an optimal method? *J Pediatr Surg* 2009; **44**: 1349-1354 [PMID: 19573660 DOI: 10.1016/j.jpedsurg.2008.10.117]
- Wang L, Li YM, Li L.** Meta-analysis of randomized and controlled treatment trials for achalasia. *Dig Dis Sci* 2009; **54**: 2303-2311 [PMID: 19107596 DOI: 10.1007/s10620-008-0637-8]
- Maksimak M, Perlmutter DH, Winter HS.** The use of nifedipine for the treatment of achalasia in children. *J Pediatr Gastroenterol Nutr* 1986; **5**: 883-886 [PMID: 3794905 DOI: 10.1097/00005176-198611000-00010]
- Hurwitz M, Bahar RJ, Ament ME, Tolia V, Molleston J, Reinstein LJ, Walton JM, Erhart N, Wasserman D, Justinich C, Vargas J.** Evaluation of the use of botulinum toxin in children with achalasia. *J Pediatr Gastroenterol Nutr* 2000; **30**: 509-514 [PMID: 10817280 DOI: 10.1097/00005176-200005000-00009]
- Ip KS, Cameron DJ, Catto-Smith AG, Hardikar W.** Botulinum toxin for achalasia in children. *J Gastroenterol Hepatol* 2000; **15**: 1100-1104 [PMID: 11106087 DOI: 10.1046/j.1440-1746.2000.02341.x]
- Khoshoo V, LaGarde DC, Udall JN Jr.** Intraspincteric injection of Botulinum toxin for treating achalasia in children. *J Pediatr Gastroenterol Nutr* 1997; **24**: 439-441 [PMID: 9144129 DOI: 10.1097/00005176-199704000-00015]
- Zaninotto G, Annese V, Costantini M, Del Genio A, Costantino M, Epifani M, Gatto G, D'Onofrio V, Benini L, Contini S, Molena D, Battaglia G, Tardio B, Andriulli A, Ancona E.** Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Ann Surg* 2004; **239**: 364-370 [PMID: 15075653 DOI: 10.1097/01.sla.0000114217.52941.c5]
- Zaninotto G, Vergadoro V, Annese V, Costantini M, Costantino M, Molena D, Rizzetto C, Epifani M, Ruol A, Nicoletti L, Ancona E.** Botulinum toxin injection versus laparoscopic myotomy for the treatment of esophageal achalasia: economic analysis of a randomized trial. *Surg Endosc* 2004; **18**: 691-695 [PMID: 15026896 DOI: 10.1007/s00464-003-8910-6]
- Berquist WE, Byrne WJ, Ament ME, Fonkalsrud EW, Euler AR.** Achalasia: diagnosis, management, and clinical course in 16 children. *Pediatrics* 1983; **71**: 798-805 [PMID: 6835765]
- Boyle JT, Cohen S, Watkins JB.** Successful treatment of achalasia in childhood by pneumatic dilatation. *J Pediatr* 1981; **99**: 35-40 [PMID: 7252667 DOI: 10.1016/S0022-3476(81)80953-5]
- Hammond PD, Moore DJ, Davidson GP, Davies RP.** Tandem balloon dilatation for childhood achalasia. *Pediatr Radiol* 1997; **27**: 609-613 [PMID: 9211959 DOI: 10.1007/s002470050196]
- Hamza AF, Awad HA, Hussein O.** Cardiac achalasia in children. Dilatation or surgery? *Eur J Pediatr Surg* 1999; **9**: 299-302 [PMID: 10584188 DOI: 10.1055/s-2008-1072268]
- Khan AA, Shah SW, Alam A, Butt AK, Shafqat F.** Efficacy of Rigidflex balloon dilatation in 12 children with achalasia: a 6-month prospective study showing weight gain and symptomatic improvement. *Dis Esophagus* 2002; **15**: 167-170 [PMID: 12220427 DOI: 10.1046/j.1442-2050.2002.00246.x]
- Piñeiro-Carrero VM, Sullivan CA, Rogers PL.** Etiology and treatment of achalasia in the pediatric age group. *Gastrointest Endosc Clin N Am* 2001; **11**: 387-408, viii [PMID: 11319069]
- Lelli JL Jr, Drongowski RA, Coran AG.** Efficacy of the transthoracic modified Heller myotomy in children with achalasia - a 21-year experience. *J Pediatr Surg* 1997; **32**: 338-341 [PMID: 9044149 DOI: 10.1016/S0022-3468(97)90206-2]
- Di Nardo G, Rossi P, Oliva S, Alois M, Cozzi DA, Frediani S, Redler A, Mallardo S, Ferrari F, Cucchiara S.** Pneumatic balloon dilation in pediatric achalasia: efficacy and factors predicting outcome at a single tertiary pediatric gastroenterology center. *Gastrointest Endosc* 2012; **76**: 927-932 [PMID: 22921148 DOI: 10.1016/j.gie.2012.06.035]
- Boeckxstaens GE, Annese V, des Varannes SB, Chaussade**

- S, Costantini M, Cuttitta A, Elizalde JI, Fumagalli U, Gaudric M, Rohof WO, Smout AJ, Tack J, Zwinderman AH, Zaninotto G, Busch OR. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011; **364**: 1807-1816 [PMID: 21561346 DOI: 10.1056/NEJMoa1010502]
- 34 **Yaghoobi M**, Mayrand S, Martel M, Roshan-Afshar I, Bijarchi R, Barkun A. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2013; **78**: 468-475 [PMID: 23684149 DOI: 10.1016/j.gie.2013.03.1335]
- 35 **Campos GM**, Vittinghoff E, Rabl C, Takata M, Gadenstätter M, Lin F, Ciofica R. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 2009; **249**: 45-57 [PMID: 19106675 DOI: 10.1097/SLA.0b013e31818e43ab]
- 36 **Heller E**. Extramucosa Kardioplastik beim chronischen Kardiospasmus mit Dilatation des Oesophagus. *Mitt Grenzgeb Med Chir* 1914; **27**: 141-149
- 37 **Zaaijer JH**. Cardiospasm in the aged. *Ann Surg* 1923; **77**: 615-617 [PMID: 17864830 DOI: 10.1097/0000658-192305000-00014]
- 38 **Jaakkola A**, Ovaska J, Isolaure J. Esophagocardiomyotomy for achalasia. Long-term clinical and endoscopic evaluation of transabdominal vs. transthoracic approach. *Eur J Surg* 1991; **157**: 407-410 [PMID: 1681919]
- 39 **Stipa SBR**. Esophagomyotomy and antireflux operation for achalasia. *Chir Gastroenterol* 1976; **10**: 3-7
- 40 **Shimi S**, Nathanson LK, Cuschieri A. Laparoscopic cardiomyotomy for achalasia. *J R Coll Surg Edinb* 1991; **36**: 152-154 [PMID: 1833541]
- 41 **Pellegrini C**, Wetter LA, Patti M, Leichter R, Mussan G, Mori T, Bernstein G, Way LW. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. *Ann Surg* 1992; **216**: 291-296; discussion 296-299 [PMID: 1417178]
- 42 **Raiser F**, Perdakis G, Hinder RA, Swanstrom LL, Filipi CJ, McBride PJ, Katada N, Neary PJ. Heller myotomy via minimal-access surgery. An evaluation of antireflux procedures. *Arch Surg* 1996; **131**: 593-597; discussion 597-598 [PMID: 8645064]
- 43 **Patti MG**, Arcerito M, De Pinto M, Feo CV, Tong J, Gantert W, Way LW. Comparison of thoracoscopic and laparoscopic Heller myotomy for achalasia. *J Gastrointest Surg* 1998; **2**: 561-566 [PMID: 10457314]
- 44 **Oelschlager BK**, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. *Arch Surg* 2003; **138**: 490-495; discussion 495-497 [PMID: 12742951 DOI: 10.1001/archsurg.138.5.490]
- 45 **Burpee SE**, Mamazza J, Schlachta CM, Bendavid Y, Klein L, Moloo H, Poulin EC. Objective analysis of gastroesophageal reflux after laparoscopic heller myotomy: an anti-reflux procedure is required. *Surg Endosc* 2005; **19**: 9-14 [PMID: 15531966 DOI: 10.1007/s00464-004-8932-8]
- 46 **Ramacciato G**, Mercantini P, Amodio PM, Corigliano N, Barreca M, Stipa F, Ziparo V. The laparoscopic approach with antireflux surgery is superior to the thoracoscopic approach for the treatment of esophageal achalasia. Experience of a single surgical unit. *Surg Endosc* 2002; **16**: 1431-1437 [PMID: 12072992 DOI: 10.1007/s00464-001-9215-2]
- 47 **Stefanidis D**, Richardson W, Farrell TM, Kohn GP, Augenstein V, Fanelli RD. SAGES guidelines for the surgical treatment of esophageal achalasia. *Surg Endosc* 2012; **26**: 296-311 [PMID: 22044977 DOI: 10.1007/s00464-011-2017-2]
- 48 **Campos GM**, Ciofica R, Takata M. Laparoscopic Myotomy. *Oper Tech Gen Surg* 2006; **8**: 161-169 [DOI:10.1053/j.optechgensurg.2006.08.001]
- 49 **Gorodner MV**, Galvani C, Patti MG. Heller Myotomy. *Oper Tech Gen Surg* 2004; **6**: 23-28 [DOI:10.1053/j.optechgensurg.2004.01.006]
- 50 **Patti MG**, Fisichella PM. Laparoscopic Heller myotomy and Dor fundoplication for esophageal achalasia. How I do it. *J Gastrointest Surg* 2008; **12**: 764-766 [PMID: 17957436 DOI: 10.1007/s11605-007-0368-8]
- 51 **Tatum RP**, Pellegrini CA. How I do it: laparoscopic Heller myotomy with Toupet fundoplication for achalasia. *J Gastrointest Surg* 2009; **13**: 1120-1124 [PMID: 18622657 DOI: 10.1007/s11605-008-0585-9]
- 52 **Caldaro T**, Familiari P, Romeo EF, Gigante G, Marchese M, Contini AC, Federici di Abriola G, Cucchiara S, De Angelis P, Torroni F, Dall'Oglio L, Costamagna G. Treatment of esophageal achalasia in children: Today and tomorrow. *J Pediatr Surg* 2015; **50**: 726-730 [PMID: 25783358 DOI: 10.1016/j.jpedsurg.2015.02.047]
- 53 **Pachl MJ**, Rex D, Decoppi P, Cross K, Kiely EM, Drake D, Pierro A, Curry JJ. Paediatric laparoscopic Heller's cardiomyotomy: a single centre series. *J Pediatr Surg* 2014; **49**: 289-292; discussion 292 [PMID: 24528969 DOI: 10.1016/j.jpedsurg.2013.11.042]
- 54 **Patti MG**, Albanese CT, Holcomb GW, Molena D, Fisichella PM, Perretta S, Way LW. Laparoscopic Heller myotomy and Dor fundoplication for esophageal achalasia in children. *J Pediatr Surg* 2001; **36**: 1248-1251 [PMID: 11479868 DOI: 10.1053/jpsu.2001.25786]
- 55 **Portale G**, Costantini M, Rizzetto C, Guirrola E, Ceolin M, Salvador R, Ancona E, Zaninotto G. Long-term outcome of laparoscopic Heller-Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. *J Gastrointest Surg* 2005; **9**: 1332-1339 [PMID: 16332491 DOI: 10.1016/j.gassur.2005.10.001]
- 56 **Bonavina L**, Incarbone R, Antoniazzi L, Reitano M, Peracchia A. Previous endoscopic treatment does not affect complication rate and outcome of laparoscopic Heller myotomy and anterior fundoplication for oesophageal achalasia. *Ital J Gastroenterol Hepatol* 1999; **31**: 827-830 [PMID: 10669988]
- 57 **Bonavina L**, Incarbone R, Reitano M, Antoniazzi L, Peracchia A. Does previous endoscopic treatment affect the outcome of laparoscopic Heller myotomy? *Ann Chir* 2000; **125**: 45-49 [PMID: 10921184 DOI: 10.1016/S0001-4001(00)99113-X]
- 58 **Patti MG**, Fisichella PM, Perretta S, Galvani C, Gorodner MV, Robinson T, Way LW. Impact of minimally invasive surgery on the treatment of esophageal achalasia: a decade of change. *J Am Coll Surg* 2003; **196**: 698-703; discussion 703-705 [PMID: 12742198 DOI: 10.1016/S1072-7515(02)01837-9]
- 59 **Richards WO**, Torquati A, Holzman MD, Khaitan L, Byrne D, Lutfi R, Sharp KW. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. *Ann Surg* 2004; **240**: 405-412; discussion 412-415 [PMID: 15319712 DOI: 10.1097/01.sla.0000136940.32255.51]
- 60 **Esposito C**, Cucchiara S, Borrelli O, Roblot-Maigret B, Desruelle P, Montupet P. Laparoscopic esophagomyotomy for the treatment of achalasia in children. A preliminary report of eight cases. *Surg Endosc* 2000; **14**: 110-113 [PMID: 10656938 DOI: 10.1007/s004640000077]
- 61 **Esposito C**, Mendoza-Sagaon M, Roblot-Maigret B, Amici G, Desruelle P, Montupet P. Complications of laparoscopic treatment of esophageal achalasia in children. *J Pediatr Surg* 2000; **35**: 680-683 [PMID: 10813322 DOI: 10.1053/jpsu.2000.5942]
- 62 **Esposito C**, Ricciettoni G, Chiarenza SF, Roberti A, Vella C, Alicchio F, Fava G, Escolino M, De Pascale T, Settini A. Long-term results of laparoscopic treatment of esophageal achalasia in children: a multicentric survey. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 955-959 [PMID: 24073839 DOI: 10.1089/lap.2013.0308]
- 63 **Garzi A**, Valla JS, Molinaro F, Amato G, Messina M. Minimally invasive surgery for achalasia: combined experience of two European centers. *J Pediatr Gastroenterol Nutr* 2007; **44**: 587-591 [PMID: 17460491 DOI: 10.1097/MPG.0b013e318032062f]
- 64 **Mattioli G**, Esposito C, Pini Prato A, Doldo P, Castagnetti M, Barabino A, Gandullia P, Staiano AM, Settini A, Cucchiara S, Montobbio G, Jasonni V. Results of the laparoscopic Heller-Dor procedure for pediatric esophageal achalasia. *Surg Endosc* 2003; **17**: 1650-1652 [PMID: 12915969 DOI: 10.1007/s00464-002-9257-0]
- 65 **Tannuri AC**, Tannuri U, Velhote MC, Romão RL. Laparoscopic extended cardiomyotomy in children: an effective procedure for the treatment of esophageal achalasia. *J Pediatr Surg* 2010; **45**: 1463-1466 [PMID: 20638525 DOI: 10.1016/j.jpedsurg.2009.08.023]
- 66 **Corda L**, Pacilli M, Clarke S, Fell JM, Rawat D, Haddad M. Laparoscopic oesophageal cardiomyotomy without fundoplication

- in children with achalasia: a 10-year experience: a retrospective review of the results of laparoscopic oesophageal cardiomyotomy without an anti-reflux procedure in children with achalasia. *Surg Endosc* 2010; **24**: 40-44 [PMID: 19495877 DOI: 10.1007/s00464-009-0513-4]
- 67 **Askegard-Giesmann JR**, Grams JM, Hanna AM, Iqbal CW, Teh S, Moir CR. Minimally invasive Heller's myotomy in children: safe and effective. *J Pediatr Surg* 2009; **44**: 909-911 [PMID: 19433168 DOI: 10.1016/j.jpedsurg.2009.01.022]
 - 68 **Shaligram A**, Unniravi J, Simorov A, Kothari VM, Oleynikov D. How does the robot affect outcomes? A retrospective review of open, laparoscopic, and robotic Heller myotomy for achalasia. *Surg Endosc* 2012; **26**: 1047-1050 [PMID: 22038167 DOI: 10.1007/s00464-011-1994-5]
 - 69 **Holcomb GW 3rd**, Richards WO, Riedel BD. Laparoscopic esophagomyotomy for achalasia in children. *J Pediatr Surg* 1996; **31**: 716-718 [PMID: 8861491 DOI: 10.1016/S0022-3468(96)90685-5]
 - 70 **Mehra M**, Bahar RJ, Ament ME, Waldhausen J, Gershman G, Georgeson K, Fox V, Fishman S, Werlin S, Sato T, Hill I, Tolia V, Atkinson J. Laparoscopic and thoracoscopic esophagomyotomy for children with achalasia. *J Pediatr Gastroenterol Nutr* 2001; **33**: 466-471 [PMID: 11698765]
 - 71 **Paidas C**, Cowgill SM, Boyle R, Al-Saadi S, Villadolid D, Rosemurgy AS. Laparoscopic Heller myotomy with anterior fundoplication ameliorates symptoms of achalasia in pediatric patients. *J Am Coll Surg* 2007; **204**: 977-983; discussion 983-986 [PMID: 17481524 DOI: 10.1016/j.jamcollsurg.2006.12.046]
 - 72 **Rothenberg SS**, Partrick DA, Bealer JF, Chang JH. Evaluation of minimally invasive approaches to achalasia in children. *J Pediatr Surg* 2001; **36**: 808-810 [PMID: 11329595 DOI: 10.1053/jpsu.2001.22967]
 - 73 **Kilic A**, Schuchert MJ, Pennathur A, Gilbert S, Landreneau RJ, Luketich JD. Long-term outcomes of laparoscopic Heller myotomy for achalasia. *Surgery* 2009; **146**: 826-831; discussion 831-833 [PMID: 19789044 DOI: 10.1016/j.surg.2009.06.049]
 - 74 **Rosemurgy AS**, Morton CA, Rosas M, Albrink M, Ross SB. A single institution's experience with more than 500 laparoscopic Heller myotomies for achalasia. *J Am Coll Surg* 2010; **210**: 637-645; discussion 645-647 [PMID: 20421021 DOI: 10.1016/j.jamcollsurg.2010.01.035]
 - 75 **Gutschow CA**, Töx U, Leers J, Schäfer H, Prenzel KL, Hölscher AH. Botox, dilation, or myotomy? Clinical outcome of interventional and surgical therapies for achalasia. *Langenbecks Arch Surg* 2010; **395**: 1093-1099 [PMID: 20845045 DOI: 10.1007/s00423-010-0711-5]
 - 76 **Ellis FH Jr**, Watkins E Jr, Gibb SP, Heatley GJ. Ten to 20-year clinical results after short esophagomyotomy without an antireflux procedure (modified Heller operation) for esophageal achalasia. *Eur J Cardiothorac Surg* 1992; **6**: 86-89; discussion 90 [PMID: 1581086 DOI: 10.1016/1010-7940(92)90080-H]
 - 77 **Chen LQ**, Chughtai T, Sideris L, Nastos D, Taillefer R, Ferraro P, Duranceau A. Long-term effects of myotomy and partial fundoplication for esophageal achalasia. *Dis Esophagus* 2002; **15**: 171-179 [PMID: 12220428 DOI: 10.1046/j.1442-2050.2002.00248.x]
 - 78 **Wright AS**, Williams CW, Pellegrini CA, Oelschlager BK. Long-term outcomes confirm the superior efficacy of extended Heller myotomy with Toupet fundoplication for achalasia. *Surg Endosc* 2007; **21**: 713-718 [PMID: 17332964 DOI: 10.1007/s00464-006-9165-9]
 - 79 **Hughes MJ**, Chowdhry MF, Walker WS. Can thoracoscopic Heller's myotomy give equivalent results to the more usual laparoscopic Heller's myotomy in the treatment of achalasia? *Interact Cardiovasc Thorac Surg* 2011; **13**: 77-81 [PMID: 21498789 DOI: 10.1510/icvts.2011.268169]
 - 80 **Mayo D**, Griffiths EA, Khan OA, Szymankiewicz MA, Wakefield CW, Thompson SK. Does the addition of a fundoplication improve outcomes for patients undergoing laparoscopic Heller's cardiomyotomy? *Int J Surg* 2012; **10**: 301-304 [PMID: 22510440 DOI: 10.1016/j.ijsu.2012.04.002]
 - 81 **Katada N**, Sakuramoto S, Kobayashi N, Futawatari N, Kuroyama S, Kikuchi S, Watanabe M. Laparoscopic Heller myotomy with Toupet fundoplication for achalasia straightens the esophagus and relieves dysphagia. *Am J Surg* 2006; **192**: 1-8 [PMID: 16769266 DOI: 10.1016/j.amjsurg.2006.01.027]
 - 82 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382 DOI: 10.1055/s-2007-966764]
 - 83 **Stavropoulos SN**, Desilets DJ, Fuchs KH, Gostout CJ, Haber G, Inoue H, Kochman ML, Modayil R, Savides T, Scott DJ, Swanstrom LL, Vassiliou MC. Per-oral endoscopic myotomy white paper summary. *Surg Endosc* 2014; **28**: 2005-2019 [PMID: 24935204 DOI: 10.1007/s00464-014-3630-7]
 - 84 **Familiari P**, Marchese M, Gigante G, Boskoski I, Tringali A, Perri V, Costamagna G. Peroral endoscopic myotomy for the treatment of achalasia in children. *J Pediatr Gastroenterol Nutr* 2013; **57**: 794-797 [PMID: 23941997 DOI: 10.1097/MPG.0b013e3182a803f7]
 - 85 **Maselli R**, Inoue H, Misawa M, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Suzuki K, Kudo S. Peroral endoscopic myotomy (POEM) in a 3-year-old girl with severe growth retardation, achalasia, and Down syndrome. *Endoscopy* 2012; **44** Suppl 2 UCTN: E285-E287 [PMID: 22933258 DOI: 10.1055/s-0032-1309924]
 - 86 **Saldaña LJ**, Targarona EM. Single-incision pediatric endosurgery: a systematic review. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 467-480 [PMID: 23560658 DOI: 10.1089/lap.2012.0467]
 - 87 **Kobayashi M**, Mizuno M, Sasaki A, Arisue A, Akiyama S, Wakabayashi G. Single-port laparoscopic Heller myotomy and Dor fundoplication: initial experience with a new approach for the treatment of pediatric achalasia. *J Pediatr Surg* 2011; **46**: 2200-2203 [PMID: 22075359 DOI: 10.1016/j.jpedsurg.2011.07.027]

P- Reviewer: Omura N S- Editor: Gong ZM L- Editor: A
E- Editor: Lu YJ



2016 Pancreatic Cancer: : Global view

Endoscopic ultrasound in the diagnosis and management of carcinoma pancreas

Rajesh Puri, Manish Manrai, Ragesh Babu Thandassery, Abdulrahman A Alfadda

Rajesh Puri, Institute of Digestive and Hepatobiliary Sciences, Medanta, The Medicity, Gurgaon 122001, Haryana, India

Manish Manrai, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Ragesh Babu Thandassery, Department of Medicine, Division of Gastroenterology, Hamad General Hospital, Doha 3050, Qatar

Abdulrahman A Alfadda, Department of Medicine, Division of Gastroenterology, King Faisal Specialist Hospital and Research Center, Riyadh 12713, Saudi Arabia

Author contributions: All authors contributed to this paper.

Conflict-of-interest statement: No potential conflicts of interest. No external funding agency.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ragesh Babu Thandassery, MD, DM, Department of Medicine, Division of Gastroenterology, Hamad General Hospital, 2 South 2, Doha 3050, Qatar. doc.ragesh@gmail.com
Telephone: +974-44-392532
Fax: +974-44-392279

Received: July 2, 2015

Peer-review started: July 7, 2015

First decision: August 5, 2015

Revised: October 30, 2015

Accepted: November 17, 2015

Article in press: November 25, 2015

Published online: January 25, 2016

Abstract

Endoscopic ultrasound (EUS) has become an important component in the diagnosis and treatment of carcinoma pancreas. With the advent of advanced imaging techniques and tissue acquisition methods the role of EUS is becoming increasingly important. Small pancreatic tumors can be reliably diagnosed with EUS. EUS guided fine needle aspiration establishes diagnosis in some cases. EUS plays an important role in staging of carcinoma pancreas and in some important therapeutic methods that include celiac plexus neurolysis, EUS guided biliary drainage and drug delivery. In this review we attempt to review the role of EUS in diagnosis and management of carcinoma pancreas.

Key words: Carcinoma pancreas; Endoscopic ultrasound; Treatment

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic ultrasound (EUS) is becoming increasingly important in the diagnosis and management of carcinoma pancreas. It helps in identification of small tumors, histological diagnosis by fine needle aspiration, staging of the disease and its treatment. Palliation of pain with celiac plexus neurolysis and palliation of jaundice by biliary drainage can be achieved with EUS guided techniques. In this review we attempt to review the role of EUS in different aspects of diagnosis and treatment of carcinoma pancreas.

Puri R, Manrai M, Thandassery RB, Alfadda AA. Endoscopic ultrasound in the diagnosis and management of carcinoma pancreas. *World J Gastrointest Endosc* 2016; 8(2): 67-76 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/67.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.67>

INTRODUCTION

Pancreatic cancer, according to SEER database in the United States, constitutes 3% of all new cancer cases. The number of new cases of pancreas cancer was 12.4 per 100000 men and women per year and the number of deaths were 10.9 per 100000 men and women per year based on 2008-2012 cases. It is more common with increasing age and slightly more common in men than women. The median age of diagnosis was 71 years, the median age of death being 73 years. It is estimated that there will be 48960 new cases of pancreas cancer and an estimated 40560 people will die of this disease in 2015. Using statistical models for analysis, rates for new pancreas cancer cases have been rising on average 0.8% each year over the last 10 years but the death rates have been stable, the 5 year survival being a dismal 5%-7.2%^[1,2]. This spells out the magnitude of the problem with this disease.

The role of endoscopic ultrasound (EUS) evaluation of pancreatic cancer was suggested as an independent predictor of survival and improvement in patients with loco regional pancreatic cancer in a recent study^[3]. We will highlight the various aspects of the role of EUS in the setting of pancreatic cancer.

EUS FEATURES OF NORMAL PANCREAS AND PANCREATIC MALIGNANCY

Nattermann *et al*^[4] and Catalano *et al*^[5] described the pancreatic parenchyma as a homogeneous fine granular, reticulated pancreas with smooth margins without evidence of side-branch ectasia. The pancreatic duct diameter in the body was 1.7 to 1.9 mm on average (range, 1-3 mm), a ventral anlage (echogenic difference between the ventral and dorsal pancreas) was seen in up to 68% of controls. These data from control populations and healthy volunteers provide important standards for the normal endosonographic appearance of the pancreas but are limited by their small numbers and potential biases in control populations.

On the other hand, neoplastic masses may obscure the normal parenchymal and ductal features. They are generally more homogeneous; hypoechoic compared to surrounding tissue and are rarely calcified. In a calcified pancreas, neoplastic lesions frequently push the calcified parenchyma towards the periphery. In addition signs of vascular invasion are highly suggestive of malignancy^[6].

DIAGNOSTIC ROLE OF EUS IN PANCREATIC CANCER

EUS has high sensitivity for detecting pancreatic neoplasms and further provides the ability to obtain samples from suspected lesions by fine needle aspiration (FNA) contributing to its accuracy in the diagnosis of pancreatic cancer. It has been considered one of the most precise methods for the detection of pancreatic

focal lesions, especially in patients with small tumors of 3 cm or less^[7,8] (Figure 1). The reported sensitivity and accuracy of combined EUS-FNA for detecting pancreatic malignancy usually exceeds 90%^[9-14]. A recent meta-analysis mentioned the pooled sensitivity and specificity of EUS FNA ranging between 87% and 96%, respectively, for diagnosing a solid pancreatic mass lesion^[15]. The sensitivity and accuracy of EUS are slightly higher than the sensitivity and accuracy of computed tomography (CT) and Magnetic resonance imaging (MRI) in detecting small pancreatic lesions^[16-19].

EUS can be used to assess TNM staging of pancreatic tumors. T1 lesions are smaller than 2 cm, T2 are lesions larger than 2 cm, tumor extending beyond the pancreas is either a T3 (portal vein, duodenum, or ampulla of Vater) or T4 lesions (extending to the celiac artery or superior mesenteric artery; being unresectable). Malignant nodes around the pancreas are N1 lesions and rarely distant metastasis may be seen (M1 lesion). The accuracy of CT, MRI, and EUS in assessing TNM staging of pancreatic cancer was compared by Soriano *et al*^[20] wherein EUS had the highest accuracy for N-staging (65%) although CT was more accurate in assessing vascular invasion and T-staging. However in a retrospective study from Russia by Egorov *et al*^[21], arterial encasement on CT did not necessarily indicate arterial invasion and in unresectable pancreatic cancers (on CT), EUS data for peripancreatic involvement might suggest possible radical resection, providing survival benefits. It has also been used as a screening tool for individuals at a high risk for pancreatic cancer with incidence of clinically relevant findings at first screening being 7% with asymptomatic cancer and 16% premalignant IPMN-like lesions in a study by Poley *et al*^[22].

The diagnostic reliability of EUS-FNA in the evaluation of pancreatic lesions is predictably affected by operator expertise, cytopathologic interpretation, and other variables including the presence of inflammatory changes^[9,23]. A definite diagnosis cannot be ascertained in a significant minority of EUS-FNA samples alone, resulting in a cytological diagnosis of suspicious or indeterminate for neoplasm which is seen in approximately 8% to 10% of EUS-FNA samples, representing a challenging diagnostic dilemma^[12,23,24]. In addition, presence of chronic pancreatitis may decrease the sensitivity of EUS-FNA as noted by Varadarajulu *et al*^[25] where in the sensitivity was ranging from 73% to 91%, being lower in patients with chronic pancreatitis; and the No Endosonographic Detection of Tumor study^[26] had revealed 60% patients with co-existing chronic pancreatitis and 15% patients with a diffuse malignancy which was not detected earlier. Furthermore Siddiqui *et al*^[27] in their retrospective cohort trial found a false positive rate for EUS-FNA of solid pancreatic lesions of 1.1% as a result of cytologic misinterpretation in the setting of chronic pancreatitis.

Few basic remedial factors to improve the yield of EUS FNA were the use of 25 gauge needle as less blood is aspirated instead of conventional 22 gauge needle^[28-30], combining cytologic and histologic analyses of the specimen to decrease the number of passes to 2^[31] from 4 to 7

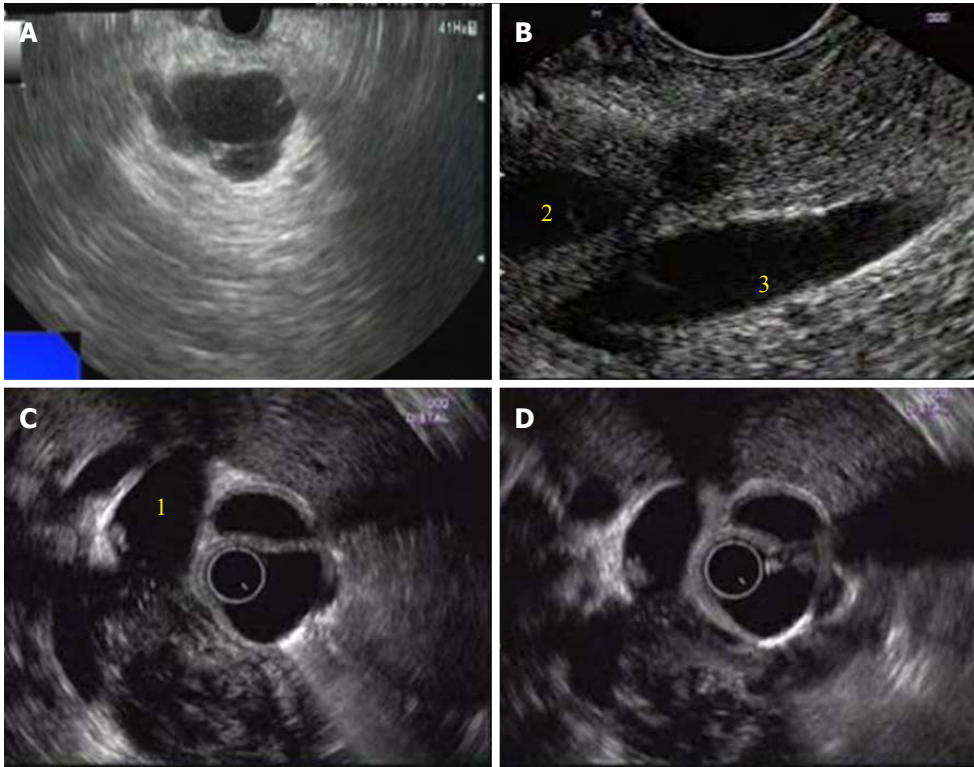


Figure 1 Endoscopic ultrasound appearance of mass lesions in pancreas. A: Serous cystic neoplasm of head of pancreas (HOP); B: Neuroendocrine tumor of head of pancreas with dilated pancreatic duct (2) and adjacent portal vein (3); C: Carcinoma HOP with loss of fat planes with confluence of superior mesenteric vein (SMV) and portal vein and dilated common bile duct (1); D: Carcinoma HOP with common bile duct and SMV infiltration..

passes^[32] (higher in pancreatic cancer than in other lesions), to cater for rapid on-site cytological evaluation^[33-35], the use of serum CA19-9^[36] and fluid CEA and CA19-9 for increasing the ability to diagnose malignancy especially in suspicious cases^[37].

WHAT IS NEW FOR DETECTION OF PANCREATIC MALIGNANCY?

Developments have taken place to further refine the ability to differentiate a malignant lesion from a benign one with a reasonable certainty and overcome other limitations. There have been improvements in the imaging techniques with EUS as well as advances in cytopathology analysis. Among the newer technologies there are EUS elastography, contrast enhanced EUS and use of chromosomal detection techniques in FNA specimen.

EUS elastography is a noninvasive technique that measures elasticity in real time by registration of differences in distortion of the EUS image after application of slight pressure by the EUS probe (Figures 2 and 3). Tissue elasticity may be altered by inflammation, fibrosis and cancer resulting in distinct elastographic appearance. Initial studies were based on qualitative elastography evaluation, using a hue-color scale representing different degrees of tissue elasticity. Giovannini *et al*^[38] had sensitivity and a specificity of 100% and 67% respectively while analyzing pancreatic masses using a scoring

system based on different color patterns to differentiate between benign and malignant pancreatic masses. In a subsequent multicenter study^[39], the sensitivity and specificity of EUS elastography to differentiate benign from malignant pancreatic lesions were 92% and 80.0%, respectively, compared to 92% and 69%, respectively, for the conventional B-mode images. In another paper by Iglesias-Garcia *et al*^[40], malignancy could be diagnosed by qualitative EUS-elastography using color patterns with a sensitivity, specificity and overall accuracy of 100%, 85.5% and 94%, respectively. Recently quantitative EUS elastography has been developed in an attempt to make the elastography interpretation less subjective. Quantitative elastography gives a numeric result, either as mean value of hues in a selected area (mean hue histogram) or as a ratio of elasticity in the target area over soft reference tissue (strain ratio). Iglesias-Garcia *et al*^[41], have evaluated strain ratio in 86 consecutive patients with solid pancreatic masses and found the strain ratio was significantly higher among patients with malignant pancreatic tumors compared to those with inflammatory masses (Normal pancreatic tissue: 1.68; inflammatory masses: 3.28; pancreatic adenocarcinoma: 18.12; and the highest strain ratio was found among endocrine tumors). The sensitivity and specificity of the strain ratio for detecting pancreatic malignancies using a cutoff value of 6.04 were 100% and 92.9%, respectively, exceeding the accuracy obtained with qualitative elastography. Săftoiu *et al*^[42] evaluated the usefulness of the hue-

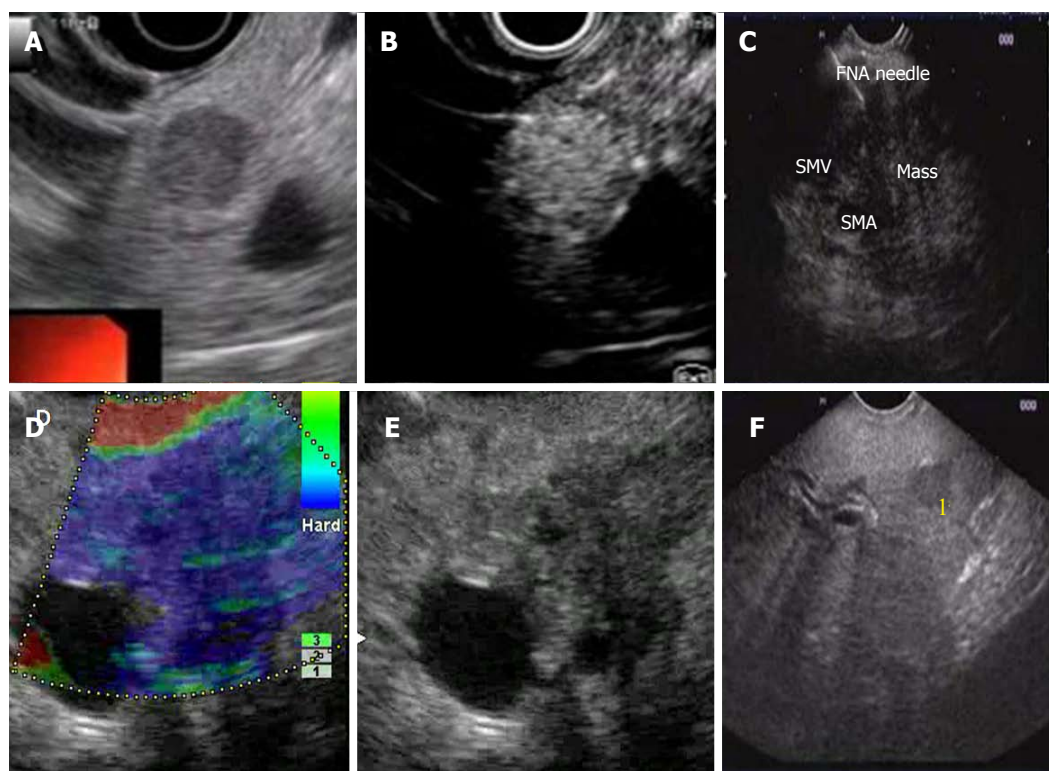


Figure 2 Contrast enhanced endoscopic ultrasound and endoscopic ultrasound elastography. A and B: Neuroendocrine tumor in the head of pancreas (HOP) before (A) and after (B) contrast administration; C: Fine needle aspiration (FNA) of mass in the HOP; D and E: Carcinoma HOP, EUS elastographic (D) appearance and B mode EUS appearance (E); F: Carcinoma HOP with metastasis (1) in the left lobe of liver..

histograms in a multicenter study wherein a sensitivity of 93.4%, a specificity of 66.0%, a positive predictive value of 92.5% and an overall accuracy of 85.4% for the mean hue-histogram in the detection of malignancy were observed. In a further development, Schrader *et al*^[43] had 100% sensitivity and specificity in differentiating benign from malignant lesions in tissues with blue color (hard tissue), on histogram with less discrimination on evaluating areas with red or green colors representing softer tissue. The role of this modality is still evolving to reduce the various biases of calculation of strain.

Contrast-enhanced (CE)-EUS consists of administration of contrast agents through the blood stream. The contrast agent contains microbubbles that can be detected by EUS in the small, low-velocity vasculature of pancreatic tumors on real-time evaluation. Initial studies using Levovist®, Albutex and FS 069 Optison as contrast agents demonstrated that the hyper vascular aspect of neuroendocrine tumors and the hypo vascular aspect of pancreatic adenocarcinoma^[44-48]. Modern contrast enhanced EUS relies on a dedicated contrast harmonic echo-EUS (CHE-EUS) technique that detects signals from micro bubbles delivered by new contrast agents like Sonovue® in vessels with very slow flow as they have longer perfusion time and stronger backscatter without the burden of Doppler-related artifacts. Fusaroli *et al*^[49] investigated 90 patients with solid pancreatic lesions by CEH-EUS, using Sonovue® as contrast agent. The finding of a hypo-enhancing mass with an inhomogeneous pattern diagnosed pancreatic adenocarcinoma with a

sensitivity of 96% and an accuracy of 82%. The study also indicated that this CEH-EUS pattern diagnosed malignancy more accurately than the finding of a hypo-echoic mass on standard EUS. Hyper-enhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%). In a study by Napoleon *et al*^[50], the finding of a hypo-enhanced lesion was able to detect malignancy with a sensitivity, specificity and accuracy of 89%, 88%, and 88.5%, respectively. Seicean *et al*^[51] investigated the possibility to use quantitative CEH-EUS data in the differential diagnosis between pancreatic cancer and chronic pancreatitis. A hypo-enhanced pattern was the most common finding both in pancreatic adenocarcinoma and in mass forming chronic pancreatitis. However, an index of contrast uptake ratio was calculated and this was significantly lower in adenocarcinoma compared to cases with mass-forming chronic with a sensitivity of 80% and a specificity of 91.7%. A recent prospective study by Kitano *et al*^[52] showed that when CH-EUS was combined with EUS-FNA, the sensitivity of EUS-FNA increased from 92.2% to 100%. Data from South Korea showed a sensitivity and diagnostic accuracy of 93% and 92%, respectively for the diagnosis of pancreatic cancer^[53]. In a recent retrospective study by Park *et al*^[54] pancreatic adenocarcinomas showed a hypo-enhanced pattern on CH-EUS with a sensitivity of 92%, the specificity of 68% and the accuracy approximately 82%.

In a recent review, Kitano *et al*^[55] have mentioned that CH-EUS identifies pancreatic adenocarcinomas

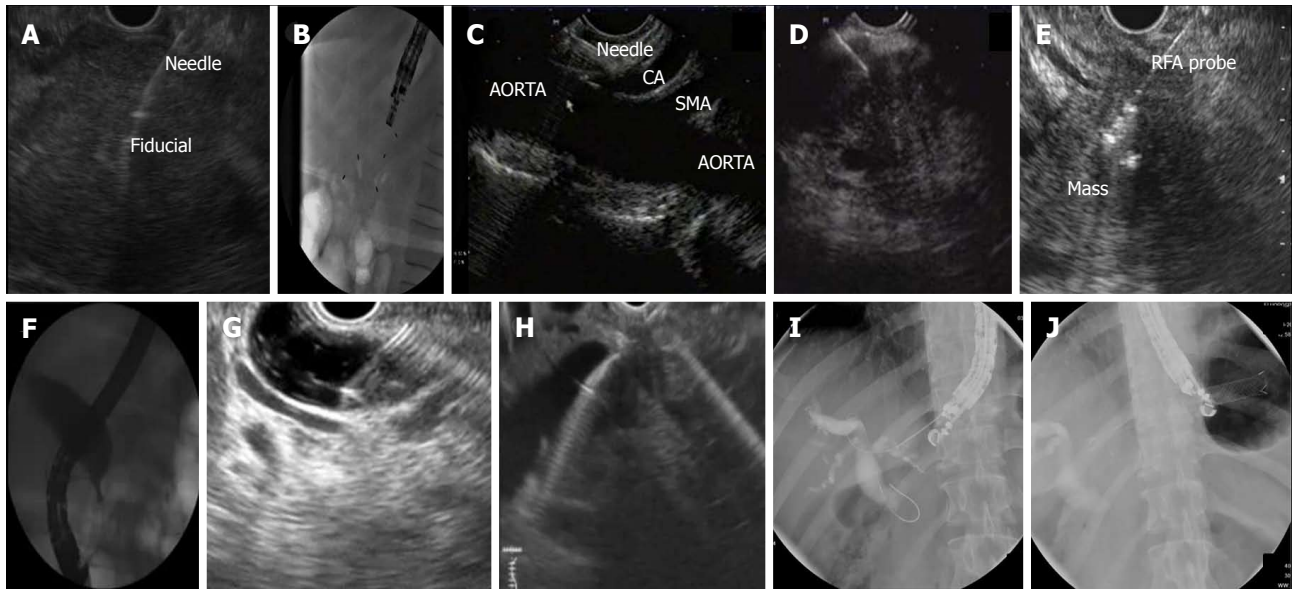


Figure 3 Endoscopic ultrasound guided interventions. A and B: fiducial placement for mass in the head of pancreas (HOP); C: celiac plexus neurolysis (CA-celiac artery, SMA-superior mesenteric artery); D: fine needle aspiration of mass in the HOP; E radiofrequency ablation (RFA) of mass in the HOP; F,G and H: choledochoduodenostomy for biliary stricture due to mass in the HOP; I and J: hepaticogastrostomy and placement of metal stent.

as solid lesions exhibiting hypo-enhancement with a sensitivity and specificity of 88%-96% and 88%-94%, respectively. In particular, 80%-100% of false-negative cases in EUS-FNA are correctly classified by CH-EUS, suggesting its complementary role. In addition, it improves depiction of some subtle lesions in conventional EUS, thus facilitating EUS-FNA. For quantitative perfusion analysis, a time-intensity curve (TIC) for the region of interest can be generated during CH-EUS. The maximum intensity gain and the echo intensity reduction rate from the peak at 1 min obtained by TIC can be used for differentiation of pancreatic adenocarcinoma from other tumors. CH-EUS is also useful for differentiation of invasive intraductal papillary mucinous neoplasms (IPMN) from non-invasive IPMN^[55]. Thus, CH-EUS technology is very promising and is likely to play a role in the precise diagnosis of malignant pancreatic lesions.

The detection of various chromosomal abnormalities in FNA aspirates is a field which is rapidly evolving. It is useful in cases with indeterminate results and might help in confirming the diagnosis of a malignancy. Among the earlier studies, telomerase activity was studied by Mishra *et al.*^[56] which on combination with cytology results increased the sensitivity from 85% to 98% with 100% specificity. The use of fluorescence *in situ* hybridization (FISH) analysis by Kubiliun *et al.*^[57] on FNA specimens with inconclusive results revealed a sensitivity of 74% for detecting pancreatic cancer which increased to 85% on combining with cytology. Reicher *et al.*^[58] from US demonstrated the use of detecting K-ras mutation in addition to FISH analysis in precisely identifying 60% of atypical FNAs with final malignant diagnosis yielding 88% sensitivity and 94% specificity with 90% accuracy. The pooled sensitivity of EUS-FNA for the differential diagnosis of pancreatic

adenocarcinoma was 80.6%, specificity was 97% and probable sensitivity and specificity were 76.8% and 93.3% for K-ras gene analysis, respectively. For combined EUS-FNA plus K-ras mutation analysis it was 88.7% and 92%, in a meta-analysis by Fuccio *et al.*^[59]. Overall, K-ras mutation testing applied to inconclusive cases by EUS-FNA reduced the false-negative rate by 55.6% albeit with a false-positive rate of 10.7%. Layfield *et al.*^[60] in their guidelines mention that many gene mutations (*KRAS*, *GNAS*, *VHL*, *RNF43*, and *CTNNB1*) may be of aid in the diagnosis of cystic neoplasms. The shortcoming of detecting chromosomal abnormalities in FNA specimens is that pancreatic cancers may express multiple mutations, detecting more might increase the sensitivity but with doubtful cost effectiveness.

ROLE OF EUS IN THERAPEUTICS OF PANCREATIC CANCER

The increasing use of EUS as a diagnostic modality has also led to its importance as an interventional tool in the management of pancreatic cancer. It ranges from assisting in radiotherapy, delivery of chemotherapeutic agents to palliation by celiac plexus neurolysis and biliary drainage wherever ERCP fails.

EUS delivery of antitumor agents is largely investigational and is still in experimental stage. The requirement to develop this option is due to pancreatic carcinoma having a poor response to chemotherapeutic agents and radiation; and neoadjuvant chemotherapy can lead to a desmoplastic reaction further impairing drug delivery. Chang *et al.*^[61] used cytoimplant (Allogenic mixed lymphocyte culture) advanced pancreatic cancer with partial response noted in two patients. TNFerade biologic

is a replication-deficient adenoviral vector that expresses tumor necrosis factor- α (TNF- α), regulated by a radiation inducible promoter; inducible by chemotherapy and radiation has been used by various authors. Hecht *et al*^[62] had shown one complete response, 3 partial responses, and 12 patients with stable disease, overall 3 survived > 24 mo. Subsequently Herman *et al*^[63], reported in the randomized phase III trial among patients with locally advanced pancreatic cancer (LAPC) that though it is safe in combination with chemotherapy, it does not increase survival. ONYX-015, an adenovirus which preferentially replicates and kills malignant cells was studied by Hecht *et al*^[64] wherein 2 patients had partial regression of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease with 2 patients each having sepsis and duodenal perforation. The injection of immature dendritic cells, which induce T-cell immune response against malignant cells, was used by Irisawa *et al*^[65] successfully into the tumors of 7 patients with unresectable pancreatic cancer, with a cohort median survival of 9.9 mo. Thereafter, Hirooka *et al*^[66] using the same therapy demonstrated effective responses in three of five patients; 1 had partial remission and 2 had long stable disease of more than 6 mo. This combined therapy was synergistically effective. Despite these studies, much more large prospective studies are required before these techniques are translated into clinical practice.

EUS guided brachytherapy has been carried out with radioactive seeds being placed into the tumour with the help of linear echoendoscope. The most popular radioactive seeds are Iodine 125, palladium 103 and iridium 192; iodine being the preferred radioactive material due to its long half life of 60 d in pancreatic cancers with rapidly dividing cells. Jin *et al*^[67] in their experience achieved partial remission in three cases, estimated median survival time of nine months with improvement in pain but no survival benefit.

EUS guided fiducial insertion is being done in pancreatic malignancy to place markers inside the tumor for guiding stereotactic body radiotherapy. These markers can be radioactive spheres, coils or seeds. Its feasibility was shown by Pishvaian *et al*^[68] wherein he reported a technical success of 85%. Subsequently in a prospective study by Park *et al*^[69] fiducial insertion was successful in 88% of the 57 patients, Sanders *et al*^[70] had a success rate of 90% for EUS fiducial insertion in a prospective study of 51 patients while DiMaio *et al*^[71] achieved a success rate of 97% with a 22-gauge needle. Law *et al*^[72] found this technique safe and feasible to assist intraoperative localization of small pancreatic neuroendocrine tumors. The 2 types of fiducials were compared by Khashab *et al*^[73] in 39 patients with advanced pancreatic cancer. Traditional fiducials of 5 mm length had better visibility scores with similar migration rates as compared to viscoil fiducials of 10 mm length.

EUS-guided cryothermal ablation has been studied by Arcidiacono *et al*^[74] in 22 patients with unresectable stage

III pancreatic adenocarcinoma with a feasibility of 73% with insignificant tumor size reduction. Further studies are required to demonstrate progression-free survival and local effects. Recently Pai *et al*^[75] used radiofrequency ablation (RF) which was applied with a monopolar RF probe (1.2 mm Habib EUS-RFA catheter) placed through a 19 or 22 gauge FNA needle after FNA was performed in patients with a tumor in the head of the pancreas with a 100% success rate. The response ranged from complete resolution to a 50% reduction in size. Oh *et al*^[76,77] used EUS-guided ethanol lavage with paclitaxel injection (EUS-EP) for cystic tumors of the pancreas in two studies and found a 62%-99% resolution rate with adequate safety and feasibility. These data indicate the need for further large prospective studies to ascertain their roles in the management of pancreatic cancer.

EUS guided celiac plexus neurolysis (CPN) provides pain relief, palliation and reduces narcotic use in patients with unresectable pancreatic cancer^[78]. The injection of a neurolytic drug into the celiac plexus disrupts the signal transmission to spinal cord and central nervous system. Due to the anatomical location of the celiac plexus around the origin of the celiac trunk and the superior-mesenteric artery, EUS- CPN provides real-time visualization for a safe approach.

EUS-CPN was demonstrated to be safe and effective in alleviating refractory pain due to pancreatic cancer in a meta-analysis of 8 studies by Puli *et al*^[79]. Alcohol-based EUS-CPN was found safe and effective in this setting providing pain relief to 73% patients^[80]. A recent RCT by Wyse *et al*^[81] in 96 patients demonstrated greater pain relief in the early EUS-CPN group at three months than in conventional management group. As compared to opioids, EUS-CPN reduced pain at four and eight weeks and significantly reduced opioid consumption^[82]. In addition a single central injection was found to be as effective as bilateral or multiple injections^[83,84]. In another comparison between EUS-CPN and EUS-celiac ganglia neurolysis (CGN), Doi *et al*^[85] observed higher treatment response rate and complete response rate in the EUS-CGN group compared to the EUS-CPN group.

EUS guided biliary drainage is another important area where therapeutic EUS is helpful. With failed ERCP, biliary drainage can be established by 3 endoscopic methods (1, transluminal biliary drainage with hepaticogastrostomy or choledochoduodenostomy, 2, EUS antegrade drainage and 3, EUS rendezvous drainage)^[86]. In 7% to 13% of patients with pancreatic head malignancy have duodenal stenosis, making ERCP technically challenging or impossible^[87].

The role EUS guided biliary drainage in pancreatic cancer in failed ERCP has been recently demonstrated by Weilert^[88] in 21 patients, 52% patients with pancreatic cancer wherein he achieved technical success in 20/21 (95.2%) and clinical success 19/21 (90.4%). He noted that EUS-guided antegrade biliary drainage using the intra-hepatic access route had high technical and clinical success with low adverse rate. In a recent study of 208

patients with malignant distal CBD obstruction requiring SEMS placement, authors compared the short-term outcome of single session EUS guided biliary drainage with ERCP^[89]. SEMS placement was successful in 97 and 98 patients in the respective groups (93.26% vs 94.23%, $P = 1.00$). The incidence of pancreatitis was higher with ERCP, and EUS group had superior treatment success rates in patients with duodenal stenosis.

CONCLUSION

EUS is rapidly becoming a sensitive and specific modality for diagnosing pancreatic cancer especially on combining with EUS-FNA albeit with difficulty in the presence of chronic pancreatitis. With the advent of newer technology in the form of EUS elastography, CE-EUS, and gene mutations detection in FNA specimens the diagnostic dilemma is better resolved. The availability of interventional EUS has allowed gastroenterologists to make significant difference in management of pancreatic cancer by its various therapeutic options including areas which have been traditionally dealt by surgeons and interventional radiologists. It is likely to become an important modality in the multidisciplinary management of pancreatic cancer.

REFERENCES

- 1 **Surveillance Research Program.** SEER Stat Fact Sheets: Pancreas Cancer. Available from: URL: <http://seer.cancer.gov/statfacts/html/pancreas.html>
- 2 **Saif MW.** Pancreatic neoplasm in 2011: an update. *JOP* 2011; **12**: 316-321 [PMID: 21737886]
- 3 **Ngamruengphong S, Li F, Zhou Y, Chak A, Cooper GS, Das A.** EUS and survival in patients with pancreatic cancer: a population-based study. *Gastrointest Endosc* 2010; **72**: 78-83, 83.e1-2 [PMID: 20620274 DOI: 10.1016/j.gie.2010.01.072]
- 4 **Nattermann C, Goldschmidt AJ, Dancygier H.** Endosonography in chronic pancreatitis--a comparison between endoscopic retrograde pancreatography and endoscopic ultrasonography. *Endoscopy* 1993; **25**: 565-570 [PMID: 8119205 DOI: 10.1055/s-2007-1010406]
- 5 **Catalano MF, Lahoti S, Geenen JE, Hogan WJ.** Prospective evaluation of endoscopic ultrasonography, endoscopic retrograde pancreatography, and secretin test in the diagnosis of chronic pancreatitis. *Gastrointest Endosc* 1998; **48**: 11-17 [PMID: 9684658 DOI: 10.1016/s0016-5107(98)70122-1]
- 6 **Holt BA, Varadarajulu S.** Features of Chronic Pancreatitis and Associated Masses: A Focus on Endosonography. *VJGIEN* 2014; **2**: 50-54
- 7 **Volmar KE, Vollmer RT, Jowell PS, Nelson RC, Xie HB.** Pancreatic FNA in 1000 cases: a comparison of imaging modalities. *Gastrointest Endosc* 2005; **61**: 854-861 [PMID: 15933687 DOI: 10.1016/s0016-5107(05)00364-0]
- 8 **Rösch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, Classen M.** Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointest Endosc* 1991; **37**: 347-352 [PMID: 2070987 DOI: 10.1016/s0016-5107(91)70729-3]
- 9 **Ardengh JC, Lopes CV, de Lima LF, de Oliveira JR, Venco F, Santo GC, Modena JL.** Diagnosis of pancreatic tumors by endoscopic ultrasound-guided fine-needle aspiration. *World J Gastroenterol* 2007; **13**: 3112-3116 [PMID: 17589929]
- 10 **Faigel DO, Ginsberg GG, Bentz JS, Gupta PK, Smith DB, Kochman ML.** Endoscopic ultrasound-guided real-time fine-needle aspiration biopsy of the pancreas in cancer patients with pancreatic lesions. *J Clin Oncol* 1997; **15**: 1439-1443 [PMID: 9193337]
- 11 **Chen J, Yang R, Lu Y, Xia Y, Zhou H.** Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol* 2012; **138**: 1433-1441 [PMID: 22752601 DOI: 10.1007/s00432-012-1268-1]
- 12 **Wiersema MJ, Vilman P, Giovannini M, Chang KJ, Wiersema LM.** Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997; **112**: 1087-1095 [PMID: 9097990 DOI: 10.1016/s0016-5085(97)70164-1]
- 13 **Bhutani MS, Hawes RH, Baron PL, Sanders-Cliette A, van Velse A, Osborne JF, Hoffman BJ.** Endoscopic ultrasound guided fine needle aspiration of malignant pancreatic lesions. *Endoscopy* 1997; **29**: 854-858 [PMID: 9476770 DOI: 10.1055/s-2007-1004321]
- 14 **Harewood GC, Wiersema MJ.** Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. *Am J Gastroenterol* 2002; **97**: 1386-1391 [PMID: 12094855 DOI: 10.1111/j.1572-0241.2002.05777.x]
- 15 **Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA.** How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: A meta-analysis and systematic review. *Pancreas* 2013; **42**: 20-26 [PMID: 23254913 DOI: 10.1097/MPA.0b013e3182546e79]
- 16 **Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L.** Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol* 2004; **99**: 844-850 [PMID: 15128348 DOI: 10.1111/j.1572-0241.2004.04177.x]
- 17 **Bronstein YL, Loyer EM, Kaur H, Choi H, David C, DuBrow RA, Broemeling LD, Cleary KR, Charnsangavej C.** Detection of small pancreatic tumors with multiphasic helical CT. *AJR Am J Roentgenol* 2004; **182**: 619-623 [PMID: 14975959 DOI: 10.2214/ajr.182.3.1820619]
- 18 **Koelblinger C, Ba-Ssalamah A, Goetzinger P, Puchner S, Weber M, Sahora K, Scharitzer M, Plank C, Schima W.** Gadobenate dimeglumine-enhanced 3.0-T MR imaging versus multiphasic 64-detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. *Radiology* 2011; **259**: 757-766 [PMID: 21436084 DOI: 10.1148/radiol.11101189]
- 19 **Arsalan A, Buanes T, Geitung JT.** Pancreatic carcinoma: MR, MR angiography and dynamic helical CT in the evaluation of vascular invasion. *Eur J Radiol* 2001; **38**: 151-159 [PMID: 11335098 DOI: 10.1016/s0720-048x(00)00280-1]
- 20 **Soriano A, Castells A, Ayuso C, Ayuso JR, de Caralt MT, Ginès MA, Real MI, Gilabert R, Quintó L, Trilla A, Feu F, Montanyà X, Fernández-Cruz L, Navarro S.** Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. *Am J Gastroenterol* 2004; **99**: 492-501 [PMID: 15056091 DOI: 10.1111/j.1572-0241.2004.04087.x]
- 21 **Egorov VI, Petrov RV, Solodina EN, Karmazanovsky GG, Starostina NS, Kuruschkina NA.** Computed tomography-based diagnostics might be insufficient in the determination of pancreatic cancer unresectability. *World J Gastrointest Surg* 2013; **5**: 83-96 [PMID: 23717744 DOI: 10.4240/wjgs.v5.i4.83]
- 22 **Poley JW, Kluijdt I, Gouma DJ, Harinck F, Wagner A, Aalfs C, van Eijck CH, Cats A, Kuipers EJ, Nio Y, Fockens P, Bruno MJ.** The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol* 2009; **104**: 2175-2181 [PMID: 19491823 DOI: 10.1038/ajg.2009.276]
- 23 **Eloubeidi MA, Jhala D, Chhieng DC, Chen VK, Eltoun I, Vickers S, Mel Wilcox C, Jhala N.** Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. *Cancer* 2003; **99**: 285-292 [PMID: 14579295 DOI: 10.1002/cncr.11643]
- 24 **Gress F, Gottlieb K, Sherman S, Lehman G.** Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. *Ann Intern Med* 2001; **134**: 459-464 [PMID: 11335098]

- 11255521 DOI: 10.7326/0003-4819-134-6-200103200-00010]
- 25 **Varadarajulu S**, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc* 2005; **62**: 728-736; quiz 751, 753 [PMID: 16246688 DOI: 10.1016/j.gie.2005.06.051]
 - 26 **Bhutani MS**, Gress FG, Giovannini M, Erickson RA, Catalano MF, Chak A, Deprez PH, Faigel DO, Nguyen CC. The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography. *Endoscopy* 2004; **36**: 385-389 [PMID: 15100944 DOI: 10.1055/s-2004-814320]
 - 27 **Siddiqui AA**, Kowalski TE, Shahid H, O'Donnell S, Tolin J, Loren DE, Infantolino A, Hong SK, Eloubeidi MA. False-positive EUS-guided FNA cytology for solid pancreatic lesions. *Gastrointest Endosc* 2011; **74**: 535-540 [PMID: 21737075 DOI: 10.1016/j.gie.2011.04.039]
 - 28 **Othman MO**, Raimondo M. Endoscopic ultrasound fine needle aspiration of pancreatic lesions: is a smaller needle safer and better? *Dig Liver Dis* 2011; **43**: 587-588 [PMID: 21665559 DOI: 10.1016/j.dld.2011.05.014]
 - 29 **Fabbri C**, Polifemo AM, Luigiano C, Cennamo V, Baccarini P, Collina G, Fornelli A, Macchia S, Zanini N, Jovine E, Fiscoletti M, Alibrandi A, D'Imperio N. Endoscopic ultrasound-guided fine needle aspiration with 22- and 25-gauge needles in solid pancreatic masses: a prospective comparative study with randomisation of needle sequence. *Dig Liver Dis* 2011; **43**: 647-652 [PMID: 21592873 DOI: 10.1016/j.dld.2011.04.005]
 - 30 **Sakamoto H**, Kitano M, Komaki T, Noda K, Chikugo T, Dote K, Takeyama Y, Das K, Yamao K, Kudo M. Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. *J Gastroenterol Hepatol* 2009; **24**: 384-390 [PMID: 19032453 DOI: 10.1111/j.1440-1746.2008.05636.x]
 - 31 **Möller K**, Papanikolaou IS, Toerner T, Delicha EM, Sarbia M, Schenck U, Koch M, Al-Abadi H, Meining A, Schmidt H, Schulz HJ, Wiedenmann B, Rösch T. EUS-guided FNA of solid pancreatic masses: high yield of 2 passes with combined histologic-cytologic analysis. *Gastrointest Endosc* 2009; **70**: 60-69 [PMID: 19394012 DOI: 10.1016/j.gie.2008.10.008]
 - 32 **LeBlanc JK**, Ciaccia D, Al-Assi MT, McGrath K, Imperiale T, Tao LC, Vallery S, DeWitt J, Sherman S, Collins E. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc* 2004; **59**: 475-481 [PMID: 15044881 DOI: 10.1016/s0016-5107(03)02863-3]
 - 33 **Jhala NC**, Eltoum IA, Eloubeidi MA, Meara R, Chhieng DC, Crowe DR, Jhala D. Providing on-site diagnosis of malignancy on endoscopic-ultrasound-guided fine-needle aspirates: should it be done? *Ann Diagn Pathol* 2007; **11**: 176-181 [PMID: 17498591 DOI: 10.1016/j.anndiagnpath.2006.03.005]
 - 34 **Klapman JB**, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol* 2003; **98**: 1289-1294 [PMID: 12818271 DOI: 10.1111/j.1572-0241.2003.07472.x]
 - 35 **Hébert-Magee S**, Bae S, Varadarajulu S, Ramesh J, Frost AR, Eloubeidi MA, Eltoum IA. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. *Cytopathology* 2013; **24**: 159-171 [PMID: 23711182 DOI: 10.1111/cyt.12071]
 - 36 **Yang D**, MoezArdalan K, Collins DP, Chauhan SS, Draganov PV, Forsmark CE, Wagh MS. Predictors of malignancy in patients with suspicious or indeterminate cytology on pancreatic endoscopic ultrasound-guided fine-needle aspiration: a multivariate model. *Pancreas* 2014; **43**: 922-926 [PMID: 24979616 DOI: 10.1097/MPA.0000000000000157]
 - 37 **Aljebreen AM**, Romagnuolo J, Perini R, Sutherland F. Utility of endoscopic ultrasound, cytology and fluid carcinoembryonic antigen and CA 19-9 levels in pancreatic cystic lesions. *World J Gastroenterol* 2007; **13**: 3962-3966 [PMID: 17663510 DOI: 10.3748/wjg.v13.i29.3962]
 - 38 **Giovannini M**, Hookey LC, Bories E, Pesenti C, Monges G, Delpero JR. Endoscopic ultrasound elastography: the first step towards virtual biopsy? Preliminary results in 49 patients. *Endoscopy* 2006; **38**: 344-348 [PMID: 16680632 DOI: 10.1055/s-2006-925158]
 - 39 **Giovannini M**, Thomas B, Erwan B, Christian P, Fabrice C, Benjamin E, Geneviève M, Paolo A, Pierre D, Robert Y, Walter S, Hanz S, Carl S, Christoph D, Pierre E, Jean-Luc VL, Jacques D, Peter V, Andrian S. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. *World J Gastroenterol* 2009; **15**: 1587-1593 [PMID: 19340900 DOI: 10.3748/wjg.15.1587]
 - 40 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. *Gastrointest Endosc* 2009; **70**: 1101-1108 [PMID: 19647248 DOI: 10.1016/j.gie.2009.05.011]
 - 41 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010; **139**: 1172-1180 [PMID: 20600020 DOI: 10.1053/j.gastro.2010.06.059]
 - 42 **Săftoiu A**, Vilmann P, Gorunescu F, Janssen J, Hocke M, Larsen M, Iglesias-Garcia J, Arcidiacono P, Will U, Giovannini M, Dietrich C, Havre R, Gheorghe C, McKay C, Gheonea DI, Ciurea T; European EUS Elastography Multicentric Study Group. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. *Endoscopy* 2011; **43**: 596-603 [PMID: 21437851 DOI: 10.1055/s-0030-1256314]
 - 43 **Schrader H**, Wiese M, Ellrichmann M, Belyaev O, Uhl W, Tannapfel A, Schmidt W, Meier J. Diagnostic value of quantitative EUS elastography for malignant pancreatic tumors: relationship with pancreatic fibrosis. *Ultraschall Med* 2012; **33**: E196-E201 [PMID: 21630184 DOI: 10.1055/s-0031-1273256]
 - 44 **Bhutani MS**, Hoffman BJ, van Velse A, Hawes RH. Contrast-enhanced endoscopic ultrasonography with galactose microparticles: SHU508 A (Levovist). *Endoscopy* 1997; **29**: 635-639 [PMID: 9360874 DOI: 10.1055/s-2007-1004270]
 - 45 **Hirooka Y**, Goto H, Ito A, Hayakawa S, Watanabe Y, Ishiguro Y, Kojima S, Hayakawa T, Naitoh Y. Contrast-enhanced endoscopic ultrasonography in pancreatic diseases: a preliminary study. *Am J Gastroenterol* 1998; **93**: 632-635 [PMID: 9576461 DOI: 10.1111/j.1572-0241.1998.179_b.x]
 - 46 **Becker D**, Strobel D, Bernatik T, Hahn EG. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. *Gastrointest Endosc* 2001; **53**: 784-789 [PMID: 11375592 DOI: 10.1067/mge.2001.115007]
 - 47 **Giovannini M**. Endosonography: new developments in 2006. *ScientificWorldJournal* 2007; **7**: 341-363 [PMID: 17334627 DOI: 10.1100/tsw.2007.28]
 - 48 **Hocke M**, Schulze E, Gottschalk P, Topalidis T, Dietrich CF. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J Gastroenterol* 2006; **12**: 246-250 [PMID: 16482625]
 - 49 **Fusaroli P**, Spada A, Mancino MG, Caletti G. Contrast harmonic echo-endoscopic ultrasound improves accuracy in diagnosis of solid pancreatic masses. *Clin Gastroenterol Hepatol* 2010; **8**: 629-34.e1-2 [PMID: 20417721 DOI: 10.1016/j.cgh.2010.04.012]
 - 50 **Napoleon B**, Alvarez-Sanchez MV, Gincoul R, Pujol B, Lefort C, Lepilliez V, Labadie M, Souquet JC, Queneau PE, Scoazec JY, Chayvialle JA, Ponchon T. Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. *Endoscopy* 2010; **42**: 564-570 [PMID: 20593334 DOI: 10.1055/s-0030-1255537]
 - 51 **Seicean A**, Badea R, Stan-Iuga R, Mocan T, Gulei I, Pascu O. Quantitative contrast-enhanced harmonic endoscopic ultrasonography for the discrimination of solid pancreatic masses. *Ultraschall Med* 2010; **31**: 571-576 [PMID: 21080306 DOI: 10.1055/s-0029-1245833]
 - 52 **Kitano M**, Kudo M, Yamao K, Takagi T, Sakamoto H, Komaki T, Kamata K, Imai H, Chiba Y, Okada M, Murakami T, Takeyama Y. Characterization of small solid tumors in the pancreas: the

- value of contrast-enhanced harmonic endoscopic ultrasonography. *Am J Gastroenterol* 2012; **107**: 303-310 [PMID: 22008892 DOI: 10.1038/ajg.2011.354]
- 53 **Lee TY**, Cheon YK, Shim CS. Clinical role of contrast-enhanced harmonic endoscopic ultrasound in differentiating solid lesions of the pancreas: a single-center experience in Korea. *Gut Liver* 2013; **7**: 599-604 [PMID: 24073319 DOI: 10.5009/gnl.2013.7.5.599]
 - 54 **Park JS**, Kim HK, Bang BW, Kim SG, Jeong S, Lee DH. Effectiveness of contrast-enhanced harmonic endoscopic ultrasound for the evaluation of solid pancreatic masses. *World J Gastroenterol* 2014; **20**: 518-524 [PMID: 24574720 DOI: 10.3748/wjg.v20.i2.518]
 - 55 **Kitano M**, Kamata K, Imai H, Miyata T, Yasukawa S, Yanagisawa A, Kudo M. Contrast-enhanced harmonic endoscopic ultrasonography for pancreatobiliary diseases. *Dig Endosc* 2015; **27** Suppl 1: 60-67 [PMID: 25639788 DOI: 10.1111/den.12454]
 - 56 **Mishra G**, Zhao Y, Sweeney J, Pineau BC, Case D, Ho C, Blackstock AW, Geisinger K, Howerton R, Levine E, Shen P, Ibdah J. Determination of qualitative telomerase activity as an adjunct to the diagnosis of pancreatic adenocarcinoma by EUS-guided fine-needle aspiration. *Gastrointest Endosc* 2006; **63**: 648-654 [PMID: 16564867 DOI: 10.1016/j.gie.2005.11.056]
 - 57 **Kubiliun N**, Ribeiro A, Fan YS, Rocha-Lima CM, Sleeman D, Merchan J, Barkin J, Levi J. EUS-FNA with rescue fluorescence in situ hybridization for the diagnosis of pancreatic carcinoma in patients with inconclusive on-site cytopathology results. *Gastrointest Endosc* 2011; **74**: 541-547 [PMID: 21752364 DOI: 10.1016/j.gie.2011.04.043]
 - 58 **Reicher S**, Boyar FZ, Albitar M, Sulcova V, Agersborg S, Nga V, Zhou Y, Li G, Venegas R, French SW, Chung DS, Stabile BE, Eysselein VE, Anguiano A. Fluorescence in situ hybridization and K-ras analyses improve diagnostic yield of endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic masses. *Pancreas* 2011; **40**: 1057-1062 [PMID: 21705950 DOI: 10.1097/MPA.0b013e3182200201]
 - 59 **Fuccio L**, Hassan C, Laterza L, Correale L, Pagano N, Bocus P, Fabbri C, Maimone A, Cennamo V, Repici A, Costamagna G, Bazzoli F, Larghi A. The role of K-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis of prospective studies. *Gastrointest Endosc* 2013; **78**: 596-608 [PMID: 23660563 DOI: 10.1016/j.gie.2013.04.162]
 - 60 **Layfield LJ**, Ehya H, Filie AC, Hruban RH, Jhala N, Joseph L, Vielh P, Pitman MB. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolaou Society of Cytopathology guidelines for pancreatobiliary cytology. *Diagn Cytopathol* 2014; **42**: 351-362 [PMID: 24639398 DOI: 10.1002/dc.23093]
 - 61 **Chang KJ**, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, Granger GA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer* 2000; **88**: 1325-1335 [PMID: 10717613 DOI: 10.1002/(sici)1097-0142(20000315)88: 6<1325: : aid-cnrcr>3.0.co; 2-t]
 - 62 **Hecht JR**, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, Hanna N, Chang KJ, Javle M, Posner M, Waxman I, Reid A, Erickson R, Canto M, Chak A, Blatner G, Kovacevic M, Thornton M. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. *Gastrointest Endosc* 2012; **75**: 332-338 [PMID: 22248601 DOI: 10.1016/j.gie.2011.10.007]
 - 63 **Herman JM**, Wild AT, Wang H, Tran PT, Chang KJ, Taylor GE, Donehower RC, Pawlik TM, Ziegler MA, Cai H, Savage DT, Canto MI, Klapman J, Reid T, Shah RJ, Hoffe SE, Rosemurgy A, Wolfgang CL, Laheru DA. Randomized phase III multi-institutional study of TNFerade biologic with fluorouracil and radiotherapy for locally advanced pancreatic cancer: final results. *J Clin Oncol* 2013; **31**: 886-894 [PMID: 23341531 DOI: 10.1200/JCO.2012.44.7516]
 - 64 **Hecht JR**, Bedford R, Abbruzzese JL, Lahoti S, Reid TR, Soetikno RM, Kirn DH, Freeman SM. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003; **9**: 555-561 [PMID: 12576418]
 - 65 **Irisawa A**, Takagi T, Kanazawa M, Ogata T, Sato Y, Takenoshita S, Ohto H, Ohira H. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine: a pilot study. *Pancreas* 2007; **35**: 189-190 [PMID: 17632329 DOI: 10.1097/01.mpa.0000250141.25639.e9]
 - 66 **Hirooka Y**, Itoh A, Kawashima H, Hara K, Nonogaki K, Kasugai T, Ohno E, Ishikawa T, Matsubara H, Ishigami M, Katano Y, Ohmiya N, Niwa Y, Yamamoto K, Kaneko T, Nieda M, Yokokawa K, Goto H. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. *Pancreas* 2009; **38**: e69-e74 [PMID: 19276867 DOI: 10.1097/MPA.0b013e318197a9e3]
 - 67 **Jin Z**, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy* 2008; **40**: 314-320 [PMID: 18283622 DOI: 10.1055/s-2007-995476]
 - 68 **Pishvaian AC**, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc* 2006; **64**: 412-417 [PMID: 16923491 DOI: 10.1016/j.gie.2006.01.048]
 - 69 **Park WG**, Yan BM, Schellenberg D, Kim J, Chang DT, Koong A, Patalano C, Van Dam J. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. *Gastrointest Endosc* 2010; **71**: 513-518 [PMID: 20189509 DOI: 10.1016/j.gie.2009.10.030]
 - 70 **Sanders MK**, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, Burton S, McGrath K. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. *Gastrointest Endosc* 2010; **71**: 1178-1184 [PMID: 20362284 DOI: 10.1016/j.gie.2009.12.020]
 - 71 **DiMaio CJ**, Nagula S, Goodman KA, Ho AY, Markowitz AJ, Schattner MA, Gerdes H. EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). *Gastrointest Endosc* 2010; **71**: 1204-1210 [PMID: 20598247 DOI: 10.1016/j.gie.2010.01.003]
 - 72 **Law JK**, Singh VK, Khashab MA, Hruban RH, Canto MI, Shin EJ, Saxena P, Weiss MJ, Pawlik TM, Wolfgang CL, Lennon AM. Endoscopic ultrasound (EUS)-guided fiducial placement allows localization of small neuroendocrine tumors during parenchymal-sparing pancreatic surgery. *Surg Endosc* 2013; **27**: 3921-3926 [PMID: 23636530 DOI: 10.1007/s00464-013-2975-7]
 - 73 **Khashab MA**, Kim KJ, Tryggstad EJ, Wild AT, Roland T, Singh VK, Lennon AM, Shin EJ, Ziegler MA, Sharaiha RZ, Canto MI, Herman JM. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. *Gastrointest Endosc* 2012; **76**: 962-971 [PMID: 23078921 DOI: 10.1016/j.gie.2012.07.006]
 - 74 **Arcidiacono PG**, Carrara S, Reni M, Petrone MC, Cappio S, Balzano G, Boemo C, Cereda S, Nicoletti R, Enderle MD, Neugebauer A, von Renteln D, Eickhoff A, Testoni PA. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. *Gastrointest Endosc* 2012; **76**: 1142-1151 [PMID: 23021160 DOI: 10.1016/j.gie.2012.08.006]
 - 75 **Pai M**, Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, Kaba I, Beckebaum S, Drymoussis P, Kahaleh M, Brugge W. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. *World J Gastrointest Surg* 2015; **7**: 52-59 [PMID: 25914783 DOI: 10.4240/wjgs.v7.i4.52]
 - 76 **Oh HC**, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 2008; **67**: 636-642 [PMID: 18262182 DOI: 10.1016/j.gie.2007.09.038]
 - 77 **Oh HC**, Seo DW, Song TJ, Moon SH, Park do H, Soo Lee S, Lee SK, Kim MH, Kim J. Endoscopic ultrasonography-guided ethanol

- lavage with paclitaxel injection treats patients with pancreatic cysts. *Gastroenterology* 2011; **140**: 172-179 [PMID: 20950614 DOI: 10.1053/j.gastro.2010.10.001]
- 78 **Penman ID**, Rösch T. EUS 2008 Working Group document: evaluation of EUS-guided celiac plexus neurolysis/block (with video). *Gastrointest Endosc* 2009; **69**: S28-S31 [PMID: 19179165 DOI: 10.1016/j.gie.2008.11.004]
- 79 **Puli SR**, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci* 2009; **54**: 2330-2337 [PMID: 19137428 DOI: 10.1007/s10620-008-0651-x]
- 80 **Kaufman M**, Singh G, Das S, Concha-Parra R, Erber J, Micames C, Gress F. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. *J Clin Gastroenterol* 2010; **44**: 127-134 [PMID: 19826273 DOI: 10.1097/MCG.0b013e3181bb854d]
- 81 **Wyse JM**, Carone M, Paquin SC, Usatii M, Sahai AV. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol* 2011; **29**: 3541-3546 [PMID: 21844506 DOI: 10.1200/JCO.2010.32.2750]
- 82 **Arcidiacono PG**, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. *Cochrane Database Syst Rev* 2011; **(3)**: CD007519 [PMID: 21412903 DOI: 10.1002/14651858.CD007519.pub2]
- 83 **LeBlanc JK**, Al-Haddad M, McHenry L, Sherman S, Juan M, McGreevy K, Johnson C, Howard TJ, Lillemoe KD, DeWitt J. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? *Gastrointest Endosc* 2011; **74**: 1300-1307 [PMID: 22000795 DOI: 10.1016/j.gie.2011.07.073]
- 84 **Téllez-Ávila FI**, Romano-Munive AF, Herrera-Esquivel Jde J, Ramírez-Luna MA. Central is as effective as bilateral endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. *Endosc Ultrasound* 2013; **2**: 153-156 [PMID: 24949384 DOI: 10.7178/eus.06.007]
- 85 **Doi S**, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, Mukai T, Katanuma A, Kubota K, Ohnishi T, Ryozaawa S, Hara K, Itoi T, Hanada K, Yamao K. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. *Endoscopy* 2013; **45**: 362-369 [PMID: 23616126 DOI: 10.1055/s-0032-1326225]
- 86 **Iwashita T**, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. *Clin J Gastroenterol* 2014; **7**: 94-102 [PMID: 24765215]
- 87 **Tuca A**, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. *Cancer Manag Res* 2012; **4**: 159-169 [PMID: 22904637]
- 88 **Weilert F**. Prospective evaluation of simplified algorithm for EUS-guided intra-hepatic biliary access and antegrade interventions for failed ERCP. *Surg Endosc* 2014; **28**: 3193-3199 [PMID: 24879144 DOI: 10.1007/s00464-014-3588-5]
- 89 **Dhir V**, Itoi T, Khashab MA, Park do H, Yuen Bun Teoh A, Attam R, Messallam A, Varadarajulu S, Maydeo A. Multicenter comparative evaluation of endoscopic placement of expandable metal stents for malignant distal common bile duct obstruction by ERCP or EUS-guided approach. *Gastrointest Endosc* 2015; **81**: 913-923 [PMID: 25484326]

P- Reviewer: Klinge U, Yoshida H **S- Editor:** Song XX

L- Editor: A **E- Editor:** Lu YJ



Drug eluting biliary stents to decrease stent failure rates: A review of the literature

Joseph Shatzel, Jisoo Kim, Kartik Sampath, Sharjeel Syed, Jennifer Saad, Zilla H Hussain, Kabir Mody, J Marc Pipas, Stuart Gordon, Timothy Gardner, Richard I Rothstein

Joseph Shatzel, J Marc Pipas, Section of Hematology-Oncology, Dartmouth Hitchcock Medical Center, Lebanon, NH 03756, United States

Jisoo Kim, Sharjeel Syed, Geisel School of Medicine at Dartmouth, Hanover, NH 03755, United States

Kartik Sampath, Zilla H Hussain, Stuart Gordon, Timothy Gardner, Richard I Rothstein, Section of Gastroenterology, Dartmouth Hitchcock Medical Center, Lebanon, NH 03756, United States

Jennifer Saad, Section of Internal Medicine, Dartmouth Hitchcock Medical Center, Lebanon, NH 03756, United States

Kabir Mody, Mayo Clinic Cancer Center, Section of Hematology/Oncology, Mayo Clinic Florida, Jacksonville, FL 32224, United States

Author contributions: All authors contributed equally to the work, researched the topic and wrote the review.

Conflict-of-interest statement: The authors have no conflict of interest related to the manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Joseph Shatzel, MD, Section of Hematology-Oncology, Dartmouth Hitchcock Medical Center, Lebanon, NH 03756, United States. joseph.j.shatzel@hitchcock.org
Telephone: +1-603-6508380
Fax: +1-603-6506122

Received: April 3, 2015
Peer-review started: April 4, 2015
First decision: June 2, 2015

Revised: August 11, 2015

Accepted: October 17, 2015

Article in press: October 28, 2015

Published online: January 25, 2016

Abstract

Biliary stenting is clinically effective in relieving both malignant and non-malignant obstructions. However, there are high failure rates associated with tumor ingrowth and epithelial overgrowth as well as internally from biofilm development and subsequent clogging. Within the last decade, the use of prophylactic drug eluting stents as a means to reduce stent failure has been investigated. In this review we provide an overview of the current research on drug eluting biliary stents. While there is limited human trial data regarding the clinical benefit of drug eluting biliary stents in preventing stent obstruction, recent research suggests promise regarding their safety and potential efficacy.

Key words: Bile ducts; Cholangiocarcinoma; Endoscopy; Pancreas

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Despite the short life expectancies of patients with biliary tract cancers, biliary stenting suffers from high stent re-obstruction rates, provoking unneeded costs, morbidity and mortality. Drug eluting stents offer the possibility of decreasing stent failure rates from both biliary stent clogging, and external obstruction from tumor and epithelial ingrowth. In this inclusive review we outline the current body of experimental literature on drug eluting stents including bench, animal and human trials, and discuss possible targets for future research.

Shatzel J, Kim J, Sampath K, Syed S, Saad J, Hussain ZH, Mody K, Pipas JM, Gordon S, Gardner T, Rothstein RI. Drug eluting biliary stents to decrease stent failure rates: A review of the literature. *World J Gastrointest Endosc* 2016; 8(2): 77-85 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/77.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.77>

INTRODUCTION

Obstruction of the bile duct results in serious clinical consequences such as cholangitis and death. Biliary stenting is an effective means of relieving obstruction, and is the preferred method of palliating patients with malignancy^[1]. Malignant obstructions in particular cause high stent obstruction rates, despite the relatively short lifespan of patients with biliary tract cancers (Table 1). Stent failure is associated with recurrent morbidity, and often necessitates repeat endoscopy with stent retrieval and replacement. These procedures carry an increased risk for procedural complications such as pancreatitis, and can result in additional hospital admissions.

Stent failure can be stratified into four primary etiologies: Internal stent failure from biliary clogging, external failure caused by tumor ingrowth or overgrowth of excessive epithelial or malignant cells, and stent migration. The incidence of each type of failure in malignant obstruction has been documented in several small prospective trials (Table 2). For the purposes of this review, only internal and external failure will be addressed.

Drug eluting stents have been used for several decades in the setting of coronary artery disease to decrease the incidence of stent failure. Currently there have only been a limited number of human trials evaluating drug eluting biliary stents to prevent external obstruction^[2,3], none of which showed a significant effect in decreasing stent failure rates. However, only one agent (paclitaxel) has been trialed in humans with malignant obstruction^[2,3]. Both trials showed the hybrid stent was safe and well tolerated when compared to traditional stenting. There is a growing body of literature looking at *in vitro* and *in vivo* models of drug eluting biliary stents as prophylaxis against internal and external sources of failure. In this review, we divide stent failure pathophysiology into internal and external mechanisms and analyze the current literature on the use of stent drug elution as prophylaxis against the respective failure types.

INTERNAL STENT FAILURE

Internal stent failure results from the accumulation of obstructing material in the stent lumen. It is a complex process involving microbial colonization and biofilm generation^[4]. This process is exacerbated by, but not dependent on, the reflux of duodenal contents into the biliary system.

A normal functioning sphincter of oddi helps to

preserve the relative sterility of the biliary tree compared to the duodenum. Stenting across the papilla allows for the reflux of intestinal contents and bacteria into the biliary system^[5]. After placement, biliary stents are quickly colonized by a diverse poly-microbial community^[6-10]. Aerobic and anaerobic bacteria are readily isolated from occluded biliary stents with *Enterococcus*, *Escherichia coli* and *Klebsiella* the most common aerobic bacteria isolated from biliary sludge, while *Clostridium* is the most common anaerobe isolated^[6-8,11]. Anaerobic bacteria may be the first to attach and may play a crucial role on biofilm initiation^[7].

Electron microscopy and biochemical analyses of explanted stents has shown that the occluding material is formed by the accumulation of multispecies bacterial colonies, fungi, microbial byproducts, crystals of calcium bilirubinate, crystals of fatty acid calcium salts, and by semi digested fibers arising from duodenal reflux^[6,7,12-14]. Surface irregularities in the stent have been postulated to facilitate the initial biofilm generation^[6,12,15].

The process of internal failure is self-perpetuating. As the stent lumen narrows with increasing biofilm generation, or external compression, bile flow decreases by an exponential rate. The precipitous decrease in bile flow seen with small decreases in stent diameters is explained by Poiseuille's law, which states that when a fluid with a stable viscosity flows through a tube, halving the radius of the tube will decrease the flow rate to 1st/16th the original flow^[9] (Figure 1). Viscous fluids also display a parabolic flow, with the lowest flow rates against the surfaces of the tube. Slowing of bile flow promotes both spontaneous and bacteria-driven bile salt precipitation, thus exacerbating the likelihood of internal failure^[4]. This has been proven clinically as failure rates have been shown to be well correlated with the diameter of the stent^[16].

DRUG ELUTION TO PREVENT INTERNAL FAILURE

Drug insertion into the biliary stent lumen can theoretically improve internal failure rates by decreasing bacterial colonization and biofilm formation. There has been a small amount of research looking at internal drug coating or drug elution to prevent internal failure (Table 3), comprising *in vitro*, *in vivo* animal and one human trial. Drugs selected for analysis can be loosely grouped into two categories: those theorized to inhibit bacterial attachment and biofilm generation and antimicrobials theorized to inhibit bacterial growth and induce sterilization of the biliary tree.

The first published example of incorporating pharmaceuticals into the internal stent lumen was bench modeling done in the late 1990's. An *in vitro* model was developed by submerging test material in culture broth and bile; it was shown that an addition of benzalkonium chloride, a commonly used antiseptic, as well as Teflon, decreased the incidence of microbial colonization^[17]. However, these studies did not accurately model the

Table 1 Current stent failure rates

Stent type	Stent failure rates in malignant obstruction
Plastic stents	30%-70%
Self expanding metal stents	19%-46%

Adapted from Ref.^[31-37].**Table 2 Causes of stent failure**

Causes of stent failure	Percent of total failures
Tumor ingrowth	66%-68%
Epithelial ingrowth	
Biliary clogging	17%-21%
Tumor overgrowth	2%-11%
Stent migration	0%-4%

Adapted from Ref.^[31-37].

polymicrobial environment of the biliary tree, utilizing just 3 cultured pathogens.

Several more *in vitro* models have been reported in the literature evaluating luminal drug elution. Of the materials tested, heparin coating has proven promising in both *in vitro* and human trials. Cetta *et al*^[18] examined stents internally coated with heparin and hyaluronic acid. The coated stents were then placed in bacterial cultures which were generated from culturing previously occluded biliary prostheses. Compared to uncoated polyurethane stents, heparin coated stents had significantly reduced biofilm formation. Later, some researchers found that stents coated with both hydrophobin and heparin decreased encrustation detected by the electron microscopy compared to hydrophobin alone in their *in vitro* model. This work was followed up by Farnbacher *et al*^[19], who devised a prospective human trial. In their study they found that explanted heparin coated stents had significantly decreased rates of luminal encrustation by visual inspection and weight.

Antibiotics, while an intuitive possibility for decreasing bacterial colonization, have failed to show any effect in decreasing internal failure rates when given both systemically or locally through drug elution. There has been a continuous effort since 1989 to identify systemic treatments which could decrease internal stent failure rates, among which antibiotics, ursodiol, mucolytic agents, and anti-inflammatory agents have been trialed (Table 4). Multiple studies as well as meta-analysis^[20] have failed to show a direct benefit from any systemic treatment in decreasing internal failure rates.

Along with a lack of benefit when given systemically, antibiotics have also failed to show any benefit when given locally. In 2011, Weickert *et al*^[21] analyzed the effect of antibiotic elution on internal failure by incubating stents in human bile. Their experiment examined the combined effect of stents combined with hydrophobin and ampicillin/sulbactam, as well as hydrophobin and levofloxacin showed that the neither antibiotic

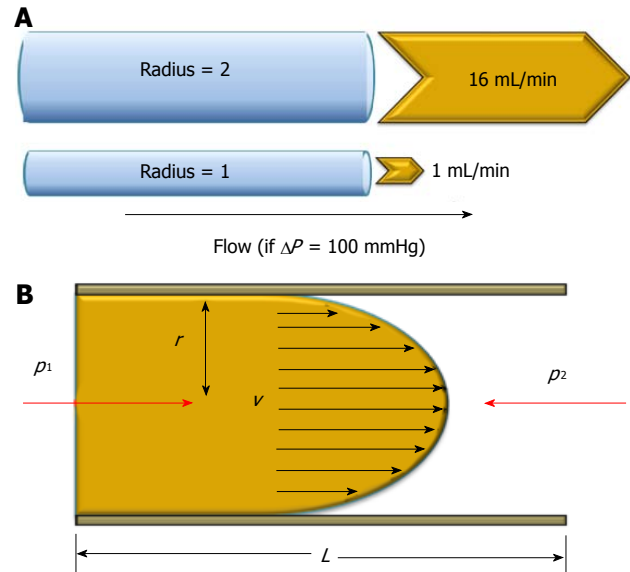


Figure 1 Change in biliary flow determined by stent radius, as described by Poiseuille's law (A) and laminar flow of viscous fluids (B). Flow = $(\pi \cdot \text{pressure difference} \cdot \text{radius}^4) / (8 \cdot \text{viscosity} \cdot \text{length})$.

reduced the amount of biofilm generation compared to hydrophobin alone. In 2012, Gwon *et al*^[22] developed a cefoxitine eluting stent and for testing in a canine model. Upon both gross inspection and analysis with electron microscopy they found no effect from cefotaxime in preventing biofilm development. The reasons behind the lack of local antibiotic efficacy can only be surmised, but may include the selection of resistant organisms in the polymicrobial biliary environment, the inability of antibiotics to permeate through biofilms, or local breakdown and inactivation of antibiotics.

EXTERNAL STENT FAILURE

Biliary obstruction is the first presenting sign of disease in 70% of patients with cancer of the pancreas and biliary system^[23]. Pancreatic cancer is common and carries significant morbidity and mortality. In the year 2000 for example, there were 217000 new cases of pancreatic cancer with 213000 pancreatic cancer deaths worldwide^[24]. Survival rates are dismal at an estimated five-year rate of 5%^[25] and have been generally stagnant with no recent advances improving mortality^[26]. Although biliary duct and gallbladder cancers have a lower incidence, their mortality is equally dismal. External stent obstruction is not only a concern in patients with pancreatobiliary malignancy, as there is also a notable population of patients with nonmalignant obstructions at risk for stent failure who could benefit from drug elution as a possible means of decreasing failure risk. Prospective studies on patients with chronic pancreatitis, autoimmune pancreatitis, and liver transplants for instance have shown that respectively up to 20%^[27], 83%^[28], and 22%-49%^[29] of patients developed biliary strictures.

There are two main categories of commercially available biliary stents for endoscopists to select from:

Table 3 Studies evaluating drug elution or coating to prevent internal failure

Ref.	Journal	Study design	Study results
<i>In vitro</i> Rees <i>et al</i> ^[17]	<i>Journal of Hospital Infection</i> (1998)	<i>In vitro</i> - control (polyurethane) - benzalkonium chloride (BZC) - ePTFE (Teflon)	BZC and Teflon reduced the number of organisms attached to stents
Cetta <i>et al</i> ^[18]	<i>The European Journal of Surgery</i> (1999)	<i>In vitro</i> 5 stents - control (polyurethane) 5 stents - heparin + hyaluronic acid	Heparin and hyaluronic acid coating reduced biofilm development
Weickert <i>et al</i> ^[21]	<i>Advances in Medical Sciences</i> (2011)	<i>In vitro</i> 7 stents - control (polyethylene) 4 stents - hydrophobin (H) 3 stents - H + ampicillin/sulbactam 3 stents - H + levofloxacin 3 stents - H + heparin	Stents coated with hydrophobin or both hydrophobin and heparin reduced clogging material scanning electron microscopy (SEM) images
Animals Gwon <i>et al</i> ^[22]	<i>Acta Radiologica</i> (2012)	Canine model 3 stents - control (ePTFE) 3 stents - 10% wt/vol cefotaxime 3 stents - 20% wt/vol cefotaxime	Cefotaxime did not prevent biofilm development (gross inspection, SEM images)
Humans Farnbacher <i>et al</i> ^[19]	<i>Scandinavian Journal of Gastroenterology</i> (2012)	Randomized prospective 13 stents - control (polyethylene) 13 stents (same patients) - heparin	Heparin is effective in preventing encrustation on stents (encrustation weighed)

plastic or metal-based stents. In regards to malignant obstruction, self-expanding metal stents (SEMS) have been found to have a decreased incidence of cholangitis, stent failure, and overall hospitalizations when compared to plastic stents^[30]. Median patency rates for SEMS have been evaluated in several studies and generally found to be at approximately 270 d in malignant obstruction^[31-33]. Biliary stents have a sub-optimal failure rate, and will occlude in 30%-70% of patients with plastic stents and in 19%-46% of patient with bare metal stents (Table 1)^[31,32,34,35]. The most common cause of failure are tumor or epithelial ingrowth (66%-68%), followed by sludge and clogging (17%-21%), tumor overgrowth (2%-11%), and stent migration (0%-4%) (Table 2)^[33,36,37].

From analysis of biopsied obstructing tissue, it was found that 44% of the tissue ingrowth was non-malignant in nature, suggesting epithelial hyperplasia plays a significant role in stent obstruction^[35]. Other studies have suggested that up to 50% of SEMS occlude secondary to epithelial hyperplasia^[35]. Considering the major mechanisms of stent obstruction, tumor ingrowth, tumor overgrowth, and epithelial hyperplasia, a stent externally coated with agents that effectively hinder tissue growth could theoretically reduce failure rate by 50%-79%. Drug incorporation into the external stent membrane appears to be an intuitive next step in stent development capable of significantly reducing stent obstruction rates^[34].

CURRENT RESEARCH ON DRUG-ELUTING BILIARY STENTS TO PREVENT EXTERNAL FAILURE

Drug-eluting stents have been well validated in the

intravascular setting and have become a staple in the management of coronary artery disease for several decades. However, despite the theoretical promise of drug-eluting biliary stents (DEBS), there has been little research on the subject to date (Table 5). Ideal agents to incorporate into the stent exterior would serve to (1) effectively inhibit the growth of malignant pancreaticobiliary cells; (2) retard the proliferation of biliary epithelial hyperplasia; and (3) display favorable histologic changes when exposed to biliary epithelium, without necrosis or risk of biliary perforation.

ANIMAL MODELS OF DRUG ELUTING BILIARY STENTS

Lee *et al*^[38] developed the first published animal models of DEBS in 2005. Their team developed a paclitaxel eluting stent for trial in a porcine model. The decision to use paclitaxel was based on bench data from Kalinowski *et al*^[39] which showed that paclitaxel, inhibited human gallbladder cells, human fibroblasts, and pancreatic cells in a dose-dependent fashion. Their model was designed to evaluate drug release dynamics and bile duct histological changes resulting from extended direct stent contact after implantation in pigs for 4 wk. Stents were developed with paclitaxel concentrations of 0%, 10% and 20%. Inflammatory cell infiltration and fibrous reactions were the commonly noted histologic changes which corresponded to the level of paclitaxel incorporated into the stent. Although the model was not designed to evaluate long term failure rates, no pigs showed clinical or laboratory signs of biliary obstruction during the trial. Their results were promising, finding acceptable histologic changes at all drug levels. Epithelial denudation, mucin hypersecretion, and epithelial metaplasia were noted in

Table 4 Trials evaluating systemic treatments to prevent internal failure

Ref.	Journal	Study design	Study results
Humans Barrioz <i>et al</i> ^[48]	<i>Lancet</i> (1994)	Randomized prospective 25 - conservative treatment 21 - ursodeoxycholic acid and norfloxacin	Drugs were associated with longer stent patency and shorter hospital stay
Coene <i>et al</i> ^[49]	<i>Scandinavian Journal of Gastroenterology</i> (1994)	Randomized prospective 60 patients received either co-trimoxazole or N-acetylcysteine	Bile clogging did not correlate with bile viscosity. Mucolytic agents or antibiotics only effective when bile is highly viscous
Smit <i>et al</i> ^[50]	<i>Gastrointestinal Endoscopy</i> (1989)	Randomized prospective 30 patients received either placebo or doxycycline or aspirin	Both doxycycline and aspirin reduced the dry weight of sludge. Doxycycline improved patient survival
Halm	<i>Endoscopy</i> (2001)	Randomized prospective 26 - ursodeoxycholic acid 26 - ursodeoxycholic acid + ofloxacin	No difference in patient survival or stent occlusion
De Lédinghen <i>et al</i> ^[51]	<i>Digestive Diseases and Sciences</i> (2000)	Randomized prospective 29 - conservative treatment 33 - ursodeoxycholic acid and norfloxacin	No difference in stent patency and patient survival
<i>In vitro</i> Tsang <i>et al</i> ^[52]	<i>Journal of Laboratory and Clinical Medicine</i> (1997)	<i>In vitro</i> 4 - porcine bile 4 - porcine bile + ampicillin + sulbactam	Ampicillin and sulbactam inhibited biofilm formation

the bile ducts that were in contact with stents containing 20% weight/volume (wt/v) paclitaxel; there was no incidence of transmural necrosis or perforation in any animal. Furthermore, the amounts of paclitaxel released over 1 wk and over 6 wk were similar, regardless of the concentration of paclitaxel incorporated in the stent. The authors ultimately found that stents with 10% (wt/v) paclitaxel in the covering membrane was superior to those with 20% (wt/v) in regards to histologic changes and drug release dynamics. The 10% (wt/v) paclitaxel stent had a more favorable histologic profile without evidence of epithelial metaplasia or other concerning local changes from excessive cytotoxic effects which could suggest a risk for necrosis or perforation, while still displaying a favorable drug release profile.

There are four other previously published animal studies involving paclitaxel eluting stents. In 2009, Lee *et al*^[40] undertook a canine model also to assess biliary duct histological changes, evaluating 20% wt/v paclitaxel DES. The authors noted biliary mucosal hyperplasia in 3/6 dogs who received paclitaxel stents (none in the control group) along with no distinct stent complications. They concluded that more research is warranted to determine the proper concentration of drug to obtain optimal tumor control in and histological remodeling of the biliary duct. In 2012, Jang *et al*^[41] used a porcine model to examine a 10% wt/v paclitaxel-eluting biliary stents using a membrane containing Pluronic F-127 in an attempt to bolster drug delivery. They again found acceptable histologic changes based on inflammatory cell infiltration and fibrotic reaction, with no incidence of obstruction or perforation. Paclitaxel was detected for 28 d in porcine serum with the 10% Pluronic concentration. However, released paclitaxel was observed for only 7 d with incorporation of higher or

lower concentrations of Pluronic. Most recently, Shi *et al*^[42] used a canine model to study the effect of paclitaxel biliary stents when used as biliary-enteric anastomosis following Roux-en-Y cholangiojejunostomy. Histology of the bile duct was observed 1, 3, 6, 9 and 18 wk following the surgery. Paclitaxel-coated stents were found to release paclitaxel for 9 wk, and dogs that had paclitaxel-coated stents placed had less granulation tissue and granular hyperplasia of the biliary-enteric anastomosis. No adverse effects of paclitaxel were observed. Lastly, Bang *et al*^[43] recently developed a mouse model xenografted with both pancreatic cancer and cholangiocarcinoma cell lines which they exposed to paclitaxel-eluting membranes, in an attempt to determine the molecular mechanisms of tumor inhibition. Paclitaxel, they discovered, inhibited tumor angiogenesis, through multiple mechanisms including suppression of mammalian target of rapamycin (mTOR) through regulation of hypoxia inducible factor 1 and increased apoptosis, as well as inhibiting tumor-stromal interaction by effecting regulation of CD44, SPARC, matrix metalloproteinase-2, and vimentin.

Besides paclitaxel, two other chemotherapeutics have been evaluated in DEBS animal models. In 2012, Lee *et al*^[44] developed a gemcitabine eluting stent membrane applied to a self-expanding Nitinol stent. They performed both *in vitro* modeling using a SK-ChA-1 cholangiocarcinoma cell line as well as *in vivo* modeling using a mouse model with colorectal carcinoma cells (CT-26). They analyzed stents developed with 0%, 8%, 10%, and 12% gemcitabine PU by weight and found the 12% concentration to be superior in terms of tumor inhibition and pro-inflammatory markers in both the *in vivo* and *in vitro* models. The authors concluded that gemcitabine eluting stents show considerable feasibility for the treatment of malignant obstruction^[44]. Furthermore, in 2012, Chung

Table 5 Studies evaluating drug elution or coating to prevent external failure

Ref.	Journal	Study design	Study results
Animals			
Lee <i>et al</i> ^[38]	<i>Gastrointestinal Endoscopy</i> (2005)	Porcine model 2 pigs - control (metallic) 2 pigs - 10% wt/v Paclitaxel 2 pigs - 20% wt/v Paclitaxel	Paclitaxel-eluting stents caused mild adverse effects, but are safe to use in porcine models
Lee <i>et al</i> ^[40]	<i>Gastrointestinal Endoscopy</i> (2009)	Canine model 5 dogs - control (metallic) 6 dogs - 20% wt/v paclitaxel	Paclitaxel-eluting stents caused mild adverse effects, but are safe to use in canine models
Lee <i>et al</i> ^[44]	<i>International Journal of Pharmaceutics</i> (2012)	<i>In vitro</i> , murine model 5 mice - no stenting 5 mice - polyurethane 5 mice - 0% wt/v gemcitabine 5 mice - 8% wt/v gemcitabine 5 mice - 12% wt/v gemcitabine	Stents coated with gemcitabine reduced the size of subcutaneous tumor <i>in vitro</i> and in mice
Chung <i>et al</i> ^[45]	<i>Journal of Gastroenterology and Hepatology</i> (2012)	Porcine model 2 pigs - 0% wt/v gemcitabine 2 pigs - 10% wt/v gemcitabine 2 pigs - 15% wt/v gemcitabine 2 pigs - 20% wt/v gemcitabine	Gemcitabine-eluting stents cause mild to severe inflammation, but are safe to use in porcine models
Jang <i>et al</i> ^[41]	<i>Endoscopy</i> (2012)	Porcine model 2 pigs - 0% wt/v paclitaxel 2 pigs - 0% Pluronic + 10% taxol 2 pigs - 10% Pluronic + 10% taxol 2 pigs - 20% Pluronic + 10% taxol	Greater patency observed when stents were coated with pluronic with paclitaxel. Stents are safe to use in porcine models
Kim do <i>et al</i> ^[46]	<i>International Journal of Nanomedicine</i> (2013)	<i>In vitro</i> , murine model 10 mice - control (no stenting) 10 mice - PCL film 10 mice - sorafenib-loaded film	Sorafenib-loaded film inhibited the growth of human cholangiocarcinoma cells <i>in vitro</i> and in mice
Shi <i>et al</i> ^[42]	<i>European Journal of Gastroenterology and Hepatology</i> (2013)	Canine model 10 dogs - control (no stenting) 10 dogs - Poly-L-lactic acid coated metallic stents (PLLA) 10 dogs - PLLA + 1 mg paclitaxel/stent 10 dogs - PLLA + 2 mg paclitaxel/stent	No adverse effects less granulation tissue and glandular hyperplasia in dogs with paclitaxel stents
Bang <i>et al</i> ^[43]	<i>Gastroenterology Research and Practice</i> (2015)	Murine model 8 mice - control (polyurethane) 8 mice - control + Pluronic 8 mice - Pluronic + 5% paclitaxel 8 mice - Pluronic + 10% paclitaxel	Tumor angiogenesis inhibited in mice with Paclitaxel stents through multiple molecular mechanisms
Humans			
Suk <i>et al</i> ^[2]	<i>Gastrointestinal Endoscopy</i> (2007)	Randomized prospective 21 patients - 10% wt/v paclitaxel	Paclitaxel-eluting stents are safe and effective. Occlusion in 9 patients, mean patency was 429 d
Jang <i>et al</i> ^[3]	<i>Digestive Diseases and Sciences</i> (2013)	Randomized prospective 46 patients - control (metallic) 60 patients - 10% wt/v paclitaxel	No significant differences in stent patency or patient survival, but stents proved safe to use in humans

et al^[45] developed a porcine model to analyze gemcitabine eluting stents, analyzing 0%, 10%, 15% and 20% gemcitabine wt/v drug DEBS. They found mild to severe inflammation in the 15% and 20% groups compared to mild inflammation in the 10% group. Fibrous reactions in the submucosal layer did not differ among groups and no biliary obstruction, necrosis or perforations were observed during the study. They found that the 10% GEM stents produced mild histologic changes and are likely most appropriate for clinical application.

Most recently in 2013, Kim do *et al*^[46] loaded sorafenib on PCL film, which was then wrapped around a metal biliary stent. They cultured human cholangiocellular carcinoma cells with the PCL films in order to examine the effect of sorafenib on angiogenesis and tumor cell growth. Additionally, a mouse model was developed using

human cholangiocarcinoma cells. The study concluded that sorafenib successfully inhibited local angiogenesis and tumor cell growth both *in vitro* and in murine models.

HUMAN TRIALS OF DRUG ELUTING BILIARY STENTS

There have been limited human trials involving DEBS. The initial human trial of paclitaxel DEBS was a single arm trial of 21 patients undertaken by Suk *et al*^[2] in 2007 in which a mean patency of 429 d and a mean survival of 350 d were found. Occlusion was observed in 9 patients due to bile sludge or clogging in 4, tumor overgrowth in 3, and tumor in-growth in 2. Furthermore, cumulative patency rates at 3, 6, and 12 mo were 100%, 71%,

and 36%, respectively. Blood levels of paclitaxel were monitored in 6 patients showing systemic levels were low, peaking between 1-10 d, suggesting systemic effects are minimal compared to local effects. This trial showed promising safety and efficacy data and prompted a follow up prospective trial^[3], comparing a 10% wt/v paclitaxel eluting bare metal stent with a traditional covered metal stent. Stents were 5-8 cm in length and 10 mm in diameter in both groups. The study was altered due to a patient preference for the DEBS, and the planned randomized controlled trial was changed to consecutively enrolling 60 patients to the paclitaxel-coated stent arm and then enrolling 46 patients to standard covered SEMS^[41]. Mean duration of stent patency was 199 ± 235 d in the paclitaxel-DEBS group and 149 ± 99 d in the covered SEMS group. Mean survival was 270 in the in the paclitaxel-DEBS arm vs 260 d in the control arm. The rates of cholangitis, pancreatitis, and stent migration were similar between the two groups. Although there was a trend towards improved patency and survival in the DEBS arm, the results did not display statistical significance. The authors concluded that although no significant difference was detected with paclitaxel DEBS, they were shown to be equally safe in human use, and further research is needed. The relatively small number of patients, as well as the shift from a prospective concurrent randomized trial to a trial with staggered accrual likely inhibited the power of the study to detect a clinical benefit from paclitaxel eluting biliary stents. These studies aside, there are multiple avenues for future human research, as well as a significant need to perform large prospective trial to evaluate the effectiveness of drug eluting biliary stents, both with paclitaxel and innumerable other compounds.

CONCLUSION

The amount of direct research involving drug eluting biliary stents has been limited, with only a few drugs having been directly examined. Considering the myriad of possible drugs which could decrease the incidence of internal failure, external failure, or both, there is ample room for further research. As described earlier, small amounts of luminal narrowing from external compression can have exponential effects on the rate of biliary flow, resulting in a significantly increased propensity for internal failure. Drug elution has theoretical benefit in decreasing internal stent failure rates, and heparin coating in particular has shown promise in small studies, which warrants further research. However, antibiotic elution has not shown a benefit in decreasing biofilm formation, which parallels trials looking at the use of systemic antibiotics to prevent stent failure. This may be secondary to multiple possible etiologies including the inability of antibiotics to permeate within biofilms, or the polymicrobial environment of the biliary tree which may quickly lead to bacterial resistance.

Only three drugs, paclitaxel, gemcitabine and sorafenib have been evaluated as possible candidates to decrease the incidence of external failure, where

paclitaxel is the sole drug evaluated in human trials. There are multiple drugs which theoretically could show a clinical benefit in decreasing stent failure rates in both malignant and nonmalignant sources of biliary stenosis. Development of an effective drug eluting stent would likely be cost effective due to the high costs involved in stent failure and has the possibility of directly decreasing patient morbidity and mortality. The high costs, and extensive time and labor requirements of large animal modeling, as well as the lack of an established reproducible bench model have likely inhibited the process of stent development thus far. Despite this, the raw theoretical benefit is evident, where the demand for new devices that reduce restenosis rates with their associated morbidity and mortality is ever present.

Among the possibilities for future DEBS research, the possibility of combination drug stents holds theoretical promise. In order to maximize stent patency rates, the ideal stent would feature both internal and external drug elution. Also, previously trialed drugs which failed to show efficacy as a single agent may have added efficacy when combined with other agents such as heparin or antibiotics, which could prove to have increase efficacy when used in concert. Future animal and human trials will benefit from the analysis of drug combinations.

One of the main limitations to the development of DEBS is the lack of cheap, reproducible models which accurately reflects the human bile duct. Internal stent failure can be reasonably modeled on the bench top by systems which propel biologically active bile through the stent^[47]. Biofilm development can then be measured by direct inspection, weight and electron microscopy^[17-19,21,22]. This model may be used to select optimal agents for further analysis. However, there are no cheap reproducible models which accurately depict the human biliary ducts tolerance to direct contact with drug elution. Drug eluting stents, particularly those with external drug elution, require animal modeling in order to assess histological changes resulting from the stent. As there are no adequate small animal models available for biliary stenting, this has previously been performed with porcine or canine modeling. This has multiple downsides including the high costs of endoscopists or surgeons to place stents, veterinarians, and the animal husbandry required for the several weeks while stents incubate in the bile duct. As the large animal model is also required to establish the ideal drug elution dosage based on histologic changes, costs inhibit the number of drug dosages trialed. Future investigators would benefit from the development of more streamlined and standardized bench top and animal models.

In conclusion, although the current research on DEBS is limited, promise is evident and holds the possibility for significantly increasing the rates of long-term stent patency. Drugs that inhibit malignant cells and non-malignant epithelia hyperplasia, while displaying reasonable histologic tolerance after exposure to the biliary epithelium, should be further examined. Previous models that are well defined can be implemented to

streamline further research. There is an obvious need in this population to decrease morbidity, and DEBS hold the possibility of a significant improvement in outcomes. Further analysis of both new pharmaceuticals and further modeling of current and combinatory drug eluting stents is needed.

REFERENCES

- Barkay O**, Mosler P, Schmitt CM, Lehman GA, Frakes JT, Johanson JF, Qaseem T, Howell DA, Sherman S. Effect of endoscopic stenting of malignant bile duct obstruction on quality of life. *J Clin Gastroenterol* 2013; **47**: 526-531 [PMID: 23269313 DOI: 10.1097/MCG.0b013e318272440e]
- Suk KT**, Kim JW, Kim HS, Baik SK, Oh SJ, Lee SJ, Kim HG, Lee DH, Won YH, Lee DK. Human application of a metallic stent covered with a paclitaxel-incorporated membrane for malignant biliary obstruction: multicenter pilot study. *Gastrointest Endosc* 2007; **66**: 798-803 [PMID: 17905025 DOI: 10.1016/j.gie.2007.05.037]
- Jang SI**, Kim JH, You JW, Rhee K, Lee SJ, Kim HG, Han J, Shin IH, Park SH, Lee DK. Efficacy of a metallic stent covered with a paclitaxel-incorporated membrane versus a covered metal stent for malignant biliary obstruction: a prospective comparative study. *Dig Dis Sci* 2013; **58**: 865-871 [PMID: 23179148 DOI: 10.1007/s10620-012-2472-1]
- Donelli G**, Guaglianone E, Di Rosa R, Fiocca F, Basoli A. Plastic biliary stent occlusion: factors involved and possible preventive approaches. *Clin Med Res* 2007; **5**: 53-60 [PMID: 17456835]
- Sung JY**, Leung JW, Shaffer EA, Lam K, Olson ME, Costerton JW. Ascending infection of the biliary tract after surgical sphincterotomy and biliary stenting. *J Gastroenterol Hepatol* 1992; **7**: 240-245 [PMID: 1611012]
- Speer AG**, Cotton PB, Rode J, Seddon AM, Neal CR, Holton J, Costerton JW. Biliary stent blockage with bacterial biofilm. A light and electron microscopy study. *Ann Intern Med* 1988; **108**: 546-553 [PMID: 2450501]
- Leung JW**, Ling TK, Kung JL, Vallance-Owen J. The role of bacteria in the blockage of biliary stents. *Gastrointest Endosc* 1988; **34**: 19-22 [PMID: 3280393]
- Di Rosa R**, Basoli A, Donelli G, Penni A, Salvatori FM, Fiocca F, Baldassarri L. A microbiological and morphological study of blocked biliary stents. *Microb Ecol Health Dis* 1999; **11**: 84-88 [DOI: 10.1080/089106099435817]
- Rey JF**, Maupetit P, Greff M. Experimental study of biliary endoprosthesis efficiency. *Endoscopy* 1985; **17**: 145-148 [PMID: 2410246]
- Guaglianone E**, Cardines R, Vuotto C, Di Rosa R, Babini V, Mastrantonio P, Donelli G. Microbial biofilms associated with biliary stent clogging. *FEMS Immunol Med Microbiol* 2010; **59**: 410-420 [PMID: 20482630 DOI: 10.1111/j.1574-695X.2010.00686]
- Dowidar N**, Kolmos HJ, Lyon H, Matzen P. Clogging of biliary endoprotheses. A morphologic and bacteriologic study. *Scand J Gastroenterol* 1991; **26**: 1137-1144 [PMID: 1754848 DOI: 10.3109/00365529108998605]
- van Berkel AM**, van Marle J, van Veen H, Groen AK, Huijbregtse K. A scanning electron microscopic study of biliary stent materials. *Gastrointest Endosc* 2000; **51**: 19-22 [PMID: 10625789 DOI: 10.1016/S0016-5107(00)70380-4]
- Basoli A**, Fiocca F, Di Rosa R, Baldassarri L, Donelli G. Biliary stent occlusion: a microbiological and scanning electron microscopy (SEM) investigation. In: Zanella E, editor. *Advances in abdominal surgery*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1999: 69-80 [DOI: 10.1007/978-94-011-4469-8_8]
- Groen AK**, Out T, Huijbregtse K, Delzenne B, Hoek FJ, Tytgat GN. Characterization of the content of occluded biliary endoprotheses. *Endoscopy* 1987; **19**: 57-59 [PMID: 3106022 DOI: 10.1055/s-2007-1018235]
- McAllister EW**, Carey LC, Brady PG, Heller R, Kovacs SG. The role of polymeric surface smoothness of biliary stents in bacterial adherence, biofilm deposition, and stent occlusion. *Gastrointest Endosc* 1993; **39**: 422-425 [PMID: 8514080 DOI: 10.1016/S0016-5107(93)70120-0]
- Kadakia SC**, Starnes E. Comparison of 10 French gauge stent with 11.5 French gauge stent in patients with biliary tract diseases. *Gastrointest Endosc* 1992; **38**: 454-459 [PMID: 1511821 DOI: 10.1016/S0016-5107(92)70476-3]
- Rees EN**, Tebbs SE, Elliott TS. Role of antimicrobial-impregnated polymer and Teflon in the prevention of biliary stent blockage. *J Hosp Infect* 1998; **39**: 323-329 [PMID: 9749404 DOI: 10.1016/S0195-6701(98)90298-5]
- Cetta F**, Rappuoli R, Montalto G, Baldi C, Gori M, Cetta D, Zuckermann M, Magnani A, Barbucci R. New biliary endoprosthesis less liable to block in biliary infections: description and in vitro studies. *Eur J Surg* 1999; **165**: 782-785 [PMID: 10494646 DOI: 10.1080/11024159950189582]
- Farnbacher MJ**, Lederer R, Blana A, Schneider HT. Does heparin coating reduce encrustation of biliary plastic endoprotheses? A prospective randomized trial. *Scand J Gastroenterol* 2012; **47**: 1141-1147 [PMID: 22861490 DOI: 10.3109/00365521.2012.711849]
- Galandi D**, Schwarzer G, Bassler D, Allgaier HP. Ursodeoxycholic acid and/or antibiotics for prevention of biliary stent occlusion. *Cochrane Database Syst Rev* 2002; **(3)**: CD003043 [PMID: 12137669 DOI: 10.1002/14651858.cd003043]
- Weickert U**, Wiesend F, Subkowski T, Eickhoff A, Reiss G. Optimizing biliary stent patency by coating with hydrophobin alone or hydrophobin and antibiotics or heparin: an in vitro proof of principle study. *Adv Med Sci* 2011; **56**: 138-144 [PMID: 21940267 DOI: 10.2478/v10039-011-0026-y]
- Gwon DI**, Lee SS, Kim EY. Cefotaxime-eluting covered self-expandable stents in a canine biliary model: scanning electron microscopic study of biofilm formation. *Acta Radiol* 2012; **53**: 1127-1132 [PMID: 23034797 DOI: 10.1258/ar.2012.120220]
- Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]
- Parkin DM**, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001; **37** Suppl 8: S4-66 [PMID: 11602373 DOI: 10.1016/S0959-8049(01)00267-2]
- Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71-96 [PMID: 18287387 DOI: 10.3322/CA.2007.0010]
- Hariharan D**, Saied A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. *HPB (Oxford)* 2008; **10**: 58-62 [PMID: 18695761 DOI: 10.1080/13651820701883148]
- Devriere J**, Cremer M, Baize M, Love J, Sugai B, Vandermeeren A. Management of common bile duct stricture caused by chronic pancreatitis with metal mesh self expandable stents. *Gut* 1994; **35**: 122-126 [PMID: 8307432 DOI: 10.1136/gut.35.1.122]
- Kamisawa T**, Tu Y, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Involvement of pancreatic and bile ducts in autoimmune pancreatitis. *World J Gastroenterol* 2006; **12**: 612-614 [PMID: 16489677]
- Orons PD**, Sheng R, Zajko AB. Hepatic artery stenosis in liver transplant recipients: prevalence and cholangiographic appearance of associated biliary complications. *AJR Am J Roentgenol* 1995; **165**: 1145-1149 [PMID: 7572493 DOI: 10.2214/ajr.165.5.7572493]
- Knyrim K**, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993; **25**: 207-212 [PMID: 8519239 DOI: 10.1055/s-2007-1010294]
- Daivids PH**, Groen AK, Rauws EA, Tytgat GN, Huijbregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; **340**: 1488-1492 [PMID: 1281903 DOI: 10.1016/0140-6736(92)92752-2]
- Kaassis M**, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, Canard JM, Fritsch J, Rey JF, Burtin P. Plastic

- or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. *Gastrointest Endosc* 2003; **57**: 178-182 [PMID: 12556780 DOI: 10.1067/mge.2003.66]
- 33 **Yoon WJ**, Ryu JK, Lee JW, Ahn DW, Kim YT, Yoon YB, Woo SM, Lee WJ. Endoscopic management of occluded metal biliary stents: metal versus 10F plastic stents. *World J Gastroenterol* 2010; **16**: 5347-5352 [PMID: 21072899 DOI: 10.3748/wjg.v16.i42.5347]
 - 34 **Shah T**. Drug-eluting stents in malignant biliary obstruction: where do we stand? *Dig Dis Sci* 2013; **58**: 610-612 [PMID: 23250674 DOI: 10.1007/s10620-012-2507-7]
 - 35 **Loew BJ**, Howell DA, Sanders MK, Desilets DJ, Kortan PP, May GR, Shah RJ, Chen YK, Parsons WG, Hawes RH, Cotton PB, Slivka AA, Ahmad J, Lehman GA, Sherman S, Neuhaus H, Schumacher BM. Comparative performance of uncoated, self-expanding metal biliary stents of different designs in 2 diameters: final results of an international multicenter, randomized, controlled trial. *Gastrointest Endosc* 2009; **70**: 445-453 [PMID: 19482279 DOI: 10.1016/j.gie.2008.11.018]
 - 36 **Yang KY**, Ryu JK, Seo JK, Woo SM, Park JK, Kim YT, Yoon YB. A comparison of the Niti-D biliary uncovered stent and the uncovered Wallstent in malignant biliary obstruction. *Gastrointest Endosc* 2009; **70**: 45-51 [PMID: 19559832 DOI: 10.1016/j.gie.2008.10.029]
 - 37 **Shah RJ**, Howell DA, Desilets DJ, Sheth SG, Parsons WG, Okolo P, Lehman GA, Sherman S, Baillie J, Branch MS, Pleskow D, Chuttani R, Bosco JJ. Multicenter randomized trial of the spiral Z-stent compared with the Wallstent for malignant biliary obstruction. *Gastrointest Endosc* 2003; **57**: 830-836 [PMID: 12776028 DOI: 10.1016/S0016-5107(03)70016-9]
 - 38 **Lee DK**, Kim HS, Kim KS, Lee WJ, Kim HK, Won YH, Byun YR, Kim MY, Baik SK, Kwon SO. The effect on porcine bile duct of a metallic stent covered with a paclitaxel-incorporated membrane. *Gastrointest Endosc* 2005; **61**: 296-301 [PMID: 15729251 DOI: 10.1016/S0016-5107(04)02570-2]
 - 39 **Kalinowski M**, Alfke H, Kleb B, Dürfeld F, Joachim Wagner H. Paclitaxel inhibits proliferation of cell lines responsible for metal stent obstruction: possible topical application in malignant bile duct obstructions. *Invest Radiol* 2002; **37**: 399-404 [PMID: 12068162 DOI: 10.1097/00004424-200207000-00007]
 - 40 **Lee SS**, Shin JH, Han JM, Cho CH, Kim MH, Lee SK, Kim JH, Kim KR, Shin KM, Won YH, Song HY. Histologic influence of paclitaxel-eluting covered metallic stents in a canine biliary model. *Gastrointest Endosc* 2009; **69**: 1140-1147 [PMID: 19243763 DOI: 10.1016/j.gie.2008.08.005]
 - 41 **Jang SI**, Kim JH, Kim M, Yang S, Jo EA, Lee JW, Na K, Kim JM, Jeong S, Lee DH, Lee DK. Porcine feasibility and safety study of a new paclitaxel-eluting biliary stent with a Pluronic-containing membrane. *Endoscopy* 2012; **44**: 825-831 [PMID: 22752887 DOI: 10.1055/s-0032-1309881]
 - 42 **Shi J**, Lv Y, Yu L, Zhang B, Zhang X, Fan C, Geng Z. Interest of a new biodegradable stent coated with paclitaxel on anastomotic wound healing after biliary reconstruction. *Eur J Gastroenterol Hepatol* 2013; **25**: 1415-1423 [PMID: 23669325 DOI: 10.1097/MEG.0b013e328361eb51]
 - 43 **Bang S**, Jang SI, Lee SY, Baek YY, Yun J, Oh SJ, Lee CW, Jo EA, Na K, Yang S, Lee DH, Lee DK. Molecular mechanism of local drug delivery with Paclitaxel-eluting membranes in biliary and pancreatic cancer: new application for an old drug. *Gastroenterol Res Pract* 2015; **2015**: 568981 [PMID: 25983747 DOI: 10.1155/2015/568981]
 - 44 **Lee JW**, Yang SG, Na K. Gemcitabine-releasing polymeric films for covered self-expandable metallic stent in treatment of gastrointestinal cancer. *Int J Pharm* 2012; **427**: 276-283 [PMID: 22366483 DOI: 10.1016/j.ijpharm.2012.02.016]
 - 45 **Chung MJ**, Kim H, Kim KS, Park S, Chung JB, Park SW. Safety evaluation of self-expanding metallic biliary stents eluting gemcitabine in a porcine model. *J Gastroenterol Hepatol* 2012; **27**: 261-267 [PMID: 21793905 DOI: 10.1111/j.1440-1746.2011.06866.x]
 - 46 **Kim do H**, Jeong YI, Chung CW, Kim CH, Kwak TW, Lee HM, Kang DH. Preclinical evaluation of sorafenib-eluting stent for suppression of human cholangiocarcinoma cells. *Int J Nanomedicine* 2013; **8**: 1697-1711 [PMID: 23658488 DOI: 10.2147/IJN.S43508]
 - 47 **Bang BW**, Jeong S, Lee DH, Lee JI, Lee SC, Kang SG. The biodegradability of covering materials for metallic stents in a bile flow phantom. *Dig Dis Sci* 2012; **57**: 1056-1063 [PMID: 22101941 DOI: 10.1007/s10620-011-1958-6]
 - 48 **Barriot T**, Ingrand P, Besson I, de Ledinghen V, Silvain C, Beauchant M. Randomised trial of prevention of biliary stent occlusion by ursodeoxycholic acid plus norfloxacin. *Lancet* 1994; **344**: 581-582 [PMID: 7914962 DOI: 10.1016/S0140-6736(94)91967-4]
 - 49 **Coene PP**, Groen AK, Davids PH, Hardeman M, Tytgat GN, Huibregtse K. Bile viscosity in patients with biliary drainage. Effect of co-trimoxazole and N-acetylcysteine and role in stent clogging. *Scand J Gastroenterol* 1994; **29**: 757-763 [PMID: 7526440 DOI: 10.3109/00365529409092506]
 - 50 **Smit JM**, Out MM, Groen AK, Huibregtse K, Jansen PL, van Marle J, Tytgat GN. A placebo-controlled study on the efficacy of aspirin and doxycycline in preventing clogging of biliary endoprotheses. *Gastrointest Endosc* 1989; **35**: 485-489 [PMID: 2689261 DOI: 10.1016/S0016-5107(89)72895-9]
 - 51 **De Ledinghen V**, Person B, Legoux JL, Le Sidaner A, Desaint B, Greef M, Moesch C, Grollier G, Ingrand P, Sautereau D, Beauchant M. Prevention of biliary stent occlusion by ursodeoxycholic acid plus norfloxacin: a multicenter randomized trial. *Dig Dis Sci* 2000; **45**: 145-150 [PMID: 10695627 DOI: 10.1023/A:1005429914955]
 - 52 **Tsang TK**, Pollack J, Chodash HB. Inhibition of biliary endoprotheses occlusion by ampicillin-sulbactam in an in vitro model. *J Lab Clin Med* 1997; **130**: 643-648 [PMID: 9422338 DOI: 10.1016/S0022-2143(97)90114-1]

P- Reviewer: Paydas S, Sakata N **S- Editor:** Ma YJ **L- Editor:** A
E- Editor: Lu YJ



Submucosal tunnel endoscopy: Peroral endoscopic myotomy and peroral endoscopic tumor resection

Nikolas Eleftheriadis, Haruhiro Inoue, Haruo Ikeda, Manabu Onimaru, Roberta Maselli, Grace Santi

Nikolas Eleftheriadis, Haruhiro Inoue, Haruo Ikeda, Manabu Onimaru, Roberta Maselli, Grace Santi, Digestive Diseases Center, Showa University, Koto Toyosu Hospital, Tokyo 135-8577, Japan

Nikolas Eleftheriadis, Gastroenterology Unit, Metropolitan Hospital, 18547 Athens, Greece

Author contributions: Eleftheriadis N wrote the paper, performed the research; Inoue H designed the research, performed the research, analyzed the data; Ikeda H, Onimaru M, Maselli R and Santi G performed the research.

Conflict-of-interest statement: All authors confirm no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Nikolas Eleftheriadis, MD, Gastroenterologist, Digestive Diseases Center, Showa University, Koto Toyosu Hospital, 5-1-38 Toyosu, Koto-ku, Tokyo 135-8577, Japan. nikoseleftheriadis@yahoo.com
Telephone: +81-3-62046000
Fax: +81-3-62046396

Received: April 23, 2015

Peer-review started: April 24, 2015

First decision: July 22, 2015

Revised: October 19, 2015

Accepted: November 24, 2015

Article in press: November 25, 2015

Published online: January 25, 2016

minimally invasive, endoscopic treatment for esophageal achalasia and other esophageal motility disorders, emerged from the natural orifice transluminal endoscopic surgery procedures, and since the first human case performed by Inoue in 2008, showed exciting results in international level, with more than 4000 cases globally up to now. POEM showed superior characteristics than the standard 100-year-old surgical or laparoscopic Heller myotomy (LHM), not only for all types of esophageal achalasia [classical (I), vigorous (II), spastic (III), Chicago Classification], but also for advanced sigmoid type achalasia (S1 and S2), failed LHM, or other esophageal motility disorders (diffuse esophageal spasm, nutcracker esophagus or Jackhammer esophagus). POEM starts with a mucosal incision, followed by submucosal tunnel creation crossing the esophagogastric junction (EGJ) and myotomy. Finally the mucosal entry is closed with endoscopic clip placement. POEM permitted relatively free choice of myotomy length and localization. Although it is technically demanding procedure, POEM can be performed safely and achieves very good control of dysphagia and chest pain. Gastroesophageal reflux is the most common troublesome side effect, and is well controllable with proton pump inhibitors. Furthermore, POEM opened the era of submucosal tunnel endoscopy, with many other applications. Based on the same principles with POEM, in combination with new technological developments, such as endoscopic suturing, peroral endoscopic tumor resection (POET), is safely and effectively applied for challenging submucosal esophageal, EGJ and gastric cardia tumors (submucosal tumors), emerged from muscularis propria. POET showed up to know promising results, however, it is restricted to specialized centers. The present article reviews the recent data of POEM and POET and discussed controversial issues that need further study and future perspectives.

Key words: Achalasia; Heller myotomy; Laparoscopic myotomy; Per-oral endoscopic myotomy; Natural orifice transluminal endoscopy surgery; Endoscopic submucosal dissection; Submucosal endoscopy; LES; Transluminal technique; Minimally invasive surgery; Peroral endoscopic

Abstract

Peroral endoscopic myotomy (POEM) is an innovative,

tumorectomy; EndoFLIP

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Submucosal tunnel endoscopy: Peroral endoscopic myotomy (POEM) and peroral endoscopic tumor resection (POET), constitutes a novel terrain for miniinvasive endoscopic treatment of diseases, where the surgical alternatives are totally incomparable, particularly in elderly. POEM showed exciting results in international level in treating all types of achalasia [classical (I), vigorous (II), spastic (III)], including advanced sigmoid type, failed surgical or laparoscopic Heller myotomy cases, and other esophageal motility disorders (diffuse esophageal spasm, nutcracker and jackhammer esophagus). POET was spawned from the success of POEM, and slowly expanded worldwide to treat muscularis based esophageal, esophagogastric junction and cardia submucosal tumors. Submucosal tunnel endoscopy further inspired other applications and opened promising future perspectives.

Eleftheriadis N, Inoue H, Ikeda H, Onimaru M, Maselli R, Santi G. Submucosal tunnel endoscopy: Peroral endoscopic myotomy and peroral endoscopic tumor resection. *World J Gastrointest Endosc* 2016; 8(2): 86-103 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/86.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.86>

INTRODUCTION

Peroral endoscopic myotomy (POEM)^[1] is a novel, incisionless, minimal invasive endoscopic surgical procedure, which has been derived from the era of natural orifice transluminal endoscopic surgery (NOTES)^[2], intended for long-term recovery from symptoms of esophageal achalasia.

POEM has successfully spread internationally, with more than fifty centers to have performed POEM worldwide^[3], following the excellent initial results from pioneering centers^[1,4] and definitely open the era of submucosal tunnel endoscopy in clinical practice. POEM has been extended to treat not only all types of esophageal achalasia [classical (I), vigorous (II) or spastic (III), Chicago classification^[5]], but other spastic esophageal motility disorders as well^[6-9].

There were modest variations among centers in technique and periprocedural management, which are currently under investigation, but all centers uniformly reported excellent efficacy and safety outcomes^[3]. POEM has been also extended to include failure of previous therapies, such as botulin toxin injection (BTI) or pneumatic balloon dilatation (PBD)^[10] or failed surgical or laparoscopic Heller myotomy (LHM)^[11,12], advanced sigmoid-type achalasia^[13-15], and also after failure of previous POEM^[13]. Up to know more than 4000 POEM cases have been successfully performed worldwide, and

currently there is an explosion of publications regarding POEM^[3].

As an extension of the POEM technique and submucosal tunnel endoscopy, peroral endoscopic submucosal tumor resection (POET) is also introduced, and is currently increases in experience, however restricted to specialized centers^[16,17].

Successful POET of esophageal and gastric SMTs is possible, due to direct access through the submucosal tunneling far from the mucosal entry, followed by successful mucosal closure even for inadvertent mucosal tunnel perforations with many techniques, such as standard clips, combined clip-endoloop technique^[18], the over-the-scope clips (OTSC)^[19], and finally the most recent technological progress of the endoscopic suturing device (OverStitch™; Apollo Endosurgery Austin, Texas)^[20].

POET is far less invasive than the surgical alternatives, which are either gastrotomy or gastrectomy and esophagectomy for gastric and esophageal SMTs respectively, while POET can be also applied in case of contraindications or serious comorbidities^[16]. However, further international experience with longer follow-up is necessary and awaited. Finally, POEM also opened other applications as well, such as endoscopic gastric pyloromyotomy for refractory gastroparesis^[21].

POEM

Historical perspective of POEM

The concept of endoscopic myotomy for treatment of achalasia, was first reported in case series in 1980^[22], but it was only in 2008 when Inoue *et al*^[1] performed the first successful clinical case of endoscopic myotomy in humans with achalasia, based on experimental data by Pasricha *et al*^[23], Sumiyama *et al*^[24] and Perretta *et al*^[25]. Inoue *et al*^[1] coined the term POEM and subsequently extended its use to treat not only achalasia, but other spastic esophageal motility disorders as well^[26].

Indications and contraindications

Currently, all types of symptomatic esophageal achalasia [classical (I), vigorous (II) or spastic (III), Chicago classification^[5]] diagnosed by high quality (preferably high resolution) esophageal manometry^[5] can be treated by POEM^[27], including failure of previous therapies, such as BTI or PBD^[10] or failed surgical or LHM^[11,12], advanced sigmoid-type achalasia^[13-15] and also after failure of previous POEM^[3,13] (Table 1). POEM has been also reported in post-gastric bypass patients with achalasia^[28].

According to international IPOEMS database 43% of subjects had prior intervention such as PBD, BTI or LHM^[3]. Previous therapies make POEM technically more challenging due to the presence of inflammatory fibrosis, adhesions and scars^[12].

Maselli *et al*^[29] also reported the first successful clinical case of POEM in a 3-year-old child with achalasia and Down syndrome, while lately other groups also reported POEM in children and adolescents^[30,31], making

Table 1 Indications and contraindications of peroral endoscopic myotomy

Indications
Absolute indications
Primary idiopathic achalasia of all types [classical (I), vigorous (II), spastic (III)] (Chicago Classification)
Relative indications
Other hypertensive motor disorders (diffuse esophageal spasm, nutcracker or jackhammer esophagus). HRTM necessary
Failed surgical myotomy (POEM at the opposite site mainly posterior POEM)
Failed pneumatic balloon dilatation
Failed previous POEM. Redo POEM at the opposite site mainly posterior POEM necessary
Advanced sigmoid type achalasia with mega esophagus (bilateral POEM may be necessary)
Children with achalasia (relative indication in experienced hands and specialized centers only)
Elderly with achalasia and comorbidities and non-surgical candidates (relative indication in experienced hands and specialized centers only)
Contraindications
Absolute contraindications
Severe cardiopulmonary disease or other serious disease
Pseudoachalasia
Failure in creating the submucosal tunnel because of severe fibrosis and adhesion
Relative contraindications
Severe esophagitis and/or very large ulcer in the lower esophagus
Recent endoscopic treatment such as EMR, ESD

POEM: Peroral endoscopic myotomy; HRTM: High resolution topographic manometry; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

age, no limitation for POEM. Currently, the pioneer centers^[1,11] have no exceptions when considering the application of the POEM.

Moreover, Inoue first extended the indications of POEM to other spastic esophageal motility disorders, such as diffuse esophageal spasm, nutcracker, and jackhammer esophagus^[7,8,32]. According to international survey (IPOEMS), 28% of the reported POEMs performed for other esophageal motility disorders, than achalasia^[3]. In these disorders POEM permitted the longer myotomy required, which cannot be achieved *via* the laparoscopic approach^[6-8,32].

POEM contraindications, according to the consensus, include severe pulmonary disease, esophageal irradiation, esophageal malignancy, bleeding disorder, including coagulopathy and recent esophageal surgery or endoscopic intervention, including endoscopic mucosal resection and endoscopic submucosal dissection (ESD)^[3].

POEM procedure

POEM starts with a mucosal incision, followed by submucosal tunnel creation crossing the EGJ and myotomy inside the tunnel and away from the mucosal entry. Finally the mucosal entry is closed with endoscopic clips. The equipment required for POEM are the same used for ESD, while carbon dioxide insufflation is obligatory through the entire procedure.

It is recommended to use spray catheter for reinjection or the injection needle to remain inside the plastic sheath, to prevent damage to the muscular layer or to mucosal flap. The width of the tunnel should be about one-third of the circumference of the esophagus. A challenge with POEM concerns the identification of the EGJ while in the tunnel, which is discussed below. At the completion of myotomy smooth passage of the endoscope through the EGJ provides confirmation of

complete myotomy. Figure 1 demonstrates the critical steps of POEM.

One day postoperatively, gastroscopy and esophagogram should be routinely performed to confirm mucosal integrity and exclude complications. Adequate esophageal empty controls the efficacy of myotomy and enables oral intake. In uncomplicated cases, patients begin by drinking liquid on day 1, a soft diet on postoperative day 2, and a normal diet on postoperative day 3, while an intravenous infusion of antibiotics should be delivered for one to three days after POEM, followed by an additional four days of oral antibiotics.

The debatable issues of POEM that need further clarification are presented in detail below (Table 2).

Knives

Currently, an important issue for discussion regarding POEM is: Which knife should be used? Inoue *et al*^[1] introduced the triangular TT-knife, that has the advantage of permitting selective dissection of the circular muscle layer, which is the responsible muscle for achalasia, while the thin outer longitudinal muscle may remain as intact as possible, as another safety margin from mediastinum and as a guide to keep a correct dissection plane.

The flat triangular base of the TT-knife is safely touched to the longitudinal layer permitting catching and selective dissection of circular muscle bundles, while lowering the risk of damage to surrounding structures, particularly for inexperienced operator (Figure 1E).

Other knives have been also successfully used for POEM, with the Water-jet (WJ) and ERBE knives the most competitive to TT-knife^[33]. They have the advantage of flushing during POEM, which, according to single center, comparative studies, resulted in shorter procedure time, mostly due to less replacement of accessories and permitted full-thickness myotomy^[33,34]. The authors



Figure 1 Peroral endoscopic myotomy stages. A: Mucosal entry after longitudinal incision at the 2-o'clock position; B: Submucosal tunneling. Ectopic innermost longitudinal muscle bundles in front of the circular muscle layer are recognized; C: Palisade vessels at the EGJ inside the tunnel; D: Blue dye at retroversion in the stomach confirms tunnel extension to gastric side; E: The sharp tip of the TT-knife is used to catch circular muscle bundles and then retract them toward the esophageal lumen; F: Longitudinal muscle is identified at the bottom of myotomy site. Longitudinal muscle fibers split each other and a gap is recognized, creating an unintentional, partly full-thickness myotomy; G: Mucosal closure with endoscopic clips. EGJ: Esophagogastric junction.

comparing WJ to TT-knife also reported larger injection volume and fewer bleeding episodes with WJ, which attributed to easier reinjection^[33,34]. However, reinjection is important only during submucosal tunnel creation and not during myotomy, which is the most important and durative part of POEM.

Lastly, a simple and efficient modified POEM technique using TT-knife and a new method of injecting dyed saline through an integrated water jet channel, to avoid exchanging the knife for a spray catheter, which is time consuming, has been described^[35].

As POEM is an innovative technique, operating time is not anymore a taboo, while the significant time variation between different groups and within the same group related to obvious inhomogeneity of achalasia patients and irrespective of the knife used, made comparative

studies difficult.

In contrary, while TT-knife permits also full-thickness myotomy, selective circular myotomy is more difficult using WJ or ERBE knife, because of the round tip of the knife that does not permit easy catching of individual muscle fibers. These knives are found more appropriate to perform intentional full-thickness myotomy, although not necessary, for treating achalasia.

To our knowledge there is no sufficient international independent data, comparing different knives and up to know no knife has been proved to be more efficacious, although the largest international experience is with the less expensive TT-knife in terms of safety and efficacy.

Coagulation parameters

High frequency electrosurgical energy generator (V/O

Table 2 Issues of peroral endoscopic myotomy that need further study

TT-knife <i>vs</i> ERBE knife <i>vs</i> other knives
Posterior <i>vs</i> anterior myotomy <i>vs</i> bilateral myotomy
Selective circular <i>vs</i> full thickness myotomy
EndoFLIP technique <i>vs</i> classical tricks to evaluate adequacy of myotomy
Mucosal closure clips <i>vs</i> OverStitch
POEM <i>vs</i> LHM or surgical myotomy
GERD after POEM (treatment necessary, <i>e.g.</i> , antireflux procedure, PPIs?)
Training system for POEM
How the risk of mishaps related to POEM can be diminished?

POEM: Peroral endoscopic myotomy; LHM: Laparoscopic Heller myotomy; GERD: Gastroesophageal reflux; PPIs: Proton pump inhibitors.

300D ERBE; Tübingen, Germany) that enables a spray-coagulation mode with noncontact tissue dissection was the standard preference of Inoue *et al.*^[1] for both submucosal tunneling and myotomy during POEM. The spray-coagulation mode makes the submucosal dissection during tunnel creation much easier, faster, and with less bleeding. Settings can be individually adjusted during the operation.

However, other coagulation modes (*i.e.*, forced coagulation) are also acceptable during submucosal dissection and myotomy, with comparable quality to spray coagulation, in terms of safety and efficacy during POEM with excellent results.

CO₂ insufflation

After frequent serious complications with room air, the POEM groups have been converted to exclusively carbon dioxide insufflation during POEM^[1]. Currently, CO₂ gas insufflation through the endoscope, during POEM, in concordance to laparoscopic techniques, is mandatory not only to reduce mediastinal emphysema, but also to reduce the risk of air embolization.

Intratracheal intubation with positive pressure ventilation should be maintained at higher pressures than those generated by endoscopic CO₂ insufflation, to reduce the risk of mediastinal emphysema during submucosal endoscopy^[26,27]. Mild subcutaneous emphysema, mediastinal emphysema or pneumoperitoneum after POEM, however, should not be considered as complications but as part of this procedure in concordance to pneumomediastinum or pneumoperitoneum after laparoscopic surgery.

Circular *vs* full thickness myotomy

One of the major concerns during POEM was how deeply the muscle layer should be divided. In surgical myotomy, full-thickness myotomy is performed, as the surgeon cut from outside first the external longitudinal muscle layer to approach the inner circular muscle layer.

In initial series of POEM performed by Inoue *et al.*^[1] and subsequently by other groups^[36-39], muscle cutting was intended to dissect only the circular muscle bundles,

which is the responsible muscle for achalasia, while the thin longitudinal muscle layer was left intact as a safety margin between submucosal space and mediastinum.

Full-thickness myotomy is not necessary for treating esophageal achalasia and other esophageal motility disorders, and selective circular myotomy can solve the problem, according to excellent results from more than 3000 selective circular POEM cases. So intentional full-thickness myotomy is not recommended to treat achalasia and other esophageal motility disorders.

However, complete true selective circular myotomy is not possible as longitudinal muscle bundles are naturally thin enough to be widely stretched and split each other during POEM, only by mild compression of the endoscope tip, creating partially full-thickness gaps, without clinical relevance or consequences^[26].

With the increasing experience in POEM and the development of sophisticated endoscopic techniques for closing mucosal gaps, some specialized centers performed intentionally full-thickness myotomy, even for achalasia, although not necessary^[40,41]. However, no significant difference to selective circular myotomy was found in all parameters studied (symptom relief, procedure related parameters, manometry) except of reduced procedure time in the group of full-thickness myotomy.

In terms of safety however, nobody knows the real risks of potential complications in inexperienced hands and the consequences of the severe capnomediastinum and capnoperitoneum, following full-thickness myotomy than selective circular myotomy. Moreover, the gastroenterologist who performs POEM is not familiar to mediastinal anatomy and may have higher risk of complications, such as making accidental injuries to structures beyond the esophageal wall.

However, full-thickness myotomy opened new perspectives in the era of NOTES for further investigation, as structures beyond the esophageal wall, such as mediastinum and retroperitoneum are directly endoscopically accessible and also structures, such as the angle of His and vagus nerve^[42] may be recognized during POEM. Potential future endoscopic procedures could be endoscopic retroperitoneoscopy or mediastinoscopy in a similar fashion to laparoscopy and thoracoscopy. However, these areas need further investigation.

Myotomy length

Myotomy length in POEM is also another controversial issue for discussion. POEM permitted control of myotomy length to be as long as we wish, and achievement of longer myotomy than any surgical myotomy^[8,26]. In initial POEM cases, a relatively short myotomy was performed, however long enough to achieve complete release of high LES pressure and resolve achalasia symptoms. Based on clinical results, the recommended myotomy length during POEM should be a minimum of 7 cm, with 2 cm gastric extension.

With the introduction of high resolution topographic manometry (HRTM)^[43] and Chicago classification^[5], achalasia is accurately classified in three major groups,

which permitted better pre-POEM evaluation of these patients.

Based on these manometric studies, patients with type II (vigorous, panesophageal pressurization) and III (spastic) achalasia, with chest pain because of spasm and/or another high-pressure zone, or other mixed esophageal motility disorders, such as diffuse esophageal spasm, nutcracker and jackhammer esophagus^[7-9], longer myotomy of more than 7 cm is necessary for appropriate symptom resolution.

Khashab *et al.*^[9] recently reported the international multicenter experience from 73 patients with spastic esophageal disorders with mean myotomy length 16 cm and maximum up to 25 cm. However, myotomy length should be individualized, based on HRTM results before POEM.

According to the consensus from IPOEMS and other studies, POEM has significant efficacy in nutcracker esophagus, hypertensive LES, diffuse esophageal spasm and type III (spastic) achalasia, because in those disorders often a longer myotomy is required than cannot be achieved *via* the laparoscopic approach^[3,6,7].

Identification of EGJ

Another fundamental issue in POEM is the extension of myotomy beyond the EGJ about 2-3 cm at the gastric side. So identification of the EGJ in the submucosal space during POEM has significant importance. As clear markers for identifying the EGJ, should be checked: (1) the insertion depth of the endoscope from the incisors; (2) a marked increase of resistance when the endoscope approaches the EGJ, followed by a prompt easing when the endoscope enters the gastric submucosal area; (3) the working space in the submucosal tunnel becomes gradually narrower when the endoscope approaches closely to the LES; (4) endoscopic visual identification of palisade vessels in the submucosal layer (Figure 1C); (5) a change of vasculature in the submucosal layer in the esophageal submucosal space few vessels are observed, while gastric submucosal vasculature suddenly becomes rich looking like a spider web and finally; and (6) the ectopic innermost longitudinal muscle bundles in front of the circular muscle layer at the level of the EGJ, finding in more than 30% of cases^[44].

Tattooing at the gastric cardia using indocyanine green (ICG) before POEM is reported to be one trick for identifying EGJ during POEM by recognition of the green dye at the EGJ within the submucosal tunnel^[32]. However, tattooing may be impractical, time consuming, and confusing particularly in sigmoid type achalasia with dilated and helicoid esophagus. However, this issue may need further study.

Orientation within the submucosal space

Ensuring that the submucosal tunnel stays in line with the esophagus is another issue with significant importance, especially in esophageal motility disorders with tight contractions during POEM and sigmoid and dilated

esophagus. There is little data regarding orientation during submucosal tunneling, and although this issue is very important it is not included in up-to-date protocols.

According to Inoue *et al.*^[26], when the cap-fitted endoscope introduced into the submucosal space and then pushed, tends to advance only in line with the esophagus and its round tip tends to move to the center of the elliptical cross-section of the submucosal tunnel.

However, this is not always the case, especially during anterior myotomy to the lesser gastric curvature, because there are no objective markers to sustain correct direction and inexperienced endoscopists may easily lose the orientation, when they are inside the submucosal space (tornado tunnel).

Orientation within submucosal space may be easier during posterior myotomy to the greater gastric curvature because the existence of more objective guiding anatomic markers, such as the ankle of His, and the compression from the spinal cord^[13]. However this issue needs further confirmation in comparative studies.

Myotomy site

Another question regarding POEM, is on which side myotomy should be done? In initial POEM cases, Inoue *et al.*^[1] performed anterior myotomy, to avoid damage to the angle of His and sling muscle bundles that are located at opposite direction at the greater gastric curvature, which might be a natural barrier to postoperative reflux of gastric contents. Since then anterior myotomy has been established and accepted by most endoscopists worldwide^[36-39]. In fact, the International Peroral myotomy survey (IPOEMS), showed that 14 of 16 centers preferred the anterior approach^[3].

Alternatively, posterior myotomy at 5 o'clock position, leading to the greater gastric curvature, is a promising safe modification of the POEM technique, with high rates of technical and clinical success, according to few centers^[13,45]. Posterior myotomy has the theoretical advantage of easy access to EGJ and better orientation within the submucosal tunnel, because of spinal cord and the ankle of His^[13].

Moreover, anterior myotomy is precluded by previous procedures such as failed surgical Heller myotomy or by other anatomic considerations that obscure the normal dissection planes^[12,13]. Also, in patients with advanced sigmoid type achalasia with megaesophagus, the identification of the EGJ may be difficult during anterior myotomy, resulted in an incomplete gastric myotomy and poor symptom relief^[13].

Posterior myotomy may be especially useful in cases of redoPOEM^[32], POEM post-Heller myotomy^[11,12] or when the EGJ is difficult to recognize because of supervening anatomic constraints or in sigmoid type achalasia with megaesophagus (Figure 2)^[15]. However, no comparative studies have been yet published. A multicenter prospective single blind randomized clinical trial is currently underway, to investigate the optimal technique to myotomy (anterior vs posterior approach)

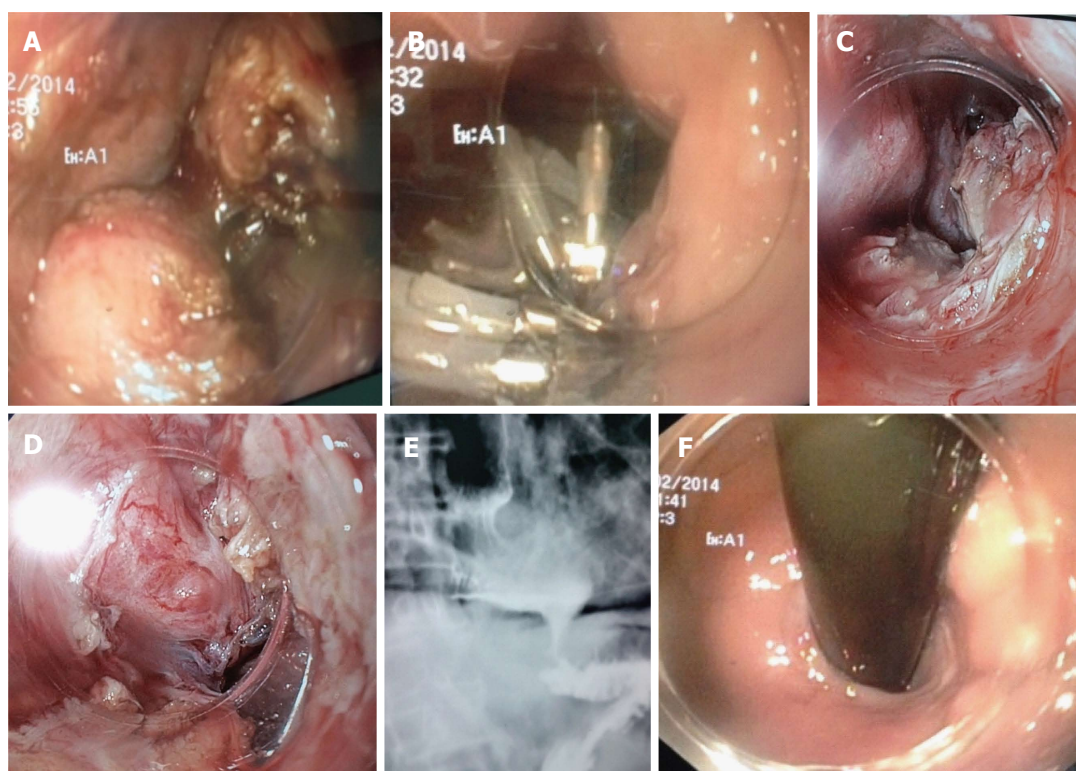


Figure 2 Bilateral peroral endoscopic myotomy in advanced sigmoid (S2) type achalasia with mega esophagus and severe dysphagia in a 74-year-old male with 35-year-old history of achalasia. A: Anterior myotomy. Circular muscle is too thick; B: Closure of the mucosal entry by clips after anterior POEM; C and D: Posterior myotomy at the opposite site. We recognize the mucosal flap and myotomy site; E: Esophagogram after redo-posterior POEM showed sigmoid and dilated esophagus but satisfactory passage of contrast; F: Open EGJ at retroversion. POEM: Peroral endoscopic myotomy; EGJ: Esophagogastric junction.

for POEM.

Mucosal closure

Maintaining the integrity of the mucosal flap and the reliable closure of the mucosal entry during POEM is paramount in preventing leakage of esophageal contents into the mediastinum. Most centers employ clips for closure of the mucosal entry of the tunnel^[1,36-39]. When a completion of the closure with standard clips is unsuccessful, the combined clip-endoloop technique has been successfully applied, comparable to endoscopic full-thickness resection in other areas of the GI tract^[18].

Alternatively, in failed cases, successful mucosal closure has been reported with the OTSC in two POEM cases^[19], and fibrin sealant^[46], however these techniques are more expensive.

There are also few groups who have also successfully used an endoscopic suture device (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas) for closure of inadvertent mucosal tunnel perforations, particularly for mucosal flap injuries at the EGJ^[20]. These groups^[11,20] are also more comfortable with full-thickness myotomy, because they have the possibility to close any perforation either by clipping or by suturing. They reported on 25 mucosal closures without statistically significant differences in closure time, complications or mean costs^[34], however these results are debatable. Moreover, there are no comparative studies between different methods of

mucosal closure, also regarding the cost-effectiveness.

Endoluminal Functional Lumen Imaging Probe system

During POEM the endoscopist is able to immediately assess the adequacy and completeness of myotomy by passing the endoscope through EGJ at the end of the procedure^[26]. The rationale of POEM is to extend myotomy 2-3 cm to the gastric side in order to cut all responsible for achalasia, circular muscle fibers at the EGJ. However, endoscopic measurements of adequate myotomy are subjective and empirical, often imprecise and may be affected by many biases.

Some POEM groups assess the EGJ distensibility quantitatively, immediately at the end of the procedure, with the EndoFLIP (Endoluminal Functional Lumen Imaging Probe) system, trying to objectively confirm the adequacy of myotomy, however without clear results and no real benefit^[47,48]. The EndoFLIP (Crospon Ltd., Galway, Ireland) system, uses impedance planimetry for real-time measurements of the EGJ diameter, through a specific balloon-tipped catheter^[48].

The rationale of the EndoFLIP use during POEM is that the possibility to measure the diameter of the EGJ before and after POEM may reveal cases of incomplete myotomy, before the closure of mucosal entry as it was the case in one patient reported by Familiari *et al.*^[48]. The endoscope was inserted again in the submucosal tunnel and additional muscular bundles were cut at the

EGJ.

According to these studies, EndoFLIP was found to be potentially useful during LHM, but no real benefit was proved in POEM cases^[48,49]. Obviously, the effects of myotomy on the diameter of EGJ are often unpredictable and not really controllable with POEM. Some authors studied the EndoFlip technique, concluded that EndoFLIP during POEM may be impractical and the real role, if any, should be evaluated in further multicenter studies^[48]. To our opinion EndoFLIP may be confusing, time consuming, troublesome, especially in advanced, sigmoid type achalasia and costly.

POEM in sigmoid-type achalasia

Sigmoid type achalasia subdivided into S1 and S2 subtypes based on radiological signs on computed tomography. In S1 achalasia, the esophageal lumen is tortuous, but the direction is still downward. S2 type is an extremely advanced sigmoid form, where the esophageal lumen is tortuous and turns upwards^[1].

Sigmoid type 2, (S2) was initially considered as an exclusion criterion for POEM. In this very advanced form of achalasia, the maximal tortuosity of the esophageal lumen does not allow smooth food passage, which occurs by gravity when the patient is upright. It was hypothesized that simple myotomy could not relieve symptoms and straightening of the curved esophagus was recommended in addition to laparoscopic myotomy^[1].

However, based on the excellent initial results, Inoue *et al.*^[1] first proceeded to successful POEM in 9 patients with sigmoid-type achalasia, and reported them in his initial publication^[1]. Since then other groups also reported successful POEM in advanced sigmoid achalasia^[14,15,50].

Currently sigmoid type of achalasia is not yet considered as a contraindication for POEM, although it may produce even more technical difficulties, especially in remaining perpendicular to circular layer during myotomy. Moreover, in advanced sigmoid type (S2) achalasia, which is usually presented in advanced age, with multiple comorbidities, and contraindications for major surgery such as esophagectomy, and with a history of potential multiple previous therapies, such as PBD or even surgery, POEM may be the only available therapy. In these advanced sigmoid type (S2) achalasia, with potential extremely thick circular muscle layer, posterior or bilateral POEM^[15] (Figure 2), may be the more appropriate approach, however without definite literature data. Further international experience in this specific subgroup is necessary and is awaited.

POEM for failed surgical myotomy

Although surgical or LHM resulted in good-excellent long-term results in 90% of achalasia patients, failures do occur^[51]. According to Gockel *et al.*^[51] the most common causes of surgical myotomy failures are persistent achalasia or early recurrence due to inadequate or incomplete myotomy; early scarring or fibrosis; early fusion or healed myotomy; while other causes are tight fundoplication; peptic stricture due to gastroesophageal

reflux (GERD); late recurrence due to progression to advanced sigmoid megaesophagus; diffuse esophageal spasm; progression to esophageal cancer; and others.

Treatment of failed surgical myotomy is a challenging, difficult urgent problem, with controversial data^[51]. Redo Heller myotomy has lower efficacy and more postoperative complications, because it is more technically demanding due to the presence of adhesions, fibrosis, and scars from previous surgery according to Wang and Li^[52].

Onimaru *et al.*^[12] and Zhou *et al.*^[11] reported successful rescue POEM on 10 and 12 achalasia patients respectively, with persistent or recurrent symptoms after previous surgical myotomy, with excellent (> 90%) short-term results and without complications.

Both LES resting pressure and symptom score were improved in short-term. The authors have not encountered any difficulties in extending the adequate POEM myotomy down to the stomach because of the presence of fundoplication.

In the rescue POEM, myotomy was performed at the axis opposite to the previous myotomy (mainly posterior axis), to avoid facing scars and submucosal fibrosis from previous surgery. In cases which the axis of previous surgical myotomy could not be clearly identified, myotomy was made at the standard 2 o'clock axis at the proximal esophagus and then rotated to a different axis at the area of the EGJ^[12]. Rescue POEM, however, is highly demanding procedure compared to standard POEM and may be better performed by experts.

POEM vs surgical myotomy for primary achalasia

As the positive international experience with POEM increases, with explosion of international centers performing POEM, there is a criticism in the literature regarding the superiority of POEM to alternative standard 100-year-old surgical or LHM^[53]. One of the major arguments for surgical myotomy is that "the approach is outside the mucosa"^[54]. However intact mucosa is not any more a "taboo" in the modern era of NOTES as mucosal gap can be safely and effectively closed after the procedure, according to excellent results from more than 4000 POEM cases worldwide, up-to date^[1,3,4,36-39]. Moreover, with surgery anatomical structures around EGJ are permanently cut and mobilized, and LHM should always be accompanied with partial fundoplication due to risk of severe GERD. Advantages and disadvantages of POEM vs LHM are presented in Table 3.

Furthermore, POEM permitted endoscopists to approach and cut the responsible muscle of achalasia (the circular muscle layer at the EGJ), through the submucosal space with the most delicate mode, leaving the surrounding structures intact^[1].

Few non-randomized studies^[53,55-57] exist comparing POEM to LHM, with conflicting results^[55]. A recent meta-analysis of comparative studies between LHM and POEM showed equivalent short-term outcomes and similar results for adverse events, perforation rate, operative time and a non-significant trend toward a reduced length of hospital stay in the POEM group^[54,58].

Table 3 Advantages and disadvantages of peroral endoscopic myotomy *vs* laparoscopic Heller myotomy

	POEM	LHM
Advantages of POEM		
Myotomy length	Longer myotomy up to 25 cm	Short myotomy maximum 6 cm
Hospitalization	Minimally invasive method	Invasive (major surgery)
Myotomy depth	Less hospitalization (1-5 d)	Longer hospitalization > 5 d
Other esophageal motility disorders	Selective circular myotomy possible	Only full-thickness myotomy
Sigmoid achalasia	Effective for esophageal spasm, nut cracker and jackhammer esophagus	Combined laparoscopic and thoracoscopic approach is necessary to obtain equivalent myotomy
Elderly patients	Effective in all types of achalasia even in end-stage, sigmoid type (S2) achalasia with megaesophagus	Major surgery such as esophagectomy may be necessary
In failed surgical	Effective in elderly with comorbidities and contraindications	Contra indication for surgery
Cost	POEM after failed surgical myotomy is effective	Redo-surgery often with high rates of failure and complications
GERD	Lower hospitalization and lower cost	Higher cost in combination to surgical procedure
	Less common and lower severity. No antireflux procedure (fundoplication) necessary at the moment.	Fundoplication necessary and routinely performed
	Further study necessary	Complications from fundoplication
	Does not preclude surgery	
	Bilateral POEM possible	POEM more difficult after LHM
Disadvantages of POEM		
Follow-up	POEM	Surgery
	Short follow-up (novel technique)	Longer follow-up
	POEM restricted to specialized centers	Common surgical or laparoscopic procedure overall available
Training	Difficult (no so many centers)	Overall available

POEM: Peroral endoscopic myotomy; LHM: Laparoscopic Heller myotomy; GERD: Gastroesophageal reflux.

Further, randomized comparative studies of LHM and POEM are required. However, conducting studies comparing a novel endoscopic procedure mainly performed by gastroenterologists to a standard LHM performed exclusively by surgeons, in a population of achalasia with large inhomogeneity regarding type, stage and severity are extremely difficult.

All studies comparing POEM to LHM have not focused to specific subgroups of achalasia patients, *i.e.*, end-stage achalasia, with sigmoid type and megaesophagus with contraindications for major surgery. In these particular cases, as well as in other mixed esophageal motility disorders, POEM is the potential only acceptable treatment, according to up-to date positive experience^[11,13,15,26]. The exciting results from POEM make objective, comparative studies to LHM difficult, with many ethical issues also emerged.

POEM after failure of previous POEM

Failure of POEM to control achalasia symptoms, does not exclude future surgery (LHM), because POEM does not involve adjacent tissues surrounding the lower esophagus^[13].

The most common causes of POEM failures are persistent achalasia or early recurrence due to inadequate or incomplete myotomy; end-stage, sigmoid type (S2) achalasia with megaesophagus, where one side (mainly anterior) myotomy is not sufficient and overlooked mixed esophageal motility disorders that need longer myotomy^[13]. In these failed POEM cases, redo-POEM at

the opposite (posterior) direction is recommended and it has been successfully reported^[13]. Longer follow-up, with greater number of patients and further studies focusing on failed POEM are necessary.

POEM RELATED COMPLICATIONS

Acute or late POEM related complications varied greatly among different reports^[59] (Table 4). According to recent pooled analyses, minor complications include: Gas-related complications, such as capno/pneumoperitoneum (30%), subcutaneous emphysema (32%), and capno/pneumomediastinum (10%-22%)^[39,58-60]. Major operative adverse events include tunnel mucosal perforation resulted to mediastinal or peritoneal leak, acute peritonitis, pleural effusion, GI fistula (0.3%), postoperative bleeding (1.1%) and a single death (1/4000 POEM cases, 0.025% mortality)^[58].

Major bleeding in the tunnel is unusual but may require reentry for hemostasis, longer hospitalization time or even blood transfusion^[29,46,61]. Post-POEM reflux esophagitis reported in 19% of patients, although there is controversy in the literature regarding incidence and severity of post-POEM GERD^[58].

Gas related complications

Minor pneumomediastinum, or mild subcutaneous emphysema, just after POEM, could be as high as 100%, with incidence between 10%-22%^[39,59,60], however, without clinical significance or requirement of special

Table 4 Complications of peroral endoscopic myotomy^[58]

Common complications
Gas-related complications (minor)
Subcutaneous emphysema (31.6%)
Capno/pneumomediastinum (10%-22%)
Capno/pneumothorax (11%)
Capno/pneumoperitoneum (30.6%) ^[58]
Mucosal injury-perforation (mediastinal or peritoneal leak) (0.3%) (major)
Mediastinitis (insufficient data)
Peritonitis (insufficient data)
Retroperitoneal abscess (2 proved cases reported)
Pleural effusion (insufficient data)
Pneumonitis (insufficient data)
GI fistula (insufficient data)
Fever (temperature > 38 °C)
Severe postoperative pain
Rare complications
Delay postoperative bleeding (1.1%)
Hematoma within the tunnel
Submucosal infection
Mortality (0.025%) (Single death/4000 POEM cases)

POEM: Peroral endoscopic myotomy; GI: Gastrointestinal.

treatment, and should not be considered as a complication. This phenomenon should be considered similar to the pneumomediastinum seen post thoracoscopic surgery or post-ESD^[26,60,62].

However, gas-related complications may cause discomfort, which is usually relieved through conservative treatment, while in more severe cases vast gas accumulation may occur in the chest, abdominal cavity, mediastinum or under the skin, while acute respiratory and circulatory failure may occur. In such setting emergency invasive interventions of deflation *via* subcutaneous puncture and if necessary closed thoracic drainage should be taken for symptom relief^[26,41,45].

Severe pneumothorax (up to 2.5%^[45]) need chest tube placement, reported in the very early series of POEM^[4], when air was insufflated instead of carbon dioxide gas, while thereafter no such severe complication is reported, at least from pioneering centers^[6,11,15].

Furthermore, despite the theoretical dangerous "downside", according to centers with large number of POEM cases, although long myotomy have been performed up to 25 cm^[8], no clinically severe mediastinitis has been reported at the moment^[4,11,26].

Selective circular myotomy is preferred by most researchers trying to preserve longitudinal muscular layer in order to reduce the chance of gas entry into the thoracic and abdominal cavity. Full-thickness myotomy, however did not increase the occurrence of gas-related complications, although further studies are necessary^[41].

Sigmoid-type esophagus was found to be independent risk factor for the occurrence of gas related complications, due to esophageal twisting, which might form a state of high pressure within the tunnel, so as to cause such complication as subcutaneous emphysema, pneumothorax and pneumoperitoneum^[59].

Tunnel mucosal perforation

Mucosal tear during POEM, particularly at the high-pressure zone of the EGJ or cardia, which are considered as true perforations, have been also reported (0.3%), particularly in early POEM series^[4,12,26,32,58]. These complications were usually treated conservatively with observation, prolonged fasting and longer intravenous antibiotic therapy. In two cases with sub diaphragmatic abscess, external drainage was necessary, with optional outcome thereafter.

The mucosal defects have been adequately closed by multiple clips^[12,26,32], fibrin sealant^[46], or by the clip-endoloop technique^[18] and lately by endoscopic suture device (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas)^[20]. Temporary dysphagia is also reported in one patient after multiple clipping at the EGJ^[26].

POEM-related mortality

According to International POEM group, only a single, unpublished^[58], POEM related death is currently reported and outside from the large POEM volume Asian centers, that reported no deaths^[32,50]. So, POEM related mortality at the moment, is estimated to be 0.025% (one out of 4000 POEM cases globally). However, POEM related mortality should be compared to mortality of the surgical alternatives, which are the surgical, or LHM. According to recent (2015) study on national outcomes, the mortality rate of LHM was (4/1237) 0.3%^[63] (almost 10-times more than POEM), with 2.4% major complications, 3.1% readmissions and 2.3% reoperation^[63].

Moreover, the existing international experience from great number of patients, showed that POEM is a totally safe procedure, applied safely and effectively to all age spectrum from children to octogenarians, and also to patients with severe co-morbidities and contraindications for surgery^[1,36-39,45,59,64,65]. However, future prospective, randomized, comparative, multicenter studies, on POEM related complications, also focusing on 30-d mortality rate after POEM (procedure and not procedure related), are necessary and awaited.

GERD after POEM

LHM is routinely accompanied by antireflux procedure, to prevent postoperative GERD, because the natural antireflux mechanisms are impaired, while in POEM no antireflux procedure is recommended, since the hiatal attachments are left untouched and the flap-valve mechanism intact^[1].

Theoretically to minimize the risk of post-POEM reflux, anterior myotomy has been recommended, to avoid damage to the angle of His, and the oblique muscle layer of the EGJ, which are natural barriers to postoperative gastric reflux, located posterior laterally^[1]. Sigmoid-type esophagus was found to be independent risk factor for the occurrence of GERD after POEM^[59].

There are controversial results regarding post-POEM GERD, with incidence varied between 5%-46%

Table 5 Efficacy and complications of peroral endoscopic myotomy

Ref.	Patients (n)	Mean age (yr)	Eckardt score (pre/post)	LES pressure (pre/post) (mmHg)	Follow-up (mo)	Efficacy	Objective GERD evidence n (%)
Onimaru <i>et al</i> ^[12] , Yokohama, Japan	300	45 (3-87)	6.13/1.33	27.3/13.4	12	98%	10%
Zhou <i>et al</i> ^[4] , Fudan, China	42	44 (10-70)			2.5 (1-6)	100%	
Minami <i>et al</i> ^[32] , Nagasaki, Japan	28	52 (19-84)	6.7/0.7	71.2/21	16	100%	Esophagitis 39.3%
Swanström <i>et al</i> ^[65] , Portland, Oregon	18	59 (22-88)	6/0	45/16.8	6	94%	Esophagitis grade 1 28% +pH study 46%
Costamagna <i>et al</i> ^[39] , Rome, Italy	11	41 (23-68)	7.1/1.1	45.1/16.9	3	100%	
Chiu <i>et al</i> ^[64] , Hong Kong, China	16	47 (22-87)	5.5/0	43.6/29.8	3	100%	+pH study 3/15 (20%)
Hungness <i>et al</i> ^[53] , Chicago, Illinois	18	38 (22-69)	7/1	19/9	63	89%	Esophagitis LA 33.3% A 13.3% B 13.3% C 6.7%
Von Renteln <i>et al</i> ^[60] , European, CT	70	45	6.9/1	27.6/8.9	12	82%	Esophagitis 42% LA class A 29.2% B 12.3%
Stavropoulos <i>et al</i> ^[85] , Mineola, New York	100	52 (17-93)	7.8/0.2	44.2/17.6	13.3	96%	17/53 (32%)
Verlaan <i>et al</i> ^[37] , Amsterdam, The Netherlands	10	43	8/1	20.5/6.8	3	100%	60% LA class A 30% B 30%

GERD: Gastroesophageal reflux.

in published series^[3,4,12,32,36-39,45,53,61,64,66] (Table 5). Inoue *et al*^[1] and other initial multicenter studies^[1,36-39,45,59], reported no symptomatic or mild endoscopic (LA grade A) post-POEM GERD, and concluded that GERD is minor or no problem after POEM. In contrary, according to a recent European multicenter study, GERD was the most common adverse event after POEM, with esophagitis diagnosed in 42% of patients, though usually mild^[60].

There is controversy between studies and within the same study regarding the definition of post-POEM GERD. GERD can be defined on base of symptoms, 24-h pH monitoring and endoscopy data. Familiari *et al*^[48] reported incidence of GERD of 57% based on pH monitoring, 33% based on endoscopic findings and 14% based on symptoms. This discrepancy is found to all studies, however, they all agree that GERD after POEM is not severe and can be successfully treated with proton-pump inhibitors.

In the largest POEM series with longer follow-up, the risk of GERD after POEM varies between 10%-30%, with average 10%, with excellent control under proton pump inhibitors (PPIs)^[32]. Although this issue needs further long-term studies, at the present no antireflux procedure is recommended during POEM.

Efficacy of POEM

The overall results of POEM worldwide, showed excellent symptom improvement (using Eckardt score pre- and post-POEM) between 82%-100%, (mean 90%)^[1,3,4,36-39]. Efficacy of POEM was also studied using manometry and timed barium esophagogram, showing significant

improvement in LES pressure and esophageal emptying in 66% and 80% post-POEM, respectively^[12,26,37,38,53,58] (Table 5). However, more data on long-term efficacy of POEM is needed, and awaited.

Training in POEM

As POEM constitutes a new endoscopic, pure NOTES procedure, which opens the era of submucosal endoscopy, emerged important ethical and training issues. Although theoretically POEM may have dangerous "downside" this has not been yet proved according to successful international experience from more than 4000 POEM cases globally. However, in order to diminish the risk of mishaps an appropriate training program for acquiring adequacy for performing safe and effective POEM is urgently needed.

A simple, cheap and reproducible, non-survival porcine animal model has been established for training in POEM, without the need for concern about complications^[67-69]. Pig is the most appropriate animal model for training in POEM, due to its similarities to the human anatomy, while the porcine esophagus has the advantage of easy mobilization due to absence of tight junctions to surrounding organs.

However, there are significant differences between the porcine and human esophagus, particularly in patients with achalasia. Human submucosa is more hard than porcine's and esophageal circular muscle layer in achalasia is thicker, with multiple high-pressure contractions, while in cadaveric pig model the muscle is thin and without any contraction. Thus, mucosotomy and submucosal tunneling dissection are difficult in porcine due to tissue pliability and poor tissue distention^[68].

The low incidence of achalasia (0.3%-1% per 100000 population)^[70], in combination with the risk of serious complications, related to the technically demanding POEM procedure, has made training difficult^[68,71]. Neither gastroenterologists nor surgeons are absolutely familiar with submucosal endoscopy. While endoscopists are familiar with endoluminal procedures and more experienced in handling endoscope within the natural lumen, surgeons, are familiar with laparoscopic/thoracoscopic procedures and can more easily recognize the structures beyond the mucosa^[68,71].

POEM however is a procedure that requires both capabilities. Good endoscope manipulation, recognition of luminal structures and surgical knowledge of extraluminal structures especially vessels, nerves and mediastinal anatomy. Moreover, delicate skills are also needed^[68,71]. With the worldwide expansion of centers starting performing POEM training program, in POEM procedure is more urgent. Until recently, there are no standard training guidelines for training. The pioneers in POEM proposed a two stage training system for POEM.

First is preclinical training, during which the experienced trainee -which is familiar with handling GI endoscope, has perfect knowledge of esophageal and EGJ anatomy, knowledge of the pathophysiology of achalasia and knowledge of the POEM procedure, including set up of device and patient care during perioperative period- has to follow observation of POEM performed by specialists, and then practice in the animal or cadaveric model, about 46 (range 12-154) hours, according to recent international consensus^[26,27,67-69,71]. Some other centers proposed use of clinical proctor system with 2 median number of proctored cases^[71].

Second step is the clinical training, with POEM in humans with achalasia, performed under careful guidance and observation by specialists, and finally, performance of POEM in humans, with 20 POEM procedures needed to cover the learning curve^[67,68,71]. However, there is still controversy in the literature regarding POEM operator background and training program focusing on "learning curve", while objective, neutral studies in this issues are difficult^[72-74].

POET

Historical perspective

The exciting results of POEM^[1,3,11,36-39] for esophageal achalasia, has further inspired other endoscopic miniinvasive treatments, such as POET^[16,17] for *en bloc* resection of SMTs using the submucosal tunnel technique, particularly for esophageal, EGJ and gastric cardia tumors originating from the muscularis propria.

Endoscopic resection of SMTs originating from the muscularis mucosa (such as leiomyomas) and possibly the submucosa, has been also reported, with a variety of other techniques^[75], from simple snaring to endoscopic submucosal dissection (ESD), because the muscle layer can be preserved^[76,77]. Tumors however, originating from the muscularis propria have to be resected by

thoracoscopy or laparoscopy^[78].

Endoscopic snare full-thickness resection with adequate closure of the perforation with OTSC^[19], or clips and an endoloop^[18] or endoscopic suturing^[20] has been successfully reported for small gastric SMTs (diameter < 2-3 cm)^[79]. ESD has been also reported for the removal of EGJ SMTs, with satisfactory results^[80]. Endoscopic partial resection using the unroofing technique has been also safely and effectively applied for definite pathological diagnosis of small SMTs^[81].

The EGJ, however, is a difficult location for endoscopic resection because it is adjacent to the diaphragm, complicating the endoscopic resection with movement from breathing as well as esophageal peristalsis, in combination with narrow lumen or sharp angle, while SMTs of the EGJ are often irregular, lobulated and may grow annularly, with potential increased risks of perforation and mediastinal infection, especially for SMTs originating from the muscularis propria. Conventional endoscopic muscularis excavation causes large mucosal defects which are difficult to close and often result in strictures^[17].

Submucosal tunnel endoscopy, permitting approach to SMTs through a submucosal tunnel, tumor dissection within the tunnel, "*en bloc*" removal through a mucosal opening far from the tumor, and finally mucosal closure by clips. Submucosal tunnel endoscopy, permitted a controlled, standardized assess to previously taboo spaces, such as the muscle layer, mediastinum and peritoneum, which has been popularized with POEM^[1,3,11,36-39].

Xu *et al*^[17] and Inoue *et al*^[16], based upon the POEM concept for treatment of achalasia, further described the technical principles for POET and performed the first successful POET clinical cases for esophageal, EGJ and gastric cardia SMTs originating from the muscularis propria. Since then POET has been used by other centers^[16,17,82,83] as well. However, further international experience is necessary and awaited before the popularization of POET.

Indications and contraindications

The absolute and relative indications and contraindications of POET are described in Table 6. POET for esophageal, EGJ or gastric cardia SMTs, is far less invasive than, the technically demanding and invasive, surgical alternatives, which are either partial proximal gastrectomy for EGJ SMTs and esophagectomy for esophageal SMTs, while for lesions in the middle or distal stomach can be resected easily *via* laparoscopic approach^[16,27] (Table 7). Moreover, surgical resection of cardia SMTs, have high risk of esophageal stricture development.

Based on the experience from specialized centers^[16,27,80,82], absolute indication for POET includes suspected or confirmed gastrointestinal stromal tumor (GIST) and leiomyoma of the esophagus, gastric cardia and EGJ larger than 2-3 cm, if they are causing symptoms, increasing in size on follow-up or have high risk features on biopsy, endoscopic ultrasound (EUS) or computed tomography^[16,27]. SMTs lower than 2 cm are low risk lesions and life-long surveillance by endoscopy/EUS is indicated. Some authors stated that in these small size (<

Table 6 Indications and contraindications of peroral endoscopic tumor resection

Absolute indications	
Suspected or confirmed GIST of the esophagus and gastric cardia larger than 2-3 cm and lower than 5 cm, and tumor growth on follow-up	
Suspected or confirmed leiomyoma of the esophagus and gastric cardia larger than > 2-3 cm and < 5 cm	
Esophageal or gastric cardia SMTs in elderly with comorbidities and non-surgical candidates completed the above criteria (only in experienced hands and specialized centers)	
POET does not exclude surgery. Complete histological diagnosis possible with POET	
Relative indications	
Esophageal and gastric SMT more than 5 cm (full-thickness resection using submucosal tunnel technique possible) (in experienced hands and specialized centers only and within studies)	
Contraindication	
Suspected or proved malignancy of SMTs	

GIST: Gastrointestinal stromal tumor; POET: Peroral endoscopic tumor resection; SMT: Submucosal tumor.

Table 7 Advantages and disadvantages of peroral endoscopic tumor resection vs surgery

Advantages of POET		
Hospitalization	POET	Surgical myotomy
	Minimally invasive method	Invasive (major surgery)
	Less hospitalization (1-5 d)	Longer hospitalization > 5 d
	Specimen for complete histology possible	
Elderly patients	Does not preclude surgery	
	Effective in elderly with comorbidities and contraindications (only specialized centers)	Contra indication for surgery
Cost	Lower hospitalization and lower cost	Higher cost in combination to surgical procedure
Disadvantages of POET		
Follow-up	POET	Surgery
	Short follow-up (novel technique)	Longer follow-up
POEM	POET restricted to specialized centers	Common surgical or laparoscopic procedure overall available
Training	Difficult (only few centers worldwide)	Overall available
Outcome	Complete curable resection may be not possible in malignant GIST cases	Complete resection possible

GIST: Gastrointestinal stromal tumor; POET: Peroral endoscopic tumor resection; POEM: Peroral endoscopic myotomy.

2 cm) SMTs, POET may offer definitive histologic diagnosis by achieving en bloc resection and may eliminate the need for life-long surveillance^[40], however the current surveillance practice has not yet changed. Contraindication for POET is suspected or confirmed malignancy. In suspected malignant cases, EUS puncture is indicated for tissue diagnosis and if malignant, the patients were primarily referred for surgical resection.

POET is also advantageous because it could be also applied in case of contraindications for the above-mentioned major operations, particularly in patients with serious comorbidities^[16]. Although, initial experience of POET in a small series of patients and from specialized centers, was exciting in terms of safety and efficacy, further international experience with greater number of patients and longer follow-up is necessary and awaited.

POET procedure

The general set up of POET is the same as during POEM procedure^[1], including longitudinal mucosal incision, entrance to the submucosal space, creation of the submucosal tunnel, and approaching the SMTs. Only the final step is different and individualized based on the specifics of each case (Figure 3).

In POET the initial 2-cm longitudinal mucosal incision, is made at approximately 5 cm orally to the proximal margin of the SMT. The submucosal tunnel is created in the same way as Inoue *et al*^[1] first described for POEM. The submucosal tunnel advanced towards the SMT and then extended beyond the tumor to prepare enough space to finally resect the tumor under direct vision.

In the final stage of POET the SMT is enucleated using combination of electrocautery knives [TT-knife and insulated tip (IT) knife] after dissection of muscle fibers connected to the SMT. The IT-knife is useful to dissect from the distal to proximal direction, and to mobilize the SMT. Then, extraction of the mobilized SMT is followed by suctioning the tumor into the cap device and removes it through the mucosal entry. Finally, the mucosal entry was closed tightly in similar manner as in POEM^[1], mainly with endoscopic clips. Endoscopic suturing is alternatively used in difficult cases, by other groups^[40].

The follow-up includes gastroscopy the following day to evaluate the mucosal integrity and contrast media swallow to check for leakage, and if normal started clear liquid diet and gradually regular diet the next days. Annual endoscopic follow-up was then recommended.

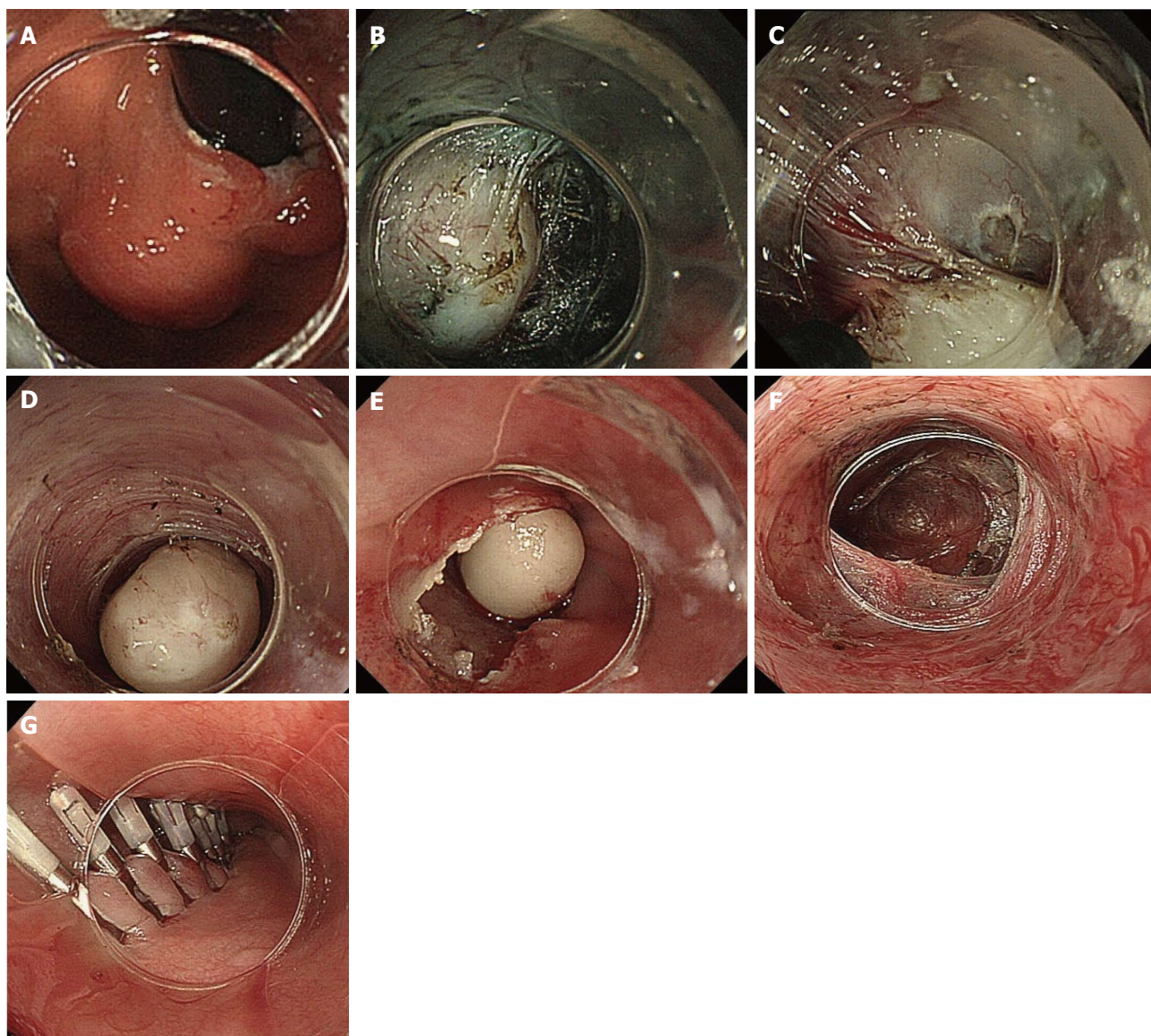


Figure 3 Schema of stages of peroral endoscopic tumor resection. A: Gastric cardia SMT in retroversion view; B: Submucosal tunneling. After initial mucosal incision approximately 5 cm proximal to the edge of the SMT, saline and indigo carmine are injected to create a mucosal bleb. A submucosal tunnel is created by dissecting the submucosal fibers. Submucosal dissection is advanced beyond the distal tumor edge; C: Tumor excision. The submucosal tumor is dissected from the muscle layer. All muscle bundles that connect to the submucosal tumor are cut with the triangle-tip knife; D and E: Removal of the submucosal tumor. The totally mobilized tumor is extracted from the submucosal space (D) through the mucosal incision (E). The submucosal tumor is caught tightly by endoscopic suction at the tip of its distal attachment. Submucosal tumors generally have an oval shape, which enables smooth removal out through the mucosal entry; F: Submucosal tunnel after removal of SMT; G: Closure of the mucosal entry incision. After confirmation of complete hemostasis in the submucosal tunnel (F), the mucosal entry is tightly closed with hemostatic clips. POET: Peroral endoscopic tumor resection; SMT: Submucosal tumor.

POET efficacy and related complications

Inoue *et al.*^[16] described successful complete POET in seven patients, four cardia and three esophageal SMTs, without complications. Histologically, one GIST, five leiomyomas and one aberrant pancreas were found. Only in the rare case of aberrant pancreas, additional mucosal resection was required, while in the other six tumors, resection margins were clear. No short-term complications reported^[16].

POET also showed excellent results in long-term, according to a recent report from a pioneering center with large number of patients (290 patients with 4 years follow-up), showing no residual tumor, local tumor

recurrence or distant metastasis^[82]. According to literature available to us, no POET-related deaths were currently reported.

However, taking into account that POET is a relatively new technique with potential dangerous “downside”, future international, prospective, multicenter studies, focusing also on complications (procedure and not procedure related), are necessary and awaited. At the moment POET is restricted only to pioneering centers and within protocols. On the other hand, POET should be also considered as endoscopic surgical procedure and should be compared to surgical equivalents, which are for esophageal and EGJ lesions the esophagectomy

Table 8 Future perspectives of submucosal tunnel endoscopy

Endoscopic vagotomy?
Endoscopic thoracoscopy?
Endoscopic retroperitoneoscopy?
Endoscopic peritoneoscopy?
Endoscopic sympathectomy

and esophagogastrectomy, respectively.

Submucosal tunnel endoscopy opened other possibilities as well, such as exploration of peritoneal and thoracic cavities through transgastric peritoneoscopy^[84] (Table 8). Lastly, another application of submucosal tunnel endoscopy, is the peroral pyloromyotomy as a potential treatment of gastroparesis using endoscopic submucosal tunneling similar to the concept of POEM^[21].

CONCLUSION

Submucosal tunnel endoscopy, including POEM and POET, constitutes a novel terrain for minimal invasive endoscopic treatment of various diseases, such as achalasia and other esophageal motility disorders and esophageal, EGJ and gastric cardia SMTs, which showed exciting results in international level, and superior characteristics than the standard 100-year-old surgical alternatives.

Technological advancements in the era of NOTES, such as endoscopic suturing techniques, permitted endoscopists to become more aggressive, with submucosal tunnel endoscopy including endoscopic full-thickness resections, to be performed safely and successfully. Submucosal tunnel endoscopy opened many possibilities for miniinvasive endoscopic treatment in diseases where the surgical equivalents in terms of aggressiveness are totally incomparable, particularly in elderly patients with comorbidities.

POEM has been globally popularized, with excellent results even from small centers, while it has been extended further to become the treatment of choice not only for all types of achalasia [classical (I), vigorous (II), spastic (III)], including advanced sigmoid (S1 and S2) type, but also for failed surgical or LHM cases, and other esophageal motility disorders (diffuse esophageal spasm, nutcracker and jackhammer esophagus).

POET was spawned from the success of POEM, and slowly expanded worldwide to safely and successfully treat muscularis propria based SMTs in challenging locations in esophagus, EGJ and gastric cardia, with minimally invasive endoscopic procedure.

However, larger number of patients and long-term outcome of POEM and more experience of POET is necessary and is awaited. POEM and POET inspire many other NOTES interventions utilizing the submucosal tunnel approach.

REFERENCES

1 Inoue H, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M,

- Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
- 2 Kalloo AN, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, Magee CA, Kantsevoy SV. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004; **60**: 114-117 [PMID: 15229442 DOI: 10.1016/S0016-5107(04)01309-4]
- 3 Stavropoulos SN, Modayil RJ, Friedel D, Savides T. The International Per Oral Endoscopic Myotomy Survey (IPOEMS): a snapshot of the global POEM experience. *Surg Endosc* 2013; **27**: 3322-3338 [PMID: 23549760 DOI: 10.1007/s00464-013-2913-8]
- 4 Zhou PH, Cai MY, Yao LQ, Zhong YS, Ren Z, Xu MD, Chen WF, Qin XY. [Peroral endoscopic myotomy for esophageal achalasia: report of 42 cases]. *Zhonghua Weichang Waike Zazhi* 2011; **14**: 705-708 [PMID: 21948538]
- 5 Pandolfino JE, Kwiatak MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008; **135**: 1526-1533 [PMID: 18722376 DOI: 10.1053/j.gastro.2008.07.022]
- 6 Kandulski A, Fuchs KH, Malfertheiner P. Jackhammer esophagus: high-resolution manometry and therapeutic approach using peroral endoscopic myotomy (POEM). *Dis Esophagus* 2014 Jan 27; Epub ahead of print [PMID: 24460870 DOI: 10.1111/dote.12182]
- 7 Minami H, Isomoto H, Yamaguchi N, Ohnita K, Takeshima F, Inoue H, Nakao K. Peroral endoscopic myotomy (POEM) for diffuse esophageal spasm. *Endoscopy* 2014; **46** Suppl 1 UCTN: E79-E81 [PMID: 24676826 DOI: 10.1055/s-0032-1309922]
- 8 Shiwaiku H, Inoue H, Beppu R, Nakashima R, Minami H, Shiroshita T, Yamauchi Y, Hoshino S, Yamashita Y. Successful treatment of diffuse esophageal spasm by peroral endoscopic myotomy. *Gastrointest Endosc* 2013; **77**: 149-150 [PMID: 22482919 DOI: 10.1016/j.gie.2012.02.008]
- 9 Khashab MA, Messallam AA, Onimaru M, Teitelbaum EN, Ujiki MB, Gitelis ME, Modayil RJ, Hungness ES, Stavropoulos SN, El Zein MH, Shiwaiku H, Kunda R, Repici A, Minami H, Chiu PW, Ponsky J, Kumbhari V, Saxena P, Maydeo AP, Inoue H. International multicenter experience with peroral endoscopic myotomy for the treatment of spastic esophageal disorders refractory to medical therapy (with video). *Gastrointest Endosc* 2015; **81**: 1170-1177 [PMID: 25634487 DOI: 10.1016/j.gie.2014.10.011]
- 10 Sharata A, Kurian AA, Dunst CM, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. *J Gastrointest Surg* 2013; **17**: 1188-1192 [PMID: 23609138 DOI: 10.1007/s11605-013-2193-6]
- 11 Zhou PH, Li QL, Yao LQ, Xu MD, Chen WF, Cai MY, Hu JW, Li L, Zhang YQ, Zhong YS, Ma LL, Qin WZ, Cui Z. Peroral endoscopic myotomy for failed Heller myotomy: a prospective single-center study. *Endoscopy* 2013; **45**: 161-166 [PMID: 23389963 DOI: 10.1055/s-0032-1326203]
- 12 Onimaru M, Inoue H, Ikeda H, Yoshida A, Santi EG, Sato H, Ito H, Maselli R, Kudo SE. Peroral endoscopic myotomy is a viable option for failed surgical esophagocardiomyotomy instead of redo surgical Heller myotomy: a single center prospective study. *J Am Coll Surg* 2013; **217**: 598-605 [PMID: 23891071 DOI: 10.1016/j.jamcollsurg.2013.05.025]
- 13 Onimaru M, Inoue H, Ikeda H, Sato C, Sato H, Phalanusitthepha C, Santi EG, Grimes KL, Ito H, Kudo SE. Greater curvature myotomy is a safe and effective modified technique in per-oral endoscopic myotomy (with videos). *Gastrointest Endosc* 2015; **81**: 1370-1377 [PMID: 25686872 DOI: 10.1016/j.gie.2014.11.014]
- 14 Hu JW, Li QL, Zhou PH, Yao LQ, Xu MD, Zhang YQ, Zhong YS, Chen WF, Ma LL, Qin WZ, Cai MY. Peroral endoscopic myotomy for advanced achalasia with sigmoid-shaped esophagus: long-term outcomes from a prospective, single-center study. *Surg Endosc* 2015; **29**: 2841-2850 [PMID: 25492452 DOI: 10.1007/s00464-014-4013-9]
- 15 Eleftheriadis N, Protopapas A, Katsogridakis J, Hatzitolios AI. Successful peroral endoscopic myotomy for radical treatment of sigmoid-type esophageal achalasia by Greek gastroenterologists.

- Ann Gastroenterol* 2014; **27**: 430-431 [PMID: 25331209]
- 16 **Inoue H**, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Maselli R, Kudo S. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. *Endoscopy* 2012; **44**: 225-230 [PMID: 22354822 DOI: 10.1055/s-0031-1291659]
 - 17 **Xu MD**, Cai MY, Zhou PH, Qin XY, Zhong YS, Chen WF, Hu JW, Zhang YQ, Ma LL, Qin WZ, Yao LQ. Submucosal tunneling endoscopic resection: a new technique for treating upper GI submucosal tumors originating from the muscularis propria layer (with videos). *Gastrointest Endosc* 2012; **75**: 195-199 [PMID: 22056087 DOI: 10.1016/j.gie.2011.08.018]
 - 18 **Ye LP**, Yu Z, Mao XL, Zhu LH, Zhou XB. Endoscopic full-thickness resection with defect closure using clips and an endoloop for gastric subepithelial tumors arising from the muscularis propria. *Surg Endosc* 2014; **28**: 1978-1983 [PMID: 24619327 DOI: 10.1007/s00464-014-3421-1]
 - 19 **Saxena P**, Chavez YH, Kord Valeshabad A, Kalloo AN, Khashab MA. An alternative method for mucosal flap closure during peroral endoscopic myotomy using an over-the-scope clipping device. *Endoscopy* 2013; **45**: 579-581 [PMID: 23592391 DOI: 10.1055/s-0032-1326398]
 - 20 **Modayil R**, Friedel D, Stavropoulos SN. Endoscopic suture repair of a large mucosal perforation during peroral endoscopic myotomy for treatment of achalasia. *Gastrointest Endosc* 2014; **80**: 1169-1170 [PMID: 24830579 DOI: 10.1016/j.gie.2014.03.035]
 - 21 **Khashab MA**, Stein E, Clarke JO, Saxena P, Kumbhari V, Chander Roland B, Kalloo AN, Stavropoulos S, Pasricha P, Inoue H. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2013; **78**: 764-768 [PMID: 24120337 DOI: 10.1016/j.gie.2013.07.019]
 - 22 **Ortega JA**, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980; **26**: 8-10 [PMID: 7358270 DOI: 10.1016/S0016-5107(80)73249-2]
 - 23 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382 DOI: 10.1055/s-2007-966764]
 - 24 **Sumiyama K**, Gostout CJ, Rajan E, Bakken TA, Knipschild MA, Marler RJ. Submucosal endoscopy with mucosal flap safety valve. *Gastrointest Endosc* 2007; **65**: 688-694 [PMID: 17324411 DOI: 10.1016/j.gie.2006.07.030]
 - 25 **Perretta S**, Dallemagne B, Donatelli G, Diemunsch P, Marescaux J. Transoral endoscopic esophageal myotomy based on esophageal function testing in a survival porcine model. *Gastrointest Endosc* 2011; **73**: 111-116 [PMID: 21092954 DOI: 10.1016/j.gie.2010.09.009]
 - 26 **Inoue H**, Tianle KM, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Minami H, Kudo SE. Peroral endoscopic myotomy for esophageal achalasia: technique, indication, and outcomes. *Thorac Surg Clin* 2011; **21**: 519-525 [PMID: 22040634 DOI: 10.1016/j.thorsurg.2011.08.005]
 - 27 **Inoue H**, Santi EG, Onimaru M, Kudo SE. Submucosal endoscopy: from ESD to POEM and beyond. *Gastrointest Endosc Clin N Am* 2014; **24**: 257-264 [PMID: 24679236 DOI: 10.1016/j.giec.2013.12.003]
 - 28 **Yang D**, Draganov PV. Peroral endoscopic myotomy (POEM) for achalasia after Roux-en-Y gastric bypass. *Endoscopy* 2014; **46** Suppl 1 UCTN: E11-E12 [PMID: 24446095 DOI: 10.1055/s-0033-1359140]
 - 29 **Maselli R**, Inoue H, Misawa M, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Suzuki K, Kudo S. Peroral endoscopic myotomy (POEM) in a 3-year-old girl with severe growth retardation, achalasia, and Down syndrome. *Endoscopy* 2012; **44** Suppl 2 UCTN: E285-E287 [PMID: 22933258 DOI: 10.1055/s-0032-1309924]
 - 30 **Familiari P**, Marchese M, Gigante G, Boskoski I, Tringali A, Perri V, Costamagna G. Peroral endoscopic myotomy for the treatment of achalasia in children. *J Pediatr Gastroenterol Nutr* 2013; **57**: 794-797 [PMID: 23941997 DOI: 10.1097/MPG.0b013e3182a803f7]
 - 31 **Chen WF**, Li QL, Zhou PH, Yao LQ, Xu MD, Zhang YQ, Zhong YS, Ma LL, Qin WZ, Hu JW, Cai MY, He MJ, Cui Z. Long-term outcomes of peroral endoscopic myotomy for achalasia in pediatric patients: a prospective, single-center study. *Gastrointest Endosc* 2015; **81**: 91-100 [PMID: 25088923 DOI: 10.1016/j.gie.2014.06.035]
 - 32 **Minami H**, Inoue H, Haji A, Isomoto H, Urabe S, Hashiguchi K, Matsushima K, Akazawa Y, Yamaguchi N, Ohnita K, Takeshima F, Nakao K. Per-oral endoscopic myotomy: emerging indications and evolving techniques. *Dig Endosc* 2015; **27**: 175-181 [PMID: 25040806 DOI: 10.1111/den.12328]
 - 33 **Cai MY**, Zhou PH, Yao LQ, Xu MD, Zhong YS, Li QL, Chen WF, Hu JW, Cui Z, Zhu BQ. Peroral endoscopic myotomy for idiopathic achalasia: randomized comparison of water-jet assisted versus conventional dissection technique. *Surg Endosc* 2014; **28**: 1158-1165 [PMID: 24232052 DOI: 10.1007/s00464-013-3300-1]
 - 34 **Friedel D**, Modayil R, Iqbal S, Grendell JH, Stavropoulos SN. Peroral endoscopic myotomy for achalasia: An American perspective. *World J Gastrointest Endosc* 2013; **5**: 420-427 [PMID: 24044040 DOI: 10.4253/wjge.v5.i9.420]
 - 35 **Khashab MA**, Messallam AA, Saxena P, Kumbhari V, Ricourt E, Aguila G, Roland BC, Stein E, Nandwani M, Inoue H, Clarke JO. Jet injection of dyed saline facilitates efficient peroral endoscopic myotomy. *Endoscopy* 2014; **46**: 298-301 [PMID: 24338241 DOI: 10.1055/s-0033-1359024]
 - 36 **von Renteln D**, Inoue H, Minami H, Werner YB, Pace A, Kersten JF, Much CC, Schachschal G, Mann O, Keller J, Fuchs KH, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: a prospective single center study. *Am J Gastroenterol* 2012; **107**: 411-417 [PMID: 22068665 DOI: 10.1038/ajg.2011.388]
 - 37 **Verlaan T**, Rohof WO, Bredenoord AJ, Eberl S, Rösch T, Fockens P. Effect of peroral endoscopic myotomy on esophagogastric junction physiology in patients with achalasia. *Gastrointest Endosc* 2013; **78**: 39-44 [PMID: 23453184 DOI: 10.1016/j.gie.2013.01.006]
 - 38 **Swanstrom LL**, Kurian A, Dunst CM, Sharata A, Bhayani N, Rieder E. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. *Ann Surg* 2012; **256**: 659-667 [PMID: 22982946 DOI: 10.1097/SLA.0b013e31826b5212]
 - 39 **Costamagna G**, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis* 2012; **44**: 827-832 [PMID: 22609465 DOI: 10.1016/j.dld.2012.04.003]
 - 40 **Friedel D**, Modayil R, Stavropoulos SN. Per-oral endoscopic myotomy: major advance in achalasia treatment and in endoscopic surgery. *World J Gastroenterol* 2014; **20**: 17746-17755 [PMID: 25548473 DOI: 10.3748/wjg.v20.i47.17746]
 - 41 **Li QL**, Chen WF, Zhou PH, Yao LQ, Xu MD, Hu JW, Cai MY, Zhang YQ, Qin WZ, Ren Z. Peroral endoscopic myotomy for the treatment of achalasia: a clinical comparative study of endoscopic full-thickness and circular muscle myotomy. *J Am Coll Surg* 2013; **217**: 442-451 [PMID: 23891074 DOI: 10.1016/j.jamcollsurg.2013.04.033]
 - 42 **Phalanusitthepha C**, Inoue H, Ikeda H, Sato H, Sato C, Hokierti C. Peroral endoscopic myotomy for esophageal achalasia. *Ann Transl Med* 2014; **2**: 31 [PMID: 25333007 DOI: 10.3978/j.issn.2305-5839.2014.02.04]
 - 43 **Pandolfino JE**, Roman S. High-resolution manometry: an atlas of esophageal motility disorders and findings of GERD using esophageal pressure topography. *Thorac Surg Clin* 2011; **21**: 465-475 [PMID: 22040629 DOI: 10.1016/j.thorsurg.2011.08.007]
 - 44 **Eleftheriadis N**, Inoue H, Ikeda H, Onimaru M, Yoshida A, Maselli R, Santi G, Kudo SE. In vivo observation of aberrant innermost longitudinal muscle bundles in front of the circular muscle layer at the level of the esophagogastric junction during peroral endoscopic myotomy. *Gastrointest Endosc* 2013; **78**: 676 [PMID: 23953234 DOI: 10.1016/j.gie.2013.07.018]
 - 45 **Ren Z**, Zhong Y, Zhou P, Xu M, Cai M, Li L, Shi Q, Yao L. Perioperative management and treatment for complications during

- and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA) (data from 119 cases). *Surg Endosc* 2012; **26**: 3267-3272 [PMID: 22609984 DOI: 10.1007/s00464-012-2336-y]
- 46 **Li H**, Linghu E, Wang X. Fibrin sealant for closure of mucosal penetration at the cardia during peroral endoscopic myotomy (POEM). *Endoscopy* 2012; **44** Suppl 2 UCTN: E215-E216 [PMID: 22622752 DOI: 10.1055/s-0032-1309358]
 - 47 **Rieder E**, Swanström LL, Perretta S, Lenglinger J, Riegler M, Dunst CM. Intraoperative assessment of esophagogastric junction distensibility during per oral endoscopic myotomy (POEM) for esophageal motility disorders. *Surg Endosc* 2013; **27**: 400-405 [PMID: 22955896 DOI: 10.1007/s00464-012-2484-0]
 - 48 **Familiari P**, Gigante G, Marchese M, Boskoski I, Bove V, Tringali A, Perri V, Onder G, Costamagna G. EndoFLIP system for the intraoperative evaluation of peroral endoscopic myotomy. *United European Gastroenterol J* 2014; **2**: 77-83 [PMID: 24918011 DOI: 10.1177/2050640614521193]
 - 49 **Teitelbaum EN**, Soper NJ, Pandolfino JE, Kahrilas PJ, Hirano I, Boris L, Nicodème F, Lin Z, Hungness ES. Esophagogastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. *Surg Endosc* 2015; **29**: 522-528 [PMID: 25055891 DOI: 10.1007/s00464-014-3733-1]
 - 50 **Li QL**, Zhou PH. Perspective on peroral endoscopic myotomy for achalasia: Zhongshan experience. *Gut Liver* 2015; **9**: 152-158 [PMID: 25721002 DOI: 10.5009/gnl14227]
 - 51 **Gockel I**, Timm S, Sgourakis GG, Musholt TJ, Rink AD, Lang H. Achalasia--if surgical treatment fails: analysis of remedial surgery. *J Gastrointest Surg* 2010; **14** Suppl 1: S46-S57 [PMID: 19856034 DOI: 10.1007/s11605-009-1018-0]
 - 52 **Wang L**, Li YM. Recurrent achalasia treated with Heller myotomy: a review of the literature. *World J Gastroenterol* 2008; **14**: 7122-7126 [PMID: 19084921 DOI: 10.3748/wjg.14.7122]
 - 53 **Hungness ES**, Teitelbaum EN, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, Soper NJ. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *J Gastrointest Surg* 2013; **17**: 228-235 [PMID: 23054897 DOI: 10.1007/s11605-012-2030-3]
 - 54 **Wei M**, Yang T, Yang X, Wang Z, Zhou Z. Peroral esophageal myotomy versus laparoscopic Heller's myotomy for achalasia: a meta-analysis. *J Laparoendosc Adv Surg Tech A* 2015; **25**: 123-129 [PMID: 25683071 DOI: 10.1089/lap.2014.0454]
 - 55 **Ujiki MB**, Yetasook AK, Zapf M, Linn JG, Carbray JM, Denham W. Peroral endoscopic myotomy: A short-term comparison with the standard laparoscopic approach. *Surgery* 2013; **154**: 893-897; discussion 897-900 [PMID: 24074429 DOI: 10.1016/j.surg.2013.04.042]
 - 56 **Teitelbaum EN**, Rajeswaran S, Zhang R, Sieberg RT, Miller FH, Soper NJ, Hungness ES. Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. *Surgery* 2013; **154**: 885-891; discussion 891-892 [PMID: 24074428 DOI: 10.1016/j.surg.2013.04.051]
 - 57 **Kumagai K**, Tsai JA, Thorell A, Lundell L, Håkanson B. Peroral endoscopic myotomy for achalasia. Are results comparable to laparoscopic Heller myotomy? *Scand J Gastroenterol* 2015; **50**: 505-512 [PMID: 25712228 DOI: 10.3109/00365521.2014.934915]
 - 58 **Patel K**, Abbassi-Ghadi N, Markar S, Kumar S, Jethwa P, Zaninotto G. Peroral endoscopic myotomy for the treatment of esophageal achalasia: systematic review and pooled analysis. *Dis Esophagus* 2015 [PMID: 26175119 DOI: 10.1111/dote.12387]
 - 59 **Wang X**, Tan Y, Zhang J, Liu D. Risk factors for gas-related complications of peroral endoscopic myotomy in achalasia. *Neth J Med* 2015; **73**: 76-81 [PMID: 25753072]
 - 60 **Von Renteln D**, Fuchs KH, Fockens P, Bauerfeind P, Vassiliou MC, Werner YB, Fried G, Breithaupt W, Heinrich H, Bredenoord AJ, Kersten JF, Verlaan T, Trevisan M, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology* 2013; **145**: 309-11.e1-3 [PMID: 23665071 DOI: 10.1053/j.gastro.2013.04.057]
 - 61 **Minami H**, Isomoto H, Yamaguchi N, Matsushima K, Akazawa Y, Ohnita K, Takeshima F, Inoue H, Nakao K. Peroral endoscopic myotomy for esophageal achalasia: clinical impact of 28 cases. *Dig Endosc* 2014; **26**: 43-51 [PMID: 23581563 DOI: 10.1111/den.12086]
 - 62 **Tamiya Y**, Nakahara K, Kominato K, Serikawa O, Watanabe Y, Tateishi H, Takedatsu H, Toyonaga A, Sata M. Pneumomediastinum is a frequent but minor complication during esophageal endoscopic submucosal dissection. *Endoscopy* 2010; **42**: 8-14 [PMID: 19899032 DOI: 10.1055/s-0029-1215215]
 - 63 **Ross SW**, Oommen B, Wormer BA, Walters AL, Matthews BD, Heniford BT, Augenstein VA. National outcomes of laparoscopic Heller myotomy: operative complications and risk factors for adverse events. *Surg Endosc* 2015; **29**: 3097-3105 [PMID: 25588362 DOI: 10.1007/s00464-014-4054-0]
 - 64 **Chiu PW**, Wu JC, Teoh AY, Chan Y, Wong SK, Liu SY, Yung MY, Lam CC, Sung JJ, Chan FK, Lau JY, Ng EK. Peroral endoscopic myotomy for treatment of achalasia: from bench to bedside (with video). *Gastrointest Endosc* 2013; **77**: 29-38 [PMID: 23043852 DOI: 10.1016/j.gie.2012.08.018]
 - 65 **Swanström LL**, Rieder E, Dunst CM. A stepwise approach and early clinical experience in peroral endoscopic myotomy for the treatment of achalasia and esophageal motility disorders. *J Am Coll Surg* 2011; **213**: 751-756 [PMID: 21996484 DOI: 10.1016/j.jamcollsurg.2011.09.001]
 - 66 **Inoue H**, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Minami H, Kudo SE. [Per-oral endoscopic myotomy (POEM) for esophageal achalasia]. *Nihon Shokakibyo Gakkai Zasshi* 2012; **109**: 728-731 [PMID: 22688097]
 - 67 **Ren Y**, Tang X, Zhi F, Liu S, Wu J, Peng Y, Jiang B, Gong W. A stepwise approach for peroral endoscopic myotomy for treating achalasia: from animal models to patients. *Scand J Gastroenterol* 2015; **50**: 952-958 [PMID: 25861971 DOI: 10.3109/00365521.2014.983152]
 - 68 **Eleftheriadis N**, Inoue H, Ikeda H, Onimaru M, Yoshida A, Hosoya T, Maselli R, Kudo SE. Training in peroral endoscopic myotomy (POEM) for esophageal achalasia. *Ther Clin Risk Manag* 2012; **8**: 329-342 [PMID: 22888256 DOI: 10.2147/TCRM.S32666]
 - 69 **Perretta S**, Dallemagne B, Marescaux J. STEPS to POEM: introduction of a new technique at the IRCAD. *Surg Innov* 2012; **19**: 216-220 [PMID: 22977085 DOI: 10.1177/1553350612458857]
 - 70 **Mikaeli J**, Islami F, Malekzadeh R. Achalasia: a review of Western and Iranian experiences. *World J Gastroenterol* 2009; **15**: 5000-5009 [PMID: 19859991 DOI: 10.3748/wjg.15.5000]
 - 71 **Stavropoulos SN**, Desilets DJ, Fuchs KH, Gostout CJ, Haber G, Inoue H, Kochman ML, Modayil R, Savides T, Scott DJ, Swanstrom LL, Vassiliou MC. Per-oral endoscopic myotomy white paper summary. *Gastrointest Endosc* 2014; **80**: 1-15 [PMID: 24950639 DOI: 10.1016/j.gie.2014.04.014]
 - 72 **Teitelbaum EN**, Soper NJ, Arafat FO, Santos BF, Kahrilas PJ, Pandolfino JE, Hungness ES. Analysis of a learning curve and predictors of intraoperative difficulty for peroral esophageal myotomy (POEM). *J Gastrointest Surg* 2014; **18**: 92-98; discussion 98-99 [PMID: 24002767 DOI: 10.1007/s11605-013-2332-0]
 - 73 **Kumta NA**, Mehta S, Kedia P, Weaver K, Sharaiha RZ, Fukami N, Minami H, Casas F, Gaidhane M, Lambroza A, Kahaleh M. Peroral endoscopic myotomy: establishing a new program. *Clin Endosc* 2014; **47**: 389-397 [PMID: 25324996 DOI: 10.5946/ce.2014.47.5.389]
 - 74 **Kurian AA**, Dunst CM, Sharata A, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic esophageal myotomy: defining the learning curve. *Gastrointest Endosc* 2013; **77**: 719-725 [PMID: 23394838 DOI: 10.1016/j.gie.2012.12.006]
 - 75 **Schmidt A**, Bauder M, Riecken B, Caca K. Endoscopic resection of subepithelial tumors. *World J Gastrointest Endosc* 2014; **6**: 592-599 [PMID: 25512768 DOI: 10.4253/wjge.v6.i12.592]
 - 76 **Schlag C**, Wilhelm D, von Delius S, Feussner H, Meining A. EndoResect study: endoscopic full-thickness resection of gastric subepithelial tumors. *Endoscopy* 2013; **45**: 4-11 [PMID: 23254401 DOI: 10.1055/s-0032-1325760]
 - 77 **Wang L**, Fan CQ, Ren W, Zhang X, Li YH, Zhao XY. Endoscopic

- dissection of large endogenous myogenic tumors in the esophagus and stomach is safe and feasible: a report of 42 cases. *Scand J Gastroenterol* 2011; **46**: 627-633 [PMID: 21366494 DOI: 10.3109/00365521.2011.561364]
- 78 **Kent M**, d'Amato T, Nordman C, Schuchert M, Landreneau R, Alvelo-Rivera M, Luketich J. Minimally invasive resection of benign esophageal tumors. *J Thorac Cardiovasc Surg* 2007; **134**: 176-181 [PMID: 17599505 DOI: 10.1016/j.jtcvs.2006.10.082]
- 79 **Kim GH**. Endoscopic resection of subepithelial tumors. *Clin Endosc* 2012; **45**: 240-244 [PMID: 22977810 DOI: 10.5946/ce.2012.45.3.240]
- 80 **Li QL**, Yao LQ, Zhou PH, Xu MD, Chen SY, Zhong YS, Zhang YQ, Chen WF, Ma LL, Qin WZ. Submucosal tumors of the esophagogastric junction originating from the muscularis propria layer: a large study of endoscopic submucosal dissection (with video). *Gastrointest Endosc* 2012; **75**: 1153-1158 [PMID: 22459663 DOI: 10.1016/j.gie.2012.01.037]
- 81 **Lee CK**, Chung IK, Lee SH, Lee SH, Lee TH, Park SH, Kim HS, Kim SJ, Cho HD. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). *Gastrointest Endosc* 2010; **71**: 188-194 [PMID: 19879567 DOI: 10.1016/j.gie.2009.07.029]
- 82 **Wang XY**, Xu MD, Yao LQ, Zhou PH, Pleskow D, Li QL, Zhang YQ, Chen WF, Zhong YS. Submucosal tunneling endoscopic resection for submucosal tumors of the esophagogastric junction originating from the muscularis propria layer: a feasibility study (with videos). *Surg Endosc* 2014; **28**: 1971-1977 [PMID: 24515260 DOI: 10.1007/s00464-014-3420-2]
- 83 **Ye LP**, Zhang Y, Mao XL, Zhu LH, Zhou X, Chen JY. Submucosal tunneling endoscopic resection for small upper gastrointestinal subepithelial tumors originating from the muscularis propria layer. *Surg Endosc* 2014; **28**: 524-530 [PMID: 24013472 DOI: 10.1007/s00464-013-3197-8]
- 84 **Lee SH**, Kim SJ, Lee TH, Chung IK, Park SH, Kim EO, Lee HJ, Cho HD. Human applications of submucosal endoscopy under conscious sedation for pure natural orifice transluminal endoscopic surgery. *Surg Endosc* 2013; **27**: 3016-3020 [PMID: 23397506 DOI: 10.1007/s00464-013-2844-4]
- 85 **Stavropoulos SN**, Harris MD, Hida S, Brathwaite C, Demetriou C, Grendell J. Endoscopic submucosal myotomy for the treatment of achalasia (with video). *Gastrointest Endosc* 2010; **72**: 1309-1311 [PMID: 21111876 DOI: 10.1016/j.gie.2010.04.016]

P- Reviewer: Buanes TA, Kopacova M, Negreanu L

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Lu YJ



Endoscopic ultrasound-guided interventions in special situations

Varayu Prachayakul, Pitulak Aswakul

Varayu Prachayakul, Siriraj Gastrointestinal Endoscopy Center, Division of Gastroenterology, Department of Internal Medicine, Siriraj Hospital, Faculty of Medicine, Mahidol University, Bangkok 10700, Thailand

Pitulak Aswakul, Liver and Digestive Institute, Samitivej Sukhumvit Hospital, Bangkok 10120, Thailand

Author contributions: Prachayakul V conceived of and designed the article; Prachayakul V and Aswakul P reviewed the literature and drafted, revised, and approved the final version of the article to be published.

Conflict-of-interest statement: Both authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Varayu Prachayakul, MD, Associate Professor, Siriraj Gastrointestinal Endoscopy Center, Division of Gastroenterology, Department of Internal Medicine, Siriraj Hospital, Faculty of Medicine, Mahidol University, 2 Prannok Road, Bangkok 10700, Thailand. kaiyjr@gmail.com
Telephone: +66-81-8654646
Fax: +66-2-4115013

Received: May 24, 2015
Peer-review started: May 25, 2015
First decision: August 16, 2015
Revised: September 7, 2015
Accepted: December 1, 2015
Article in press: December 2, 2015
Published online: January 25, 2016

Abstract

Endoscopic ultrasound (EUS) was introduced in 1982

and has since become a popular advanced procedure for diagnosis and therapeutic intervention. Initially, EUS was most commonly used for the diagnosis of pancreatobiliary diseases and tissue acquisition. EUS was first used for guided cholangiography in 1996, followed by EUS-guided biliary drainage in 2001. Advancements in equipment and endoscopic accessories have led to an expansion of EUS-guided procedures, which now include EUS-guided drainage of intra-abdominal abscesses or collections, intra-vascular treatment of refractory variceal and nonvariceal bleeding, transmural pancreatic drainage, common bile duct stone clearance, enteral feeding tube placement and entero-enteric anastomosis. Patients with surgically altered upper gastrointestinal anatomies have greatly benefited from EUS also. This systematic review describes and discusses EUS procedures performed in uncommon diseases and conditions, as well as applications on more vulnerable patients such as young children and pregnant women. In these cases, routine approaches do not always apply, and thus may require the use of innovative and unconventional techniques. Increased knowledge of such special applications will help increase the success rates of these procedures and provide a foundation for additional advances and utilizations of the technique.

Key words: Children; Endoscopic ultrasonography; Intra-abdominal abscesses; Pregnancy; Special situation; Surgically altered anatomy; Therapeutic; Uncommon

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This article reviews the clinical applications of endoscopic ultrasound-guided interventions reported to date, including drainage of intra-abdominal collections, gallbladder and pancreas. Procedures used in pregnant women and children are also described. The aim of this review was to promote knowledge of special clinical applications in which endoscopic ultrasound is applicable.

Prachayakul V, Aswakul P. Endoscopic ultrasound-guided interventions in special situations. *World J Gastrointest Endosc*

2016; 8(2): 104-112 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/104.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.104>

INTRODUCTION

Human endoscopic ultrasound (EUS), first described in 1982 by Dimagno *et al*^[1], has become a popular procedure for diagnosis and therapeutic intervention. Since the first report on EUS-guided cholangiography, advances in equipment and the development of endoscopic accessories have led to a substantial growth in the number and types of EUS-guided therapies^[2]. These techniques allow for real-time visualization of structures beyond the endoscopic view, thus increasing the success rate and minimizing complications associated with the procedures. As a result, EUS has also been applied to uncommon or special clinical scenarios recently, such as intra-abdominal abscesses or collections, refractory variceal and non-variceal bleeding, and transmural pancreatic drainage. Furthermore, pregnant women and children have greatly benefited from EUS applications. The aim of this review was to identify and highlight these additional uses for EUS. The PubMed database was searched for human studies written in the English language and published between 1990 and March 2015. The following keywords were used either alone or in combination with EUS: Children, pregnancy, pancreatic drainage, surgically altered anatomy, refractory bleeding and angio-therapeutic interventions, tumor ablation, tumor injection, anti-tumoral therapy, and common bile duct (CBD) stone. The references in the identified articles were also searched for potentially relevant studies. The initial search identified 196 articles, of which 89 full-text articles were considered to be related to this topic and were chosen for review and analysis.

COMMON EUS-GUIDED INTERVENTIONS

Currently, the most common EUS applications are for diagnosing pancreatobiliary disease and tissue acquisition. EUS provides a precise evaluation of the pancreas, peripancreatic organs, CBD and gallbladder. Soon after its original use for pancreatic pseudocyst drainage, EUS was utilized for biliary drainage in cases where endoscopic retrograde cholangiopancreatography (ERCP) had failed. In fact, EUS produced superior outcomes in patients with post-surgical altered anatomy, according to both technical and clinical success rates compared to enteroscopic-based ERCP-related procedures (89%-100% vs 50%-95%, respectively)^[3-11]. The complication rates in the EUS-guided procedure, such as procedures with a transpapillary approach, using transgastric or transduodenal routes for EUS-guided rendezvous, or a transmural approach in EUS-guided hepaticogastrostomy or choledochoduodenostomy, were in an acceptable range (25%-35%)^[5-11]. However, despite their relative success and routine performance,

the feasibility and possibility of complications should always be considered when performing these advanced procedures^[12,13]. EUS-guided pancreatic pseudocyst drainage is commonly accepted in the treatment of fluid collection due to acute pancreatitis; however, this particular application will not be reviewed in the present article.

SPECIAL EUS-GUIDED INTERVENTIONS

EUS-guided interventions have also been utilized when dealing with uncommon diseases or conditions. More susceptible patients, such as young children and critically ill or pregnant patients, have greatly benefited from EUS-guided procedures. Since these groups of patients usually require alternative approaches, each application will be reviewed and described in detail.

EUS-guided pancreatic drainage

EUS-guided pancreatic duct drainage is one of the most difficult and advanced endosonography-based interventions. This procedure is associated with relatively high complication rates, up to 43%^[14-20], and thus should be carried out only by dedicated and highly skilled endoscopists with extensive experience in therapeutic ERCP and EUS procedures. Although similar to EUS-guided biliary drainage, EUS-guided pancreatic drainage is limited to patients in whom ERCP has failed, such as those with symptomatic chronic pancreatitis and pancreatic duct obstruction (due to stone or stricture).

EUS-guided pancreatic duct drainage can be performed in two ways: EUS-guided rendezvous of the pancreatic duct and EUS-guided pancreaticogastrostomy. For EUS-guided rendezvous of the main pancreatic duct, the approach involves puncture from a gastric site and guidewire manipulation until it is passed down to the ampulla, followed by guidewire grasping and scope exchange. For EUS-guided pancreaticogastrostomy, the main pancreatic duct is punctured using a transgastric approach, which is followed by neo-tract creation-dilation and stent insertion from the pancreatic duct through the gastric cavity. The success of both of these procedures is due in part to improvements in the techniques and use of the proper instruments (dilating catheters, dilating balloons, or cauterizing devices for pancreatogastric tract creation). The case series and case reports^[21-26] involving EUS-guided pancreatic duct drainage are shown in Table 1.

EUS-guided biliary interventions due to surgically altered anatomy

ERCP with overtube-assisted enteroscopy has a success rate average of 75% with 3%-5% complication rates, while percutaneous biliary drainage, with similar success rate, has 0.5%-15% complication rates, including 0%-4.9% mortality^[27,28]. Currently, EUS-guided biliary drainage is a preferred alternative treatment option when the patient with surgically altered anatomy prefers internal drainage. Approximately one-third of the patients

Table 1 Clinical details of case series on endoscopic ultrasound-guided pancreatic duct drainage

Ref.	Technical success	Clinical success	Complications
Shah <i>et al</i> ^[21] (n = 25)	Pancreatography, 100% Pancreatic rendezvous, 50% Pancreatic duct intervention, 71%	N/A	10.5% (pneumoperitoneum, severe pancreatitis)
Ergun <i>et al</i> ^[22] (n = 20)	Pancreaticogastrostomy, 79% Rendezvous, 100%	Long-term, 72% Mean FU time = 7 mo FU range: 3 mo to 120 mo	10% (bleeding, peripancreatic collection) Long-term: Stent dysfunction 50% (plastic stents in all cases)
Will <i>et al</i> ^[23] (n = 12)	Pancreaticogastrostomy and rendezvous, 69%	73.2% FU range: 1 mo to 72 mo	42.9% (bleeding, perforation, pain)
Tessier <i>et al</i> ^[24] (n = 36)	Pancreaticogastrostomy and pancreaticobulbostomy, 92%	69.4% Mean FU time = 14.5 mo FU range: 4 mo to 55 mo	13.2% (fluid collection, hematoma)
Fujii <i>et al</i> ^[25] (n = 43)	Pancreaticogastrostomy, (antegrade: 18, retrograde: 14) overall: 74%	83% Mean FU time = 23 mo	Major: 6% (bleeding, perforation), overall: 24%
Barkay <i>et al</i> ^[26] (n = 21)	Pancreatography, 86% Pancreatic duct drainage, 48%	70% Mean FU time = 1 yr	2% (peri-pancreatic abscess, guidewire shearing)

N/A: Data not available; FU: Follow-up.

who undergo EUS-guided pancreatic duct drainage and one-fifth who undergo EUS-guided biliary drainage have surgically altered anatomies. This is typically due to a preceding Whipple's operation (pancreaticoduodenectomy-choledochojejunostomy and pancreatojejunostomy), post-gastrectomy, or other internal bypass surgeries. Prior to the advent of EUS procedures, the only treatment options for these patients were percutaneous drainage or repeat surgical operations. Advancements in EUS techniques provided alternatives, including EUS-guided rendezvous followed by ERCP or enteroscopy-assisted ERCP, EUS-guided transmural drainage procedures (hepaticogastrostomy, choledochoduodenostomy, or pancreaticogastrostomy), and EUS-guided antegrade stent insertion. The techniques for these EUS-guided interventions are the same as the ones used for conventional (non-altered anatomy) cases, with technical and clinical success rates of 85%-100% and acceptable complications^[28]. The EUS-guided biliary drainage is performed as follows: the punctured site is first localized (intra or extra-hepatic bile duct), followed by a neo-tract creation (either by cauterization or non-cauterization methods), neo-tract dilation (either by graded dilation or balloon dilatation techniques) and finally a stent placement (either plastic or metallic stents)^[5,6,28,29]. Details of the case series and case reports involving EUS-guided interventions in patients with surgically altered upper gastrointestinal anatomy are shown in Table 2.

EUS-guided CBD stone clearance

The conventional CBD stone removal fails in 5%-10% of cases^[30,31], half of which require other treatments such as intraductal therapy (laser lithotripsy or electrohydraulic lithotripsy)^[32,33]. Patients with a surgically altered anatomy are at an increased risk for clearance failure. Itoi *et al*^[29] reported a case series of 5 patients with surgically altered upper gastrointestinal anatomy who underwent EUS-guided transhepatic antegrade CBD stone removal. The success rate of complete CBD stone clearance in one

session was 60%. The group used transgastric (3 cases) or transjejunum (2 cases) puncture of the CBD with a 19- or 22-gauge needle and a contrast study to evaluate the CBD stones. Next, a guidewire was introduced, traversing the ampulla down to the duodenum, and the papilla was dilated in an antegrade fashion *via* inflation of a balloon catheter to push the stones down until they passed the ampulla. In cases of incomplete CBD stone clearance, a stent was inserted.

A randomized controlled trial showed an equivalent success rate of EUS-guided CBD stone removal compared to standard ERCP for the treatment of small (< 10 mm) CBD stones^[34]. The success rate was calculated based on the CBD clearance rate, procedure time, and complications. In the trial, CBD cannulation was performed only under EUS guidance to demonstrate the feasibility of EUS-only CBD stone removal. Hence, the need for fluoroscopy was eliminated, providing a feasible alternative for treatment of pregnant patients or in bedside procedures performed in the intensive care unit.

EUS-guided enteral feeding tube placement and enteric anastomosis

EUS guidance can be utilized for placement of enteral feeding tubes, such as in the case of gastrostomy or internal anastomosis. Khashab *et al*^[35] described a case report involving EUS-guided gastroenterostomy. For this technique, the desired duodenal or jejunal loop closest to the EUS curvilinear echoscope was identified, and the lumen was punctured to allow passage of a 0.035-inch guidewire. The sphincterotome was inserted over the guidewire for infusion of water (< 500 mL to avoid metabolic derangement), and the gastroenteric tract was dilated in preparation for placement of the anastomotic stent. There is a risk of leakage with this technique due to the mobility of the small bowel, particularly the jejunum. A recent report by Ikeuchi *et al*^[36] described an endoscopic treatment in a patient with afferent loop syndrome who underwent surgical bypass. The neo-gastrojejunal

Table 2 Clinical details of case series on endoscopic ultrasound-guided biliary drainage due to surgically altered anatomy

Ref.	Etiology	Procedure (technical success rate, %)	Complications
Iwashita <i>et al</i> ^[28] (<i>n</i> = 7)	Stone (<i>n</i> = 5) Stricture (<i>n</i> = 1) Malignant (<i>n</i> = 1)	Stone removal, 100% Dilation, 100% Stent placement, 100% (SEMS)	Minor: 28%
Itoi <i>et al</i> ^[29] (<i>n</i> = 14)	Stone (<i>n</i> = 14)	Single session clearance, 60% Overall clearance, 71.4%	None

SEMS: Self-expandable metallic stent.

tract was created using a curvilinear echoscope, and a 19-gauge needle passed from the stomach into the bowel lumen. After guidewire insertion, the two lumens were stabilized, and a lumen-apposing metal stent was inserted and deployed. This neo-type of lumen secures the tract and prevents leakage, the most common problem encountered with this type of procedure. Recently, Itoi *et al*^[37] reported a case series of EUS-guided gastrojejunostomy using a special gastrojejunal tube with balloon fixation technique. This specific instrument was developed to stabilize the jejunal lumen allowing for easier creation of a neo-gastrojejunal tract while minimizing the occurrence of complications, especially of leakage or perforation. Firstly, the gastroscope with overtube was inserted into the strictured region, followed by placement of a guidewire *via* the strictured region to the jejunum. After the scope was removed, a special gastrojejunal tube with balloon fixation was inserted over the guidewire down to the jejunum (in the same fashion as a naso-jejunal tube placement). Secondly, the two balloons were inflated separately using contrast media followed by water infusion through the catheter (the opening of the water channel was located between these two balloons) to form a fixed jejunal segment-like tubular structure that was easy to find with an echoscope. Therefore, this particular jejunal segment was fully dilated and very close to the gastric wall. Then, EUS was performed to locate the puncture site, which appeared on the endosonographer as a sausage-like hypoechoic structure very close to the gastric wall. A 19-gauge needle was used to puncture into that segment and a guidewire was inserted and looped. Finally, a single-step lumen-apposing stent with cautery enable-access catheter unit (Hot AXIOS stent; Xlumen Inc., Mountain View, CA, United States) was inserted over the guidewire and deployed. EUS-guided gastrojejunostomy performed by Itoi *et al*^[37] appears to be safer than two other techniques mentioned previously. The new incoming type of lumen-apposing stent is currently being developed, aiming at the possibility of greater ease of deployment compared to the previous model^[38].

EUS-guided intra-abdominal abscess and collection drainage

EUS-guided drainage of an intra-abdominal abscess was first reported by Giovannini *et al*^[39] in 2001. EUS-guided procedures have also been reported in the drainage of pelvic and hepatic abscesses (tuberculous,

pyogenic/ruptured, and concealed), as well as for prostatic, mediastinum, sub-phrenic and retroperitoneal abscesses^[40-50]. These procedures use the curvilinear echoscope to locate the abscess and verify that it is well formed. After ensuring that there are no intervening blood vessels, the abscess is punctured and contents aspirated with a 19-gauge needle. Next, a guidewire is inserted into the abscess and a contrast agent is injected to allow for visualization. Then, a small-caliber sphincterotome or catheter is inserted to flush the abscess cavity with saline (50 mL). The tract is then gradually dilated using either a graded dilation technique or a balloon dilation to allow for insertion of a 7 Fr, 8.5 Fr or 10 Fr straight stent, or a single/double pigtail stent with or without nasal-abscess drainage catheter for routine flushing of saline to enhance the drainage. Follow-up studies are still needed to verify resolution of the abscesses. The size of abscesses involved varied from 4 cm to 12 cm in diameter, and the time for resolution of these abscess ranged from 3 mo to 10 mo. Details on the case series involving EUS-guided intra-abdominal abscess drainage are shown in Table 3.

EUS-guided arteriovenous interventions

In 2000, Lee *et al*^[51] was first to report EUS-guided injection of cyanoacrylate for stoppage of gastric variceal bleeding. In 2008, Levy *et al*^[52] combined the glue injection with microcoil embolization to treat refractory gastric variceal bleeding. Since then, there have been additional reports demonstrating success of this procedure, with variceal and non-variceal re-bleeding rates of < 10% in most cases^[53-58]. A similar clinical outcome was reported by Kinzel *et al*^[59] for a 31-year-old man with duodenal variceal bleeding.

Kuramochi *et al*^[60] used EUS to demonstrate the increased risk of recurrence of esophageal varices in high-risk patients who exhibited anterior branch dominance and flow velocity of 12 cm/s. EUS was found to be a very sensitive tool for early detection of heightened portal pressure, observed as dilation of the collateral circulation and small gastroesophageal varices, which are often missed *via* endoscopic evaluation^[61]. EUS has been shown to improve the detection and diagnosis of gastroesophageal varices and collateral veins. Furthermore, EUS can be used as an endoscopic therapy of gastroesophageal varices, such as EUS-guided sclerotherapy of esophageal collateral vessels and EUS-

Table 3 Case series on endoscopic ultrasound-guided abscess drainage

Ref.	Location of abscesses/size	Route of drainage	Complete resolution/complications
Mandai <i>et al</i> ^[40] (<i>n</i> = 4)	Post-operative abscess/4.5 cm to 7.0 cm	TG	100%/none
Hadithi <i>et al</i> ^[41] (<i>n</i> = 8)	Perirectal (<i>n</i> = 6), Perisigmoid (<i>n</i> = 2)/4.0 cm to 9.0 cm	TR	100%/none
Puri <i>et al</i> ^[42] (<i>n</i> = 30)	Periprostic (<i>n</i> = 4) Perirectal (<i>n</i> = 19) Perisigmoid (<i>n</i> = 7)/2.5 cm to 5.4 cm	TR/TS	93.4%/none Re-intervention 16.5%
Varadarajulu <i>et al</i> ^[43] (<i>n</i> = 25)	Perirectal (<i>n</i> = 19), Perisigmoid (<i>n</i> = 6)/5.0 cm to 6.9 cm	TR/TS	96%/none Re-intervention 3%
Wehrmann <i>et al</i> ^[44] (<i>n</i> = 20)	Para-esophageal (<i>n</i> = 15)/> 2 cm	TE	95%/mortality 7%

N/A: Data not available; TG: Transgastric route; TR: Transrectal route; TS: Transsigmoid route; TE: Transesophageal route.

Table 4 Case series on endoscopic ultrasound-guided interventions in gastrointestinal oncology

Ref.	Diseases	Therapeutic interventions	Clinical response rate	Complications
Pai <i>et al</i> ^[70] (<i>n</i> = 8)	Pancreatic cyst (<i>n</i> = 6) Pancreatic NET (<i>n</i> = 2)	RFA	100% Complete, 20%	20% (pain)
Park do <i>et al</i> ^[71] (<i>n</i> = 11)	Pancreatic NET (<i>n</i> = 11)	Alcohol injection volume: 0.5 mL to 7.0 mL Mass size: 9 mm to 19 mm	61.50% Single session, 53.3%	36.30% (pancreatitis, pain)
DeWitt <i>et al</i> ^[72] (<i>n</i> = 22)	Pancreatic cyst (<i>n</i> = 22)	Alcohol + Paclitaxel Cyst size: 15 mm to 43 mm	Complete, 50% No response, 25%	13% (pancreatitis, peritonitis)
Oh <i>et al</i> ^[73] (<i>n</i> = 14)	Pancreatic cyst (<i>n</i> = 14)	Alcohol + Paclitaxel Mass size: 17 mm to 52 mm	Complete, 78% No response, 7%	7% (pancreatitis)
Wang <i>et al</i> ^[74] (<i>n</i> = 23)	Pancreatic cancer (<i>n</i> = 23)	I ¹²⁵ seed	Partial pain control at 12 wk, 77.8%	12.50% (constipation, nausea/vomiting)

RFA: Radio frequency ablation; NET: Neuroendocrine tumor.

guided cyanoacrylate (glue) injection of gastric varices. EUS can also provide knowledge on the efficacy of pharmacotherapy of portal hypertension. Furthermore, EUS can provide assessment and prediction of variceal recurrence after endoscopic therapy and assessment of portal hemodynamics, such as the E-Flow Doppler ultrasound study of the azygous and portal veins. Additionally, Giday *et al*^[62,63] demonstrated the feasibility of portal vein puncture for measuring pressure and injection of contrast agents without inducing liver injury in an animal model. This was followed by a case report by Buscaglia *et al*^[64] describing EUS-guided insertion of an intrahepatic portosystemic shunt. Matthes *et al*^[65] demonstrated the feasibility of EUS-guided portal vein embolization using Enteryx, a swine model. However, there is no report in the literature of these invasive portal vein interventions being applied in a clinical setting as of yet.

EUS-guided interventions in gastrointestinal oncology

Patients with pancreatobiliary malignancy who were not surgical candidates benefited from EUS-guided interventions for local control and treatment of tumors. Many treatment applications have been used in these cases, including ablative therapy (by absolute alcohol

injection), thermal ablative therapy using radio frequency ablation, or cold therapy by the cryo-based probe, or a combination of the techniques. In all these techniques, the catheter was introduced through the echoscope channel, localizing the treatment location under EUS guidance^[66,67]. Intra-tumoral injections of cell products such as tumoral dendritic cells, TNFerade or brachytherapy using I¹²⁵ have also been reported^[68,69]. However, the clinical outcomes of these therapeutic platforms were not impressive. Although newer treatment modalities, such as new cell types and new chemical situations, are being developed, there is yet too little information available for a reasonable discussion in this review. The large case series on local tumor treatments are shown in Table 4^[70-74].

EUS in pregnancy

The incidence of pancreatobiliary disease, including choledocholithiasis, in pregnant women, is estimated to be 2%-6%^[75]. However, ERCP, the conventional method for CBD clearance, is not appropriate for these patients due to risks associated with fluoroscopy. Thus, EUS-guided CBD stone removal with or without intraductal visualization *via* spyglass or cholangioscopy represents a suitable alternative. With this method, CBD diagnosis

can be confirmed *via* radial EUS, followed by intraductal evaluation or CBD cannulation *via* duodenoscopy^[76-78]. The position of the CBD stone can be confirmed through detection of aspirated bile content allowing for a complete stone removal and/or a stent placement to avoid recurrence.

EUS in children

EUS-guided interventions are equally feasible in pediatric patients. However, compared to adults, the child's organs and ducts are smaller, requiring extra care by the endoscopists who perform the procedures. The first EUS-guided intervention in a pediatric patient was reported in 1993, and it used a fine-needle aspiration (FNA)^[79]. Since then, additional advanced procedures have been performed in pediatric patients^[80,81]. In 2009, Attila *et al.*^[82] reported a case series of EUS procedures performed in 38 children. Of these, 30% of the cases used EUS with FNA, which established the correct diagnosis in 75% of the patients who underwent FNA without any complication. Recently, Scheers *et al.*^[83] also reported a case series of EUS procedures in 48 children. In this case series, 13 therapeutic EUS procedures, including 9 combined EUS-ERCP procedures, were performed without adverse events. The authors also proposed that the adult endoscopes and accessories can be used safely in children > 3 years of age (or > 15 kg body weight) and that a single endoscopic treatment session is feasible in children.

CONCLUSION

EUS-guided interventions can be used to treat various conditions, with favorable outcomes in most cases. In addition to pancreatic and biliary draining procedures, EUS guidance has been utilized in CBD stone clearance, enteral feeding tube placement, enteric anastomosis, and intra-abdominal abscess drainage. Such techniques are particularly well suited for patients with altered anatomy, pregnant women, or children. Increased knowledge of such special applications will help increase the success rates of these procedures and provide a foundation for additional advances and utilizations of EUS.

REFERENCES

- 1 Dimagno EP, Regan PT, Clain JE, James EM, Buxton JL. Human endoscopic ultrasonography. *Gastroenterology* 1982; **83**: 824-829 [PMID: 7106513]
- 2 Wiersema MJ, Sandusky D, Carr R, Wiersema LM, Erdel WC, Frederick PK. Endosonography-guided cholangiopancreatography. *Gastrointest Endosc* 1996; **43**: 102-106 [PMID: 8635700 DOI: 10.1016/S0016-5107(06)80108-2]
- 3 Itokawa F, Itoi T, Ishii K, Sofuni A, Moriyasu F. Single- and double-balloon enteroscopy-assisted endoscopic retrograde cholangiopancreatography in patients with Roux-en-Y plus hepaticojejunostomy anastomosis and Whipple resection. *Dig Endosc* 2014; **26** Suppl 2: 136-143 [PMID: 24750164 DOI: 10.1111/den.12254]
- 4 Skinner M, Popa D, Neumann H, Wilcox CM, Mönkemüller K. ERCP with the overtube-assisted enteroscopy technique: a systematic review. *Endoscopy* 2014; **46**: 560-572 [PMID: 24839188 DOI: 10.1055/s-0034-1365698]
- 5 Prichard D, Byrne MF. Endoscopic ultrasound guided biliary and pancreatic duct interventions. *World J Gastrointest Endosc* 2014; **6**: 513-524 [PMID: 25400865 DOI: 10.4253/wjge.v6.i11.513]
- 6 Fabbri C, Luigiano C, Lisotti A, Cennamo V, Virgilio C, Caletti G, Fusaroli P. Endoscopic ultrasound-guided treatments: are we getting evidence based—a systematic review. *World J Gastroenterol* 2014; **20**: 8424-8448 [PMID: 25024600 DOI: 10.3748/wjg.v20.i26.8424]
- 7 Iwashita T, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. *Clin J Gastroenterol* 2014; **7**: 94-102 [PMID: 24765215]
- 8 Kedia P, Gaidhane M, Kahaleh M. Endoscopic guided biliary drainage: how can we achieve efficient biliary drainage? *Clin Endosc* 2013; **46**: 543-551 [PMID: 24143319 DOI: 10.5946/ce.2013.46.5.543]
- 9 Kawakubo K, Isayama H, Kato H, Itoi T, Kawakami H, Hanada K, Ishiwatari H, Yasuda I, Kawamoto H, Itokawa F, Kuwatani M, Iiboshi T, Hayashi T, Doi S, Nakai Y. Multicenter retrospective study of endoscopic ultrasound-guided biliary drainage for malignant biliary obstruction in Japan. *J Hepatobiliary Pancreat Sci* 2014; **21**: 328-334 [PMID: 24026963 DOI: 10.1002/jhbp.27]
- 10 Itoi T, Itokawa F, Tsuchiya T, Tsuji S, Tonozuka R. Endoscopic ultrasound-guided choledochostomy as an alternative extrahepatic bile duct drainage method in pancreatic cancer with duodenal invasion. *Dig Endosc* 2013; **25** Suppl 2: 142-145 [PMID: 23617666 DOI: 10.1111/den.12065]
- 11 Gupta K, Perez-Miranda M, Kahaleh M, Artifon EL, Itoi T, Freeman ML, de-Serna C, Sauer B, Giovannini M. Endoscopic ultrasound-assisted bile duct access and drainage: multicenter, long-term analysis of approach, outcomes, and complications of a technique in evolution. *J Clin Gastroenterol* 2014; **48**: 80-87 [PMID: 23632351 DOI: 10.1097/MCG.0b013e31828c6822]
- 12 Varadarajulu S, Hawes RH. EUS-guided biliary drainage: taxing and not ready. *Gastrointest Endosc* 2013; **78**: 742-743 [PMID: 24120336 DOI: 10.1016/j.gie.2013.06.009]
- 13 Kahaleh M. Training the next generation of advanced endoscopists in EUS-guided biliary and pancreatic drainage: learning from master endoscopists. *Gastrointest Endosc* 2013; **78**: 638-641 [PMID: 24054742 DOI: 10.1016/j.gie.2013.05.034]
- 14 Takikawa T, Kanno A, Masamune A, Hamada S, Nakano E, Miura S, Ariga H, Unno J, Kume K, Kikuta K, Hirota M, Yoshida H, Katayose Y, Unno M, Shimosegawa T. Pancreatic duct drainage using EUS-guided rendezvous technique for stenotic pancreaticojejunostomy. *World J Gastroenterol* 2013; **19**: 5182-5186 [PMID: 23964156 DOI: 10.3748/wjg.v19.i31.5182]
- 15 François E, Kahaleh M, Giovannini M, Matos C, Devière J. EUS-guided pancreaticogastrostomy. *Gastrointest Endosc* 2002; **56**: 128-133 [PMID: 12085052 DOI: 10.1067/mge.2002.125547]
- 16 Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. EUS-guided pancreaticogastrostomy: analysis of its efficacy to drain inaccessible pancreatic ducts. *Gastrointest Endosc* 2007; **65**: 224-230 [PMID: 17141775 DOI: 10.1016/j.gie.2006.05.008]
- 17 Kurihara T, Itoi T, Sofuni A, Itokawa F, Moriyasu F. Endoscopic ultrasonography-guided pancreatic duct drainage after failed endoscopic retrograde cholangiopancreatography in patients with malignant and benign pancreatic duct obstructions. *Dig Endosc* 2013; **25** Suppl 2: 109-116 [PMID: 23617660 DOI: 10.1111/den.12100]
- 18 Itoi T, Kasuya K, Sofuni A, Itokawa F, Kurihara T, Yasuda I, Nakai Y, Isayama H, Moriyasu F. Endoscopic ultrasonography-guided pancreatic duct access: techniques and literature review of pancreatography, transmural drainage and rendezvous techniques. *Dig Endosc* 2013; **25**: 241-252 [PMID: 23490022 DOI: 10.1111/den.12048]
- 19 Itoi T, Yasuda I, Kurihara T, Itokawa F, Kasuya K. Technique of

- endoscopic ultrasonography-guided pancreatic duct intervention (with videos). *J Hepatobiliary Pancreat Sci* 2014; **21**: E4-E9 [PMID: 24123911 DOI: 10.1002/jhbp.43]
- 20 **Giovannini M.** EUS-guided pancreatic duct drainage: ready for prime time? *Gastrointest Endosc* 2013; **78**: 865-867 [PMID: 24237945 DOI: 10.1016/j.gie.2013.10.019]
 - 21 **Shah JN**, Marson F, Weilert F, Bhat YM, Nguyen-Tang T, Shaw RE, Binmoeller KF. Single-operator, single-session EUS-guided antegrade cholangiopancreatography in failed ERCP or inaccessible papilla. *Gastrointest Endosc* 2012; **75**: 56-64 [PMID: 22018554 DOI: 10.1016/j.gie.2011.08.032]
 - 22 **Ergun M**, Aouattah T, Gillain C, Gigot JF, Hubert C, Deprez PH. Endoscopic ultrasound-guided transluminal drainage of pancreatic duct obstruction: long-term outcome. *Endoscopy* 2011; **43**: 518-525 [PMID: 21437853 DOI: 10.1055/s-0030-1256333]
 - 23 **Will U**, Fuedner F, Thieme AK, Goldmann B, Gerlach R, Wanzar I, Meyer F. Transgastric pancreatography and EUS-guided drainage of the pancreatic duct. *J Hepatobiliary Pancreat Surg* 2007; **14**: 377-382 [PMID: 17653636]
 - 24 **Tessier G**, Bories E, Arvanitakis M, Hittelet A, Pesenti C, Le Moine O, Giovannini M, Devière J. EUS-guided pancreatogastrostomy and pancreatobulbostomy for the treatment of pain in patients with pancreatic ductal dilatation inaccessible for transpapillary endoscopic therapy. *Gastrointest Endosc* 2007; **65**: 233-241 [PMID: 17258981]
 - 25 **Fujii LL**, Topazian MD, Abu Dayyeh BK, Baron TH, Chari ST, Farnell MB, Gleeson FC, Gostout CJ, Kendrick ML, Pearson RK, Petersen BT, Truty MJ, Vege SS, Levy MJ. EUS-guided pancreatic duct intervention: outcomes of a single tertiary-care referral center experience. *Gastrointest Endosc* 2013; **78**: 854-864.e1 [PMID: 23891418 DOI: 10.1016/j.gie.2013.05.016]
 - 26 **Barkay O**, Sherman S, McHenry L, Yoo BM, Fogel EL, Watkins JL, DeWitt J, Al-Haddad MA, Lehman GA. Therapeutic EUS-assisted endoscopic retrograde pancreatography after failed pancreatic duct cannulation at ERCP. *Gastrointest Endosc* 2010; **71**: 1166-1173 [PMID: 20303489 DOI: 10.1016/j.gie.2009.10.048]
 - 27 **Siripun A**, Sripongpun P, Ovarltamporn B. Endoscopic ultrasound-guided biliary intervention in patients with surgically altered anatomy. *World J Gastrointest Endosc* 2015; **7**: 283-289 [PMID: 25789101 DOI: 10.4253/wjge.v7.i3.283]
 - 28 **Iwashita T**, Yasuda I, Doi S, Uemura S, Mabuchi M, Okuno M, Mukai T, Itoi T, Moriwaki H. Endoscopic ultrasound-guided antegrade treatments for biliary disorders in patients with surgically altered anatomy. *Dig Dis Sci* 2013; **58**: 2417-2422 [PMID: 23535877 DOI: 10.1007/s10620-013-2645-6]
 - 29 **Itoi T**, Sofuni A, Tsuchiya T, Iijima M, Iwashita T. Endoscopic ultrasonography-guided transhepatic antegrade stone removal in patients with surgically altered anatomy: case series and technical review (with videos). *J Hepatobiliary Pancreat Sci* 2014; **21**: E86-E93 [PMID: 25231935 DOI: 10.1002/jhbp.165]
 - 30 **Moon JH**, Choi HJ, Lee YN. Endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc* 2014; **80**: 388-391 [PMID: 25127941 DOI: 10.1016/j.gie.2014.07.004]
 - 31 **Choudhary A**, Winn J, Siddique S, Arif M, Arif Z, Hammoud GM, Puli SR, Ibdah JA, Bechtold ML. Effect of precut sphincterotomy on post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. *World J Gastroenterol* 2014; **20**: 4093-4101 [PMID: 24744601 DOI: 10.3748/wjg.v20.i14.4093]
 - 32 **Moon JH**, Ko BM, Choi HJ, Koo HC, Hong SJ, Cheon YK, Cho YD, Lee MS, Shim CS. Direct peroral cholangioscopy using an ultra-slim upper endoscope for the treatment of retained bile duct stones. *Am J Gastroenterol* 2009; **104**: 2729-2733 [PMID: 19623165 DOI: 10.1038/ajg.2009.435]
 - 33 **Sauer BG**, Cereface M, Swartz DC, Gaidhane M, Jain A, Haider S, Kahaleh M. Safety and efficacy of laser lithotripsy for complicated biliary stones using direct choledochoscopy. *Dig Dis Sci* 2013; **58**: 253-256 [PMID: 22903184 DOI: 10.1007/s10620-012-2359-1]
 - 34 **Artifon EL**, Kumar A, Eloubeidi MA, Chu A, Halwan B, Sakai P, Bhutani MS. Prospective randomized trial of EUS versus ERCP-guided common bile duct stone removal: an interim report (with video). *Gastrointest Endosc* 2009; **69**: 238-243 [PMID: 19185687 DOI: 10.1016/j.gie.2008.05.020]
 - 35 **Khashab MA**, Baron TH, Binmoeller KF, Itoi T. EUS-guided gastroenterostomy: a new promising technique in evolution. *Gastrointest Endosc* 2015; **81**: 1234-1236 [PMID: 25864896 DOI: 10.1016/j.gie.2014.12.053]
 - 36 **Ikeuchi N**, Itoi T, Tsuchiya T, Nagakawa Y, Tsuchida A. One-step EUS-guided gastrojejunostomy with use of lumen-apposing metal stent for afferent loop syndrome treatment. *Gastrointest Endosc* 2015; **82**: 166 [PMID: 25887724 DOI: 10.1016/j.gie.2015.01.010]
 - 37 **Itoi T**, Ishii K, Tanaka R, Umeda J, Tonoizuka R. Current status and perspective of endoscopic ultrasonography-guided gastrojejunostomy: endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy (with videos). *J Hepatobiliary Pancreat Sci* 2015; **22**: 3-11 [PMID: 25155270 DOI: 10.1002/jhbp.148]
 - 38 **Itoi T**, Itokawa F, Uraoka T, Gotoda T, Horii J, Goto O, Moriyasu F, Moon JH, Kitagawa Y, Yahagi N. Novel EUS-guided gastrojejunostomy technique using a new double-balloon enteric tube and lumen-apposing metal stent (with videos). *Gastrointest Endosc* 2013; **78**: 934-939 [PMID: 24237949 DOI: 10.1016/j.gie.2013.09.025]
 - 39 **Giovannini M**, Pesenti C, Rolland AL, Moutardier V, Delperro JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. *Endoscopy* 2001; **33**: 473-477 [PMID: 11437038]
 - 40 **Mandai K**, Uno K, Yasuda K. Endoscopic ultrasound-guided drainage of postoperative intra-abdominal abscesses. *World J Gastroenterol* 2015; **21**: 3402-3408 [PMID: 25805951 DOI: 10.3748/wjg.v21.i11.3402]
 - 41 **Hadithi M**, Bruno MJ. Endoscopic ultrasound-guided drainage of pelvic abscess: A case series of 8 patients. *World J Gastrointest Endosc* 2014; **6**: 373-378 [PMID: 25132921 DOI: 10.4253/wjge.v6.i8.373]
 - 42 **Puri R**, Eloubeidi MA, Sud R, Kumar M, Jain P. Endoscopic ultrasound-guided drainage of pelvic abscess without fluoroscopy guidance. *J Gastroenterol Hepatol* 2010; **25**: 1416-1419 [PMID: 20659232 DOI: 10.1111/j.1440-1746.2010.06328.x]
 - 43 **Varadarajulu S**, Drelichman ER. Effectiveness of EUS in drainage of pelvic abscesses in 25 consecutive patients (with video). *Gastrointest Endosc* 2009; **70**: 1121-1127 [PMID: 19962502 DOI: 10.1016/j.gie.2009.08.034]
 - 44 **Wehrmann T**, Stergiou N, Vogel B, Riphaut A, Köckerling F, Frenz MB. Endoscopic debulking of paraesophageal, mediastinal abscesses: a prospective case series. *Gastrointest Endosc* 2005; **62**: 344-349 [PMID: 16111949]
 - 45 **Itoi T**, Ang TL, Seewald S, Tsuji S, Kurihara T, Tanaka R, Itokawa F. Endoscopic ultrasonography-guided drainage for tuberculous liver abscess drainage. *Dig Endosc* 2011; **23** Suppl 1: 158-161 [PMID: 21535224 DOI: 10.1111/j.1443-1661.2011.01115.x]
 - 46 **Decker C**, Varadarajulu S. EUS-guided drainage of an intra-abdominal abscess after liver transplantation. *Gastrointest Endosc* 2011; **73**: 1056-1058 [PMID: 21111412 DOI: 10.1016/j.gie.2010.09.006]
 - 47 **Noh SH**, Park do H, Kim YR, Chun Y, Lee HC, Lee SO, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided drainage of hepatic abscesses not accessible to percutaneous drainage (with videos). *Gastrointest Endosc* 2010; **71**: 1314-1319 [PMID: 20400078 DOI: 10.1016/j.gie.2009.12.045]
 - 48 **Ang TL**, Seewald S, Teo EK, Fock KM, Soehendra N. EUS-guided drainage of ruptured liver abscess. *Endoscopy* 2009; **41** Suppl 2: E21-E22 [PMID: 19219764 DOI: 10.1055/s-0028-1103468]
 - 49 **Trevino JM**, Drelichman ER, Varadarajulu S. Modified technique for EUS-guided drainage of pelvic abscess (with video). *Gastrointest Endosc* 2008; **68**: 1215-1219 [PMID: 19028235 DOI: 10.1016/j.gie.2008.07.016]
 - 50 **Lee DH**, Cash BD, Womeldorph CM, Horwhat JD. Endoscopic therapy of a splenic abscess: definitive treatment via EUS-guided

- transgastric drainage. *Gastrointest Endosc* 2006; **64**: 631-634 [PMID: 16996360 DOI: 10.1016/j.gie.2006.04.031]
- 51 **Lee YT**, Chan FK, Ng EK, Leung VK, Law KB, Yung MY, Chung SC, Sung JJ. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc* 2000; **52**: 168-174 [PMID: 10922086]
 - 52 **Levy MJ**, Wong Kee Song LM, Kendrick ML, Misra S, Gostout CJ. EUS-guided coil embolization for refractory ectopic variceal bleeding (with videos). *Gastrointest Endosc* 2008; **67**: 572-574 [PMID: 17997404]
 - 53 **Levy MJ**, Wong Kee Song LM. EUS-guided angiotherapy for gastric varices: coil, glue, and sticky issues. *Gastrointest Endosc* 2013; **78**: 722-725 [PMID: 24120335 DOI: 10.1016/j.gie.2013.07.004]
 - 54 **Storm AC**, Kumbhari V, Saxena P, Canto MI, Azola A, Messallam AA, O'Broin-Lennon AM, Khashab MA. EUS-guided angiotherapy. *Gastrointest Endosc* 2014; **80**: 164-165 [PMID: 24950644 DOI: 10.1016/j.gie.2014.04.005]
 - 55 **Rana SS**, Bhasin DK, Sharma V, Chaudhary V, Sharma R, Singh K. Clinical, endoscopic and endoscopic ultrasound features of duodenal varices: A report of 10 cases. *Endosc Ultrasound* 2014; **3**: 54-57 [PMID: 24949411 DOI: 10.4103/2303-9027.121243]
 - 56 **Bokun T**, Grgurevic I, Kujundzic M, Banic M. EUS-Guided Vascular Procedures: A Literature Review. *Gastroenterol Res Pract* 2013; **2013**: 865945 [PMID: 23737766 DOI: 10.1155/2013/865945]
 - 57 **Levy MJ**, Wong Kee Song LM, Farnell MB, Misra S, Sarr MG, Gostout CJ. Endoscopic ultrasound (EUS)-guided angiotherapy of refractory gastrointestinal bleeding. *Am J Gastroenterol* 2008; **103**: 352-359 [PMID: 17986314]
 - 58 **Levy MJ**, Chak A, EUS 2008 Working Group. EUS 2008 Working Group document: evaluation of EUS-guided vascular therapy. *Gastrointest Endosc* 2009; **69**: S37-S42 [PMID: 19179168 DOI: 10.1016/j.gie.2008.11.009]
 - 59 **Kinzel J**, Pichetshote N, Dredar S, Aslanian H, Nagar A. Bleeding from a duodenal varix: a unique case of variceal hemostasis achieved using EUS-guided placement of an embolization coil and cyanoacrylate. *J Clin Gastroenterol* 2014; **48**: 362-364 [PMID: 24518801 DOI: 10.1097/MCG.0000000000000004]
 - 60 **Kuramochi A**, Imazu H, Kakutani H, Uchiyama Y, Hino S, Urashima M. Color Doppler endoscopic ultrasonography in identifying groups at a high-risk of recurrence of esophageal varices after endoscopic treatment. *J Gastroenterol* 2007; **42**: 219-224 [PMID: 17380280]
 - 61 **Hammoud GM**, Ibdah JA. Utility of endoscopic ultrasound in patients with portal hypertension. *World J Gastroenterol* 2014; **20**: 14230-14236 [PMID: 25339809 DOI: 10.3748/wjg.v20.i39.14230]
 - 62 **Giday SA**, Clarke JO, Buscaglia JM, Shin EJ, Ko CW, Magno P, Kantsevov SV. EUS-guided portal vein catheterization: a promising novel approach for portal angiography and portal vein pressure measurements. *Gastrointest Endosc* 2008; **67**: 338-342 [PMID: 18226699 DOI: 10.1016/j.gie.2007.08.037]
 - 63 **Giday SA**, Ko CW, Clarke JO, Shin EJ, Magno P, Jagannath SB, Buscaglia JM, Kantsevov SV. EUS-guided portal vein carbon dioxide angiography: a pilot study in a porcine model. *Gastrointest Endosc* 2007; **66**: 814-819 [PMID: 17905028 DOI: 10.1016/j.gie.2007.05.056]
 - 64 **Buscaglia JM**, Dray X, Shin EJ, Magno P, Chmura KM, Surti VC, Dillon TE, Ducharme RW, Donatelli G, Thuluvath PJ, Giday SA, Kantsevov SV. A new alternative for a transjugular intrahepatic portosystemic shunt: EUS-guided creation of an intrahepatic portosystemic shunt (with video). *Gastrointest Endosc* 2009; **69**: 941-947 [PMID: 19327481 DOI: 10.1016/j.gie.2008.09.051]
 - 65 **Matthes K**, Sahani D, Holalkere NS, Mino-Kenudson M, Brugge WR. Feasibility of endoscopic ultrasound-guided portal vein embolization with Enteryx. *Acta Gastroenterol Belg* 2005; **68**: 412-415 [PMID: 16432991]
 - 66 **Carrara S**, Petrone MC, Testoni PA, Arcidiacono PG. Tumors and new endoscopic ultrasound-guided therapies. *World J Gastrointest Endosc* 2013; **5**: 141-147 [PMID: 23596535 DOI: 10.4253/wjge.v5.i4.141]
 - 67 **Luz LP**, Al-Haddad MA, Sey MS, DeWitt JM. Applications of endoscopic ultrasound in pancreatic cancer. *World J Gastroenterol* 2014; **20**: 7808-7818 [PMID: 24976719 DOI: 10.3748/wjg.v20.i24.7808]
 - 68 **Yan BM**, Van Dam J. Endoscopic ultrasound-guided intratumoral therapy for pancreatic cancer. *Can J Gastroenterol* 2008; **22**: 405-410 [PMID: 18414717]
 - 69 **Seo DW**. EUS-Guided Antitumor Therapy for Pancreatic Tumors. *Gut Liver* 2010; **4** Suppl 1: S76-S81 [PMID: 21103299 DOI: 10.5009/gnl.2010.4.S1.S76]
 - 70 **Pai M**, Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, Kaba I, Beckebaum S, Drymoussis P, Kahaleh M, Brugge W. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. *World J Gastrointest Surg* 2015; **7**: 52-59 [PMID: 25914783 DOI: 10.4240/wjgs.v7.i4.52]
 - 71 **Park do H**, Choi JH, Oh D, Lee SS, Seo DW, Lee SK, Kim MH. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. *Clin Endosc* 2015; **48**: 158-164 [PMID: 25844345 DOI: 10.5946/ce.2015.48.2.158]
 - 72 **DeWitt JM**, Al-Haddad M, Sherman S, LeBlanc J, Schmidt CM, Sandrasegaran K, Finkelstein SD. Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. *Endoscopy* 2014; **46**: 457-464 [PMID: 24770971 DOI: 10.1055/s-0034-1365496]
 - 73 **Oh HC**, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 2008; **67**: 636-642 [PMID: 18262182 DOI: 10.1016/j.gie.2007.09.038]
 - 74 **Wang KX**, Jin ZD, Du YQ, Zhan XB, Zou DW, Liu Y, Wang D, Chen J, Xu C, Li ZS. EUS-guided celiac ganglion irradiation with iodine-125 seeds for pain control in pancreatic carcinoma: a prospective pilot study. *Gastrointest Endosc* 2012; **76**: 945-952 [PMID: 22841501 DOI: 10.1016/j.gie.2012.05.032]
 - 75 **Vohra S**, Holt EW, Bhat YM, Kane S, Shah JN, Binmoeller KF. Successful single-session endosonography-based endoscopic retrograde cholangiopancreatography without fluoroscopy in pregnant patients with suspected choledocholithiasis: a case series. *J Hepatobiliary Pancreat Sci* 2014; **21**: 93-97 [PMID: 23798477 DOI: 10.1002/jhbp.7]
 - 76 **Girotra M**, Jani N. Role of endoscopic ultrasound/SpyScope in diagnosis and treatment of choledocholithiasis in pregnancy. *World J Gastroenterol* 2010; **16**: 3601-3602 [PMID: 20653072 DOI: 10.3748/wjg.v16.i28.3601]
 - 77 **Chong VH**, Jalihal A. Endoscopic management of biliary disorders during pregnancy. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 180-185 [PMID: 20382591]
 - 78 **Chong VH**. EUS complements ERCP during pregnancy. *Gastrointest Endosc* 2009; **70**: 1285-1286; author reply 1286-1287 [PMID: 19962506 DOI: 10.1016/j.gie.2009.03.036]
 - 79 **Kato S**, Fujita N, Shibuya H, Nakagawa H. Endoscopic ultrasonography in a child with chronic pancreatitis. *Acta Paediatr Jpn* 1993; **35**: 151-153 [PMID: 8389090 DOI: 10.1111/j.1442-200X.1993.tb03028.x]
 - 80 **Varadarajulu S**, Wilcox CM, Eloubeidi MA. Impact of EUS in the evaluation of pancreaticobiliary disorders in children. *Gastrointest Endosc* 2005; **62**: 239-244 [PMID: 16046987 DOI: 10.1016/S0016-5107(05)00312-3]
 - 81 **Ramesh J**, Bang JY, Trevino J, Varadarajulu S. Endoscopic ultrasound-guided drainage of pancreatic fluid collections in children. *J Pediatr Gastroenterol Nutr* 2013; **56**: 30-35 [PMID: 22785412 DOI: 10.1097/MPG.0b013e318267c113]
 - 82 **Attila T**, Adler DG, Hilden K, Faigel DO. EUS in pediatric patients. *Gastrointest Endosc* 2009; **70**: 892-898 [PMID: 19577744 DOI: 10.1016/j.gie.2009.04.012]
 - 83 **Scheers I**, Ergun M, Aouattah T, Piessevaux H, Borbath I, Stephenne X, De Magnée C, Reding R, Sokal E, Veyckemans F,

Weynand B, Deprez PH. Diagnostic and Therapeutic Roles of Endoscopic Ultrasound in Pediatric Pancreaticobiliary Disorders. *J*

Pediatr Gastroenterol Nutr 2015; **61**: 238-247 [PMID: 25564818 DOI: 10.1097/MPG.0000000000000692]

P- Reviewer: Tadic M, Tepes B **S- Editor:** Gong ZM
L- Editor: A **E- Editor:** Lu YJ



Retrospective Study

Evidence to suggest adoption of water exchange deserves broader consideration: Its pain alleviating impact occurs in 90% of investigators

Sergio Cadoni, Mauro Liggi, Premysl Falt, Stefano Sanna, Mariangela Argiolas, Viviana Fanari, Paolo Gallittu, Donatella Mura, Maria L Porcedda, Vit Smajstrla, Matteo Erriu, Felix W Leung

Sergio Cadoni, Mauro Liggi, Paolo Gallittu, Donatella Mura, Digestive Endoscopy Unit, St. Barbara Hospital, 09016 Iglesias, Italy

Premysl Falt, Vit Smajstrla, Digestive Diseases Center, Vitkovice Hospital, 703 84 Ostrava, Czech Republic

Stefano Sanna, Mariangela Argiolas, Viviana Fanari, Maria L Porcedda, Digestive Endoscopy Unit, N. S. di Bonaria Hospital, 09037 San Gavino Monreale, Italy

Matteo Erriu, Department of Surgical Sciences, University of Cagliari, 09121 Cagliari, Italy

Felix W Leung, Sepulveda Ambulatory Care Center, Veterans Affairs Greater Los Angeles Healthcare System, North Hills, CA 91343, United States

Felix W Leung, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90024, United States

Author contributions: Cadoni S, Liggi M, Falt P and Leung FW defined the research theme, designed methods, interpreted the results and wrote the paper; Cadoni S, Liggi M, Falt P, Sanna S, Argiolas M, Fanari V, Gallittu P, Mura D, Porcedda ML and Smajstrla V contributed to the acquisition and interpretation of data, drafting and critical revision of the manuscript for important intellectual content; Erriu M did the statistical analysis of the data; all the authors have approved the final draft submitted.

Institutional review board statement: The study protocols relative to this retrospective study and the use of their data were reviewed and approved by the local Ethics Committee of the St. Barbara Hospital, Vitkovice Hospital and N. S. di Bonaria Hospital.

Informed consent statement: Patients agreed to the study by written consent at enrollment, even if the analysis used anonymous clinical data. For full disclosure, the details of the study are published on the website of the Institution of the St. Barbara Hospital under the section "Archivio Delibere" (Resolutions Archive).

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Sergio Cadoni, MD, Digestive Endoscopy Unit, St. Barbara Hospital, Via San Leonardo 1, 09016 Iglesias, Italy. cadonisergio@gmail.com
Telephone: +39-0781-3922858
Fax: +39-0781-3922323

Received: June 15, 2015

Peer-review started: June 30, 2015

First decision: July 31, 2015

Revised: August 18, 2015

Accepted: December 13, 2015

Article in press: December 15, 2015

Published online: January 25, 2016

Abstract

AIM: To determine variations in colonoscopy real-time insertion pain among investigators using three different insertion techniques.

METHODS: From March 2013 through June 2014, 18-85-year-old diagnostic and 50-70-year-old screening patients were enrolled at each center to on-demand sedation colonoscopy with water exchange (WE), water immersion

(WI) and insufflation with air or CO₂ for insertion and withdrawal [air or carbon dioxide (AICD)]. Data were aggregated for analysis. Primary outcome: Variations in real-time maximum insertion pain (0 = none, 1-2 = discomfort, 10 = worst).

RESULTS: One thousand and ninety-one cases analyzed: WE ($n = 371$); WI ($n = 338$); AICD ($n = 382$). Demographics and indications were comparable. The WE group had the lowest real-time maximum insertion pain score, mean (95%CI): WE 2.8 (2.6-3.0), WI 3.8 (3.5-4.1) and AICD 4.4 (4.1-4.7), $P < 0.0005$. Ninety percent of the colonoscopists were able to use water exchange to significantly decrease maximum insertion pain scores. One investigator had high insertion pain in all groups, nonetheless WE achieved the lowest real-time maximum insertion pain score. WE had the highest proportions of patients with painless unsedated colonoscopy (*vs* WI, $P = 0.013$; *vs* AICD, $P < 0.0005$); unsedated colonoscopy with only minor discomfort (*vs* AICD, $P < 0.0005$), and completion without sedation (*vs* AICD, $P < 0.0005$).

CONCLUSION: Aggregate data confirm superiority of WE in lowering colonoscopy real-time maximum insertion pain and need for sedation. Ninety percent of investigators were able to use water exchange to significantly decrease maximum insertion pain scores. Our results suggest that the technique deserves consideration in a broader scale.

Key words: Colonoscopy; Painless colonoscopy; Water immersion; Water exchange; Colonoscopy pain

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Randomized controlled trials (RCTs) have shown water exchange (WE) to have considerable advantage in decreasing colonoscopy insertion pain. Assessment of individual investigators' performance using WE in RCTs is usually not reported. We assessed the performance of individual investigators in 3 RCTs comparing WE, water immersion and gas insufflation (with air or carbon dioxide) during insertion, to determine whether observations are reproducible across investigators and what factors might contribute to variations. Aggregate data show that individual investigators had significant variations in insertion pain scores and use of adjunct maneuvers together with short insertion time, but the pain alleviating impact of WE occurs in 90% of them. WE has the highest proportions of patients with painless unsedated colonoscopy; complete unsedated colonoscopy with only minor discomfort and completion without sedation.

Cadoni S, Liggi M, Falt P, Sanna S, Argiolas M, Fanari V, Gallittu P, Mura D, Porcedda ML, Smajstrla V, Erriu M, Leung FW. Evidence to suggest adoption of water exchange deserves broader consideration: Its pain alleviating impact occurs in 90% of investigators. *World J Gastrointest Endosc* 2016; 8(2): 113-121 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i2/113.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i2.113>

INTRODUCTION

Water exchange (WE) and water immersion (WI) are two colonoscopy techniques that entail infusion of water to distend the lumen during the insertion phase. Randomized controlled trials (RCTs) have shown WE (airless insertion, infused water aspirated predominantly during insertion to clear the view and minimize distension) to have considerable advantage in decreasing colonoscopy real-time maximum insertion pain when compared with WI (water infused as adjunct to insufflation, and aspirated predominantly during withdrawal without attempting to maximize colon cleanliness during insertion) and air^[1-3] or carbon dioxide insufflation^[3,4]. WE is a relatively new technique, and requires new maneuvers not entirely intuitive to colonoscopists^[5]. In spite of this, in a previous report focused on individual investigators' performance^[6], WE has shown reproducibility and repeatability in decreasing maximum insertion pain, usually not reported in RCTs. Some of the factors associated with difficult colonoscopy (e.g., prior abdominal surgery, low body mass index) and insertion pain are favorably influenced by WE^[2,3,7,8].

We assessed the performance of individual investigators in three recently completed RCTs in a multinational setting, to determine whether the effect of WE in reducing real-time maximum insertion pain is reproducible across investigators and what factors (e.g., use of adjunct maneuvers of loop reduction and abdominal compression, insertion time, etc.) might contribute to variations among them.

MATERIALS AND METHODS

Patient-related and procedure-related factors were collected prospectively at our centers (NCT01781650, 01780818, 01954862): St. Barbara Hospital, Iglesias (Italy); N. S. di Bonaria Hospital, San Gavino Monreale (Italy) and the Vitkovice Hospital, Ostrava (Czech Republic).

From March 2013 through June 2014, 18-85-year-old diagnostic and 50-70-year-old screening patients were enrolled and randomized to WE, WI or insufflation with air or carbon dioxide (AICD) at each site. Sedation was available on-demand at patients' request^[2,3]. Local Ethics Committees approved the protocols. Written informed consent was obtained from all patients at enrollment. All authors had access to the study data, reviewed and approved the final manuscript. Statistical review of the study was performed by a biomedical statistician.

Study procedures

Colonoscopies were performed by 10 board-certified endoscopists, five with experience in about 10000 AICD, 260 WE and 120 WI. One investigator had experience in about 7200 AICD, 260 WE, 800 WI. The last four investigators had experience in about 3000-7000 AICD and 150 WE. One had experience in 800 WI, the

remaining three in 90 WI.

A split-dose bowel preparation was used to clean the colon^[2,3]. Enrolled patients were assigned to the different insertion techniques by computer-generated lists, with block allocation and stratification based on participating endoscopists. Group assignment was kept in sealed envelopes that were opened just before the start of the procedure. The patients, but not endoscopists and assisting nurses, were blinded to the insertion method used: The monitors were concealed from patients' view. Endoscopists were blinded to insufflation gas used: Light source and insufflators were concealed from the view. At discharge patients were asked to guess which insertion method had been used (infusion of water or insufflation), and investigators which gas had been insufflated. If no more than half of the responses were correct, their blinding was considered adequate^[2,3].

Colonoscopy began with the patients in the left lateral position without premedication. High-resolution wide-angle variable-stiffness adult video colonoscopes (Olympus HD 180) were used. Variable stiffness was used at the discretion of the investigators, but its record was not kept^[2,3]. Cardiopulmonary function was monitored throughout.

In patients randomized to WE and WI, insufflation was turned off before starting the procedure. After the rectosigmoid junction was reached, the colon was irrigated with water at 37 °C using flushing pumps^[2,3].

Water exchange involved infusion of water during insertion to distend the lumen to the minimum required to reach the cecum. When opaque water was encountered, infusion and near-simultaneous suction were applied until clear water was in front of the instrument. Residual air pockets, feces and infused water were removed predominantly during insertion^[2,3].

Water immersion involved the infusion of water during the insertion phase to aid passage to the cecum without attempting to clear the colon contents, with limited use of insufflation when necessary^[2,3]. Infused water was removed predominantly during withdrawal.

In the AICD group colonoscopy was performed in the usual fashion with the minimal insufflation required to reach the cecum^[2,3]. In all arms insufflation was used during withdrawal to obtain adequate distension of the lumen for exploration^[2,3].

In all groups loop reduction, position change and abdominal compression were applied in that sequence as needed when the instrument failed to advance, and not per protocol at determined anatomic locations. Cecal intubation was defined as reaching beyond the ileocecal valve with adequate visualization of the appendix orifice.

Pain assessment and sedation

Pain was assessed using a numeric rating scale (NRS) with faces outlines and verbal descriptors, with a score 0 = absence of pain, 1-2 = simply "discomfort", 10 = the worst possible pain. Before the procedure, a

nurse explained the NRS to the patients. They were informed that the request for pain information was meant to assess the need and dosage of sedation^[2,3], and to let the colonoscopist be alerted to the need to use maneuvers to minimize discomfort (e.g., removal of colonic content, loop reduction, change in patient position and/or abdominal compression). At the discretion of the assisting nurse, at irregular intervals, patients were asked about discomfort or pain several times during the procedure and encouraged to report it spontaneously. Responses were recorded and the real-time maximum insertion pain score noted. On-demand sedation was offered at a NRS score ≥ 2 (discomfort). If patients accepted, sedation was started with an intravenous dose of 2 mg of midazolam, with step-ups of 1 mg (up to 5 mg) if the patients continued to report pain^[2,3]. To avoid bias by the colonoscopist, medication was administered based on the patients' confirmation that the pain was no longer tolerable, and not at the discretion of the endoscopist. No other analgesic or sedative medications were administered. At discharge, a blinded nurse recorded patients' recalled maximum insertion pain using the same NRS in the absence the personnel who performed the procedure.

Study endpoints

The primary outcome was real-time maximum insertion pain score recorded during the insertion phase of colonoscopy. Secondary outcomes included recalled pain at discharge, individual performance of investigators in terms of several procedural outcomes; analysis of painless unsedated colonoscopy, unsedated colonoscopy completed with only discomfort (NRS = 1-2), and complete unsedated colonoscopy with any pain score.

Statistical analysis

Standard descriptive statistics were used to assess the distribution of the study variables and to compare them. Pain values were computed using mean at 95%CI and analyzed by using the *t*-test and analysis of variance (ANOVA) where appropriate. *P* values < 0.05 were considered significant.

RESULTS

The database stored data relative to 1091 patients randomly allocated to WE (*n* = 371), WI (*n* = 338) or AICD (*n* = 382). Overall, demographics, body mass index (BMI), previous abdominal surgery and indications were comparable (Table 1).

In greater detail, age was comparable among the study groups and individual investigators. Abdominal pain had comparable proportions among methods and individual investigators, except for Investigator number 1 and Investigator number 8 that had significantly higher proportions in the WE group. The other indications were comparable among methods, except for Anemia (0.048).

Table 2 shows that female patients were equally

Table 1 Water-aided colonoscopy and insufflation colonoscopy: Baseline characteristics and indications of 1091 patients

	WE (<i>n</i> = 371)	WI (<i>n</i> = 338)	AICD (<i>n</i> = 382)	<i>P</i> value ¹
Age, yr, mean (± SD)	59 (12.2)	59 (11.6)	59 (12.0)	0.627
Females, <i>n</i> (%)	149 (40.2)	140 (41.4)	151 (39.5)	0.873
Males, <i>n</i> (%)	222 (59.8)	198 (58.6)	231 (60.5)	
BMI, mean (± SD)	26.7 (4.8)	26.5 (4.7)	26.4 (4.7)	0.607
Previous abdominal surgery, <i>n</i> (%)	141 (38.0)	116 (34.3)	116 (30.4)	0.087
Indications for colonoscopy, <i>n</i> (%)				
Abdominal pain	68 (18.3)	52 (15.4)	59 (15.4)	0.127
Bleeding	90 (24.3)	89 (26.3)	108 (28.3)	0.076
Change in bowel habits	73 (19.7)	64 (18.9)	60 (15.7)	0.977
Anemia	8 (2.2)	12 (3.6)	7 (1.8)	0.048
Diverticulosis	4 (1.1)	5 (1.5)	7 (1.8)	0.787
Other	46 (12.4)	37 (10.9)	46 (12.0)	0.403
Screening	82 (22.1)	79 (23.4)	95 (24.9)	0.361

¹ANOVA. *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO₂ for withdrawal; WI: Water immersion for insertion, insufflation with air or CO₂ for withdrawal; AICD: Insufflation with air or CO₂ for insertion and withdrawal; SD: Standard deviation.

Table 2 Variations among investigators

	Real-time maximum insertion pain, mean (95%CI)			<i>P</i> value					
	WE (<i>n</i> = 371)	WI (<i>n</i> = 338)	AICD (<i>n</i> = 382)						
All investigators	2.8 (2.6-3.0)	3.8 (3.5-4.1)	4.4 (4.1-4.7)	< 0.0005¹ WE vs WI < 0.0005² WE vs AICD < 0.0005² WI vs AICD 0.002²					
Investigator	WE	WI	AICD	Females (%)	BMI (± SD)	Previous abdominal surgery (%)	Abdominal compression (%)	Loop reduction (%)	Insertion time, min (± SD)
1	2.1 (1.7-2.5)	4.0 (3.4-4.7)	4.7 (4.1-5.3)	46.3	26.1 (4.9)	51.3	57.5	61.3	13 (6.5)
2	2.9 (2.4-3.3)	3.3 (2.8-3.9)	4.1 (3.5-4.7)	32.9	27.0 (4.8)	46.8	67.1	63.3	11 (5.5)
3	2.3 (1.0-3.6)	2.3 (1.0-3.6)	4 (2.9-5.2)	28.6	27.5 (4.4)	7.1	57.1	7.1	11 (4.4)
4	2.4 (1.7-3.2)	1.9 (0.6-3.3)	2.8 (2.0-3.5)	28.6	25.6 (4.2)	10.7	71.4	21.4	15 (6.7)
5	2.9 (1.8-4.0)	3.7 (2.3-5.1)	3.5 (2.2-4.8)	46.2	24.6 (3.3)	7.7	92.3	84.6	9 (2.8)
6	2.4 (1.6-3.3)	2.6 (1.5-3.7)	3.5 (2.5-4.5)	60.9	28.4 (6.8)	13.0	73.9	52.2	10 (4.0)
7	2.4 (1.6-3.2)	3.7 (2.3-5.1)	4.3 (3.0-5.6)	17.6	26.4 (2.5)	41.2	64.7	82.4	12 (7.2)
8	2.8 (2.0-3.6)	2.4 (1.7-3.0)	2.4 (1.4-3.3)	50.0	25.6 (4.0)	35.7	92.9	92.9	15 (5.2)
9	2.9 (2.3-3.5)	4.1 (3.4-4.9)	6.0 (5.3-6.7)	37.7	28.4 (5.2)	45.9	36.1	34.4	9 (3.1)
10	5.3 (4.4-6.2)	7.1 (6.3-8.0)	7.0 (6.2-7.9)	50	27.2 (5.6)	35.7	21.4	10.7	8 (3.0)
<i>P</i> values	< 0.0005 ¹	< 0.0005 ¹	< 0.0005 ¹	0.074 ¹	0.025 ¹	< 0.0005 ¹	< 0.0005 ¹	< 0.0005 ¹	< 0.0005 ¹

¹ANOVA; ²χ². *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO₂ for withdrawal; WI: Water immersion for insertion, insufflation with air or CO₂ for withdrawal; AICD: Insufflation with air or CO₂ for insertion and withdrawal; SD: Standard deviation; BMI: Body mass index.

distributed among study groups and individual investigators. There were significant differences in terms of BMI within the WE and WI groups ($P = 0.025$ and $P < 0.0005$, respectively). The AICD group had the lowest proportion of patients with previous abdominal surgery, comparable among individual investigators ($P = 0.405$). Among

the 10 individual investigators there were significant differences in terms of use of abdominal compression, loop reduction and cecal intubation time.

Primary outcome analysis

The number of patients examined by each colonoscopist

Table 3 Water exchange for insertion group, significant factors associated with increased pain score of Investigator number 8 *vs* all the other investigators, *n* (%)

	Investigator number 8 (<i>n</i> = 28)	All other investigators (<i>n</i> = 343)	<i>P</i> value
Abdominal pain as indication, females and males	11 (39.3)	57 (16.6)	0.003 ¹
Females with abdominal pain as indication	9 (32.1)	21 (6.1)	< 0.0005 ¹
Females with previous abdominal surgery, any indication for colonoscopy	6 (21.4)	24 (7.0)	0.018 ¹

¹ χ^2 .**Table 4** Investigator number 8, significant differences associated with increase in real-time maximum insertion pain score among methods, *n* (%)

	WE (<i>n</i> = 28)	WI (<i>n</i> = 28)	AICD (<i>n</i> = 24)	<i>P</i> value
Females and males, abdominal pain as indication	11 (39.3)	2 (7.1)	7 (29.2)	0.017 ¹ WE <i>vs</i> WI 0.004 ² WE <i>vs</i> AICD 0.446 ² WI <i>vs</i> AICD 0.064 ²
Females with abdominal pain as indication	9 (32.1)	1 (3.6)	3 (12.5)	0.008 ¹ WE <i>vs</i> WI 0.005 ² WE <i>vs</i> AICD 0.059 ² WI <i>vs</i> AICD 0.352 ²
Females with abdominal pain as indication and previous abdominal surgery	6 (21.4)	1 (3.6)	1 (4.2)	0.031 ¹ WE <i>vs</i> WI 0.043 ² WE <i>vs</i> AICD 0.069 ² WI <i>vs</i> AICD 0.911 ²

¹ANOVA; ² χ^2 ; *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO₂ for withdrawal; WI: Water immersion for insertion, insufflation with air or CO₂ for withdrawal; AICD: Insufflation with air or CO₂ for insertion and withdrawal; SD: Standard deviation; BMI: Body mass index.

ranged from 12 to 80 per group.

Table 2 shows the analysis of the performance of the individual investigators. There were significant differences of mean real-time maximum insertion pain score among WE, WI and AICD, mean (95%CI): WE 2.8 (2.6-3.0), WI 3.8 (3.5-4.1) and AICD 4.4 (4.1-4.7), *P* < 0.0005; differences were significant also within each study group. WE consistently showed the lowest real-time maximum insertion pain scores, and with the exception of Investigator number 8, who showed WE to have higher pain scores than all the other insertion techniques, the trend that WE was the least painful was observed in all the rest of investigators, regardless of their prior experience with the insertion technique used (Table 2). The WE group showed significant variations in terms of BMI, previous abdominal surgery, abdominal compression, loop reduction and insertion time among individual investigators.

Table 3 shows that, compared with all the other investigators, the WE group of Investigator number 8 had a significantly higher proportion of patients with abdominal pain as indication (39.3% *vs* 16.6%, *P* = 0.003), cohort that included mostly irritable bowel syndrome (IBS) patients; and a significantly higher proportion of female patients (32.1% *vs* 7.0%, *P* < 0.0005) with a significantly higher incidence of previous abdominal surgery: 21.4% *vs* 7.0%, *P* = 0.018 (Table 3).

The same analysis across Investigator's number 8 study groups (Table 4) showed that his WE group had a higher proportion of cases with abdominal pain as indication (ANOVA among groups *P* = 0.017; WE 39.3% *vs* WI 7.1%, *P* = 0.004); in particular women (ANOVA among groups *P* = 0.008; WE 32.1% *vs* WI 3.6%, *P* = 0.005; *vs* AICD 12.5%, *P* = 0.059). This WE group of female patients with abdominal pain as indication showed also a higher incidence of previous abdominal surgery (ANOVA among groups *P* = 0.031): WE 21.4% *vs* WI 3.6%, *P* = 0.043; *vs* AICD 4.2%, *P* = 0.069. The comparisons of WE *vs* AICD lacked enough power (type II error) to show significance.

Investigator number 10, with infrequent use of loop reduction or abdominal compression and short mean insertion time (Table 2), had high real-time maximum insertion pain scores in all groups, but the use of WE brought insertion pain down in this investigator: ANOVA among groups *P* = 0.004.

Secondary outcomes analysis

Compared with AICD and WI, WE had the highest proportion of patients with painless unsedated colonoscopy (Table 5): 13.5%, *vs* WI 7.7% (*P* = 0.013); *vs* AICD 6.0% (*P* < 0.0005). Compared with AICD, WE and WI showed a significantly higher proportion of unsedated colonoscopies with only discomfort, corresponding to NRS values of 1-2: WE 36.1%, *vs* WI 31.4% (*P* =

Table 5 Pain during insertion, patients' tolerance and sedation, *n* (%)

	WE (<i>n</i> = 371)	WI (<i>n</i> = 338)	AICD (<i>n</i> = 382)	<i>P</i> value
Painless unsedated colonoscopy ²	50 (13.5)	26 (7.7)	23 (6.0)	WE vs WI 0.013 ¹ WE vs AICD < 0.0005 ¹ WI vs AICD 0.374 ¹
Unsedated, completed with only discomfort ²	134 (36.1)	106 (31.4)	87 (22.8)	WE vs WI 0.180 ¹ WE vs AICD < 0.0005 ¹ WI vs AICD 0.009 ¹
Completed without sedation	321 (86.5)	287 (84.9)	292 (76.4)	WE vs WI 0.537 ¹ WE vs AICD < 0.0005 ¹ WI vs AICD 0.004 ¹
On-demand sedation	50 (13.5)	51 (15.1)	90 (23.6)	WE vs WI 0.537 ¹ WE vs AICD < 0.0005 ¹ WI vs AICD 0.004 ¹

¹χ²; ²Pain score based on numeric rating scale (NRS): 0 = absence of pain, 1-2 = discomfort, 10 = maximum pain. *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO₂ for withdrawal; WI: Water immersion for insertion, insufflation with air or CO₂ for withdrawal; AICD: Insufflation with air or CO₂ for insertion and withdrawal; SD: Standard deviation.

0.180); vs AICD 22.8% ($P < 0.0005$); WI vs AICD $P = 0.009$ (Table 5). WE and WI achieved also a significantly higher proportion of procedures completed without sedation: WE 86.5%, vs WI 84.9% ($P = 0.537$); vs AICD 76.4% ($P < 0.0005$); WI vs AICD $P = 0.004$ (Table 5). Accordingly, WE and WI showed low proportions of patients requesting on-demand sedation: WE 13.5%, vs WI 15.1% ($P = 0.537$); vs AICD 23.6% ($P < 0.0005$); WI vs AICD $P = 0.004$ (Table 5).

Procedural outcomes

Cecal intubation rates (WE 98.7%, WI 97.9% and AICD 97.9%; $P = 0.692$) and total procedure times [minutes (\pm standard deviation, SD): WE 23 (9.7), WI 22 (11.7) and AICD 22 (11.0), $P = 0.177$] were comparable. A complete report has already been presented elsewhere^[2,3]. Comparisons of amount of water infused and aspirated during insertion and during withdrawal attested to the correct application of WE and WI methods^[2,3].

DISCUSSION

In this study aggregate data confirm superiority of WE in lowering insertion pain compared with WI and AICD. The pain alleviating impact of water exchange shows the lowest mean real-time maximum insertion pain scores in 90% of the investigators, despite their pain scores were significantly different within the WE, WI and AICD groups, and regardless their significantly different individual performances in terms of use of adjunct maneuvers and insertion time (Table 2). A plausible explanation of the effect of WE in decreasing real-time maximum insertion pain is the avoidance of the variable elongation of the colon induced by different amounts of insufflated gas, with the associated loop formation^[9] that leads to insertion pain^[10]. Full understanding, however, will require additional investigation.

Previous abdominal surgery is associated with higher colonoscopy pain score^[11-14] or with difficult procedures^[15]. The AICD group showed the lowest

proportion of patients with previous abdominal surgery and had comparable BMI values among individual investigators; nevertheless, AICD pain scores were almost invariably higher than the other two groups (Table 2). Compared with WE, WI had a lower proportion of patients with previous abdominal surgery; and yet also WI showed a trend toward higher pain scores than WE (Table 2).

With the exception of Investigator number 8, the consistent pattern of pain scores being lowest in the WE group qualifies WE as the best method for achieving low pain scores during the insertion phase of colonoscopy, with a reproducible effect among different colonoscopists. Several factors contributed to the aberrant finding of Investigator's number 8 higher real-time maximum insertion pain score in the WE group compared with the WI and AICD groups: His WE group had a significantly higher proportion of female patients with abdominal pain as indication (this cohort comprised IBS cases) and with previous abdominal surgery. All these are risk factors for difficult^[15] or painful colonoscopy^[1,11-14,16-22], with expected laborious intubation and increased need for sedation^[11,22,23].

Moreover, Investigator number 8 had experience in only 150 WE and 90 WI procedures. WE is a relatively new technique, and requires new maneuvers not entirely intuitive to colonoscopists. Collectively, all these factors contributed to the higher real-time maximum insertion pain score achieved in his WE group of patients.

Our data show that WE is effective in achieving significantly higher proportions of painless unsedated procedures, completion with only minor discomfort or without sedation. These two last outcomes are also achieved by WI.

Unsedated colonoscopy represents an important option for many patients^[24,25] and has important implications in terms of patient satisfaction, medical related complications^[26,27] and cost savings in health care systems, particularly in settings where the use of sedation is discretionary and targeted also to low-risk patients^[28,29].

The scheduled unsedated option may also have an impact on no-show due to lack of an escort, improving patients' adherence to colonoscopy, particularly important in screening settings^[30].

Promotion of on-demand sedation colonoscopy and successful completion of the unsedated option minimizes institutional resources and lessens patients' burdens^[6,31].

Multiple published reports have indicated colonoscopists around the world were able to harness the pain reduction impact of WE^[2,3,7,8,32-40].

The limitations of our study require comment. The endoscopists and the nurse assistants were not blinded to the WE and WI insertion techniques. However, interactions with patients were standardized, colonoscopists' bias was minimized and pain recording was very accurate^[2,3]. The unblinded real-time maximum insertion pain scores obtained during colonoscopy were internally validated by correlating them with the blinded recalled maximum insertion pain scores recorded at discharge: the Pearson correlation range was 0.6-0.9 ($P < 0.0005$)^[2,3]. The blinded pain recording after the procedure validated the unblinded one collected during the examination^[2,3]. Mean correct patients' guesses about insertion method used (36%) and investigators' about insufflated gas (41%) confirmed their adequate blinding^[2,3].

Our study has certain notable features. To the best of our knowledge, it has the largest sample of multiple individual investigators' real-time maximum insertion pain scores obtained in a head-to-head randomized controlled comparison of WE, WI and AICD. Patients were recruited from a routine clinical setting in different community hospitals at multinational sites. The important finding is the reproducibility and repeatability of WE in attenuation of maximum insertion pain when compared with WI and AICD.

In summary, in this head-to-head randomized controlled comparison of WE, WI and AICD with reliable real-time maximum insertion pain scores, minimization of investigators' bias and adequate patient blinding, despite variations in pain scores by individual investigators, WE is superior to WI and AICD in attenuating real-time maximum insertion pain.

We conclude that the high proportion of colonoscopists able to use WE to decrease insertion pain in the current study, as well as in previous published reports, suggest that the technique deserves consideration in a broader scale.

COMMENTS

Background

Water exchange (WE) and water immersion (WI) are two colonoscopy techniques that entail infusion of water to distend the lumen during the insertion phase. WE is characterized by airless introduction to the cecum, infused water is aspirated predominantly during this phase to clear the view and minimize distension. In WI water is infused as an adjunct to insufflation and aspirated predominantly during withdrawal, without attempting to maximize colon cleanliness during insertion. Randomized controlled trials (RCTs) have shown WE to have considerable advantage in decreasing colonoscopy real-time maximum insertion pain when compared with WI or with air or carbon

dioxide insufflation. WE shows its beneficial effect in decreasing colonoscopy pain also in patients presenting with factors associated with difficult and painful colonoscopy (e.g., prior abdominal surgery, low body mass index).

Research frontiers

The authors assessed the performance of individual investigators in three recently completed RCTs in a multinational setting, to determine whether the effect of WE in reducing real-time maximum insertion pain is reproducible across investigators, and what procedural factors (e.g., use of adjunct maneuvers of loop reduction and abdominal compression, insertion time, etc.) might contribute to variations among them.

Innovations and breakthroughs

The study has the largest sample of multiple individual investigators' real-time maximum insertion pain scores obtained in a head-to-head randomized controlled comparison of WE, WI and air or carbon dioxide (AICD). Patients were recruited from a routine clinical setting in different community hospitals at multinational sites. The data confirm superiority of WE in lowering insertion pain compared with WI and AICD. Its pain alleviating impact shows the lowest mean real-time maximum insertion pain scores in 90% of the investigators, despite their significantly different insertion pain scores within the WE, WI and AICD groups, along with significantly different individual performances in terms of use of adjunct maneuvers and insertion time.

Applications

WE achieves higher proportions of painless unsedated procedures, or completed with only minor discomfort, decreasing the need for sedation. Promotion of on-demand sedation colonoscopy and successful completion of the unsedated procedures lessens patient's burdens.

Terminology

WE: A colonoscopy insertion technique that entails airless insertion; water is infused to facilitate progression of the instrument to the cecum and is aspirated predominantly during this phase to clear the view and minimize distension. WI: A colonoscopy insertion technique that entails infusion of water as an adjunct to insufflation to help reaching the cecum; water is aspirated predominantly during withdrawal, without attempting to maximize colon cleanliness during insertion.

Peer-review

The article described the difference in colonoscopy real-time maximum insertion pain among WE, WI and AICD and among individual investigators in routine clinical settings. It is useful to analyze colonoscopy pain produced by different techniques in order to reduce the suffering of patients. It is a meaningful research in clinical practice. The study had a logical design in methods, the analysis of the difference of pain among WE, WI and AICD was detailed and produced credible results.

REFERENCES

- 1 Hsieh YH, Koo M, Leung FW. A patient-blinded randomized, controlled trial comparing air insufflation, water immersion, and water exchange during minimally sedated colonoscopy. *Am J Gastroenterol* 2014; **109**: 1390-1400 [PMID: 24890443 DOI: 10.1038/ajg.2014.126]
- 2 Cadoni S, Sanna S, Gallittu P, Argiolas M, Fanari V, Porcedda ML, Erriu M, Leung FW. A randomized, controlled trial comparing real-time insertion pain during colonoscopy confirmed water exchange to be superior to water immersion in enhancing patient comfort. *Gastrointest Endosc* 2015; **81**: 557-566 [PMID: 25262100 DOI: 10.1016/j.gie.2014.07.029]
- 3 Cadoni S, Falt P, Gallittu P, Liggi M, Mura D, Smajstrla V, Erriu M, Leung FW. Water Exchange Is the Least Painful Colonoscope Insertion Technique and Increases Completion of Unsedated Colonoscopy. *Clin Gastroenterol Hepatol* 2015; **13**: 1972-1980.e3 [PMID: 25956838 DOI: 10.1016/j.cgh.2015.04.178]
- 4 Garborg K, Kaminski MF, Lindner W, Wiig H, Hasund A, Wronska E, Bie RB, Kleist B, Løvdaal L, Holme Ø, Kalager

- M, Hoff G, Bretthauer M. Water exchange versus carbon dioxide insufflation in unsedated colonoscopy: a multicenter randomized controlled trial. *Endoscopy* 2015; **47**: 192-199 [PMID: 25412093 DOI: 10.1055/s-0034-1390795]
- 5 **Leung FW**. Water-aided colonoscopy. *Gastroenterol Clin North Am* 2013; **42**: 507-519 [PMID: 23931857 DOI: 10.1016/j.gtc.2013.05.006]
 - 6 **Cadoni S**, Sanna S, Gallittu P, Argiolas M, Fanari V, Porcedda ML, Erriu M, Leung FW. Water exchange minimizes magnitude and variations in maximum insertion pain among colonoscopists (and potentially enhances cost savings by promoting completion of unsedated colonoscopy). *J Interv Gastroenterol* 2014; **4**: 56-62 [DOI: 10.7178/jig.157]
 - 7 **Leung FW**, Mann SK, Leung JW, Siao-Salera RM, Jackson G. The water method is effective in difficult colonoscopy - it enhances cecal intubation in unsedated patients with a history of abdominal surgery. *J Interv Gastroenterol* 2011; **1**: 172-176 [PMID: 22586531]
 - 8 **Luo H**, Zhang L, Liu X, Leung FW, Liu Z, Wang X, Xue L, Wu K, Fan D, Pan Y, Guo X. Water exchange enhanced cecal intubation in potentially difficult colonoscopy. Unsedated patients with prior abdominal or pelvic surgery: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2013; **77**: 767-773 [PMID: 23394837 DOI: 10.1016/j.gie.2012.12.007]
 - 9 **Leung JW**, Vakulchik VM, Liu J, Pearcy J, Yen AW, Leung FW. Water aided colonoscopy without air insufflation - a comparison of suction removal of infused water during withdrawal versus during insertion. *J Interv Gastroenterol* 2014; **4**: 63-67 [DOI: 10.7178/jig.158]
 - 10 **Shah SG**, Brooker JC, Thapar C, Williams CB, Saunders BP. Patient pain during colonoscopy: an analysis using real-time magnetic endoscopy imaging. *Endoscopy* 2002; **34**: 435-440 [PMID: 12048623]
 - 11 **Holme O**, Bretthauer M, de Lange T, Seip B, Huppertz-Hauss G, Høie O, Sandvei P, Ystrøm CM, Hoff G. Risk stratification to predict pain during unsedated colonoscopy: results of a multicenter cohort study. *Endoscopy* 2013; **45**: 691-696 [PMID: 23884794 DOI: 10.1055/s-0033-1344239]
 - 12 **Oh SY**, Sohn CI, Sung IK, Park DI, Kang MS, Yoo TW, Park JH, Kim HJ, Cho YK, Jeon WK, Kim BI. Factors affecting the technical difficulty of colonoscopy. *Hepatogastroenterology* 2007; **54**: 1403-1406 [PMID: 17708264]
 - 13 **Park DI**, Kim HJ, Park JH, Cho YK, Sohn CI, Jeon WK, Kim BI, Ryu SH, Sung IK. Factors affecting abdominal pain during colonoscopy. *Eur J Gastroenterol Hepatol* 2007; **19**: 695-699 [PMID: 17625440]
 - 14 **Jang HW**, Cheon JH, Nam CM, Moon CM, Lee JH, Jeon SM, Park JJ, Kim TI, Kim WH. Factors affecting insertion time for colonoscopy performed under intramuscular analgesia in patients with history of colorectal resection. *Surg Endosc* 2011; **25**: 2316-2322 [PMID: 21298530 DOI: 10.1007/s00464-010-1555-3]
 - 15 **Shah HA**, Paszat LF, Saskin R, Stukel TA, Rabeneck L. Factors associated with incomplete colonoscopy: a population-based study. *Gastroenterology* 2007; **132**: 2297-2303 [PMID: 17570204]
 - 16 **Elphick DA**, Donnelly MT, Smith KS, Riley SA. Factors associated with abdominal discomfort during colonoscopy: a prospective analysis. *Eur J Gastroenterol Hepatol* 2009; **21**: 1076-1082 [PMID: 19339891 DOI: 10.1097/MEG.0b013e32832357b3]
 - 17 **Kim ES**, Cheon JH, Park JJ, Moon CM, Hong SP, Kim TI, Kim WH. Colonoscopy as an adjunctive method for the diagnosis of irritable bowel syndrome: focus on pain perception. *J Gastroenterol Hepatol* 2010; **25**: 1232-1238 [PMID: 20594249 DOI: 10.1111/j.1440-1746.2010.06338.x]
 - 18 **Imai A**, Kato M, Ono S, Shimizu Y, Takeda H, Asaka M. Efficacy of carbon dioxide-insufflating colonoscopy in patients with irritable bowel syndrome: a randomized double-blind study. *J Gastroenterol Hepatol* 2012; **27**: 1623-1628 [PMID: 22694488 DOI: 10.1111/j.1440-1746.2012.07208.x]
 - 19 **Denters MJ**, Schreuder M, Depla AC, Mallant-Hent RC, van Kouwen MC, Deutekom M, Bossuyt PM, Fockens P, Dekker E. Patients' perception of colonoscopy: patients with inflammatory bowel disease and irritable bowel syndrome experience the largest burden. *Eur J Gastroenterol Hepatol* 2013; **25**: 964-972 [PMID: 23660935 DOI: 10.1097/MEG.0b013e328361dcd3]
 - 20 **Takahashi Y**, Tanaka H, Kinjo M, Sakumoto K. Prospective evaluation of factors predicting difficulty and pain during sedation-free colonoscopy. *Dis Colon Rectum* 2005; **48**: 1295-1300 [PMID: 15793639]
 - 21 **Paggi S**, Radaelli F, Amato A, Meucci G, Spinzi G, Rondonotti E, Terruzzi V. Unsedated colonoscopy: an option for some but not for all. *Gastrointest Endosc* 2012; **75**: 392-398 [PMID: 22248607 DOI: 10.1016/j.gie.2011.09.015]
 - 22 **Saunders BP**, Fukumoto M, Halligan S, Jobling C, Moussa ME, Bartram CI, Williams CB. Why is colonoscopy more difficult in women? *Gastrointest Endosc* 1996; **43**: 124-126 [PMID: 8635705]
 - 23 **Pohl J**, Messer I, Behrens A, Kaiser G, Mayer G, Ell C. Water infusion for cecal intubation increases patient tolerance, but does not improve intubation of unsedated colonoscopies. *Clin Gastroenterol Hepatol* 2011; **9**: 1039-1043.e1 [PMID: 21749850 DOI: 10.1016/j.cgh.2011.06.031]
 - 24 **Petrini JL**, Egan JV, Hahn WV. Unsedated colonoscopy: patient characteristics and satisfaction in a community-based endoscopy unit. *Gastrointest Endosc* 2009; **69**: 567-572 [PMID: 19231501 DOI: 10.1016/j.gie.2008.10.027]
 - 25 **Leung J**, Mann S, Siao-Salera R, Ransibrahmanakul K, Lim B, Canete W, Samson L, Gutierrez R, Leung FW. A randomized, controlled trial to confirm the beneficial effects of the water method on U.S. veterans undergoing colonoscopy with the option of on-demand sedation. *Gastrointest Endosc* 2011; **73**: 103-110 [PMID: 21184876 DOI: 10.1016/j.gie.2010.09.020]
 - 26 **Sharma VK**, Nguyen CC, Crowell MD, Lieberman DA, de Garmo P, Fleischer DE. A national study of cardiopulmonary unplanned events after GI endoscopy. *Gastrointest Endosc* 2007; **66**: 27-34 [PMID: 17591470]
 - 27 **Ko CW**, Riffle S, Michaels L, Morris C, Holub J, Shapiro JA, Ciol MA, Kimmey MB, Seeff LC, Lieberman D. Serious complications within 30 days of screening and surveillance colonoscopy are uncommon. *Clin Gastroenterol Hepatol* 2010; **8**: 166-173 [PMID: 19850154 DOI: 10.1016/j.cgh.2009.10.007]
 - 28 **Liu H**, Waxman DA, Main R, Matke S. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. *JAMA* 2012; **307**: 1178-1184 [PMID: 22436958 DOI: 10.1001/jama.2012.270]
 - 29 **Al-Awabdy B**, Wilcox CM. Use of anesthesia on the rise in gastrointestinal endoscopy. *World J Gastrointest Endosc* 2013; **5**: 1-5 [PMID: 23330047 DOI: 10.4253/wjge.v5.i1.1]
 - 30 **Leung FW**, Cohen H, Dea SK, Jensen DM, Kovacs TO, Lam E, Ohning GV, Pisegna JR, Russell MM, Sedarat A, Sheinbaum A, Simmons TC, Slomovic R, Spiegel BM, Spirt MJ, Sul J, Watson RR. Scheduled unsedated colonoscopy - a novel tool for managing no shows due to lack of escorts required for conscious sedation. *J Interv Gastroenterol* 2014; **4**: 91-92 [DOI: 10.7178/jig.160]
 - 31 **Granados-Savatgy L**, Bradham DD, Blohm L, Siao-Salera R, Leung JW, Leung FW. Cost benefit analysis and cost estimating: sedated vs. unsedated colonoscopy at one VAMC. *American Journal Clinical Medicine* 2010; **7**: 147-150
 - 32 **Leung FW**, Harker JO, Jackson G, Okamoto KE, Behbahani OM, Jamgotchian NJ, Aharonian HS, Guth PH, Mann SK, Leung JW. A proof-of-principle, prospective, randomized, controlled trial demonstrating improved outcomes in scheduled unsedated colonoscopy by the water method. *Gastrointest Endosc* 2010; **72**: 693-700 [PMID: 20619405 DOI: 10.1016/j.gie.2010.05.020]
 - 33 **Ransibrahmanakul K**, Leung JW, Mann SK, Siao-Salera R, Lim BS, Hasyagar C, Yen D, Nastaskin I, Leung FW. Comparative effectiveness of water vs. air methods in minimal sedation colonoscopy performed by supervised trainees in the US - Randomized Controlled Trial. *American Journal Clinical Medicine* 2010; **7**: 113-118
 - 34 **Ramirez FC**, Leung FW. A head-to-head comparison of the water vs. air method in patients undergoing screening colonoscopy. *J Interv Gastroenterol* 2011; **1**: 130-135 [PMID: 22163084 DOI: 10.4161/jig.1.3.18512]

- 35 **Portocarrero DJ**, Che K, Olafsson S, Walter MH, Jackson CS, Leung FW, Malamud A. A pilot study to assess feasibility of the water method to aid colonoscope insertion in community settings in the United States. *J Interv Gastroenterol* 2012; **2**: 20-22 [PMID: 22586546 DOI: 10.4161/jig.20130]
- 36 **Leung FW**, Cheung R, Fan RS, Fischer LS, Friedland S, Ho SB, Hsieh YH, Hung I, Li MK, Matsui S, Mcquaid KR, Ohning G, Ojuri A, Sato T, Shergill AK, Shoham MA, Simons TC, Walter MH, Yen A. The water exchange method for colonoscopy-effect of coaching. *J Interv Gastroenterol* 2012; **2**: 122-125 [PMID: 23805391 DOI: 10.4161/jig.23732]
- 37 **Fischer LS**, Lumsden A, Leung FW. Water exchange method for colonoscopy: learning curve of an experienced colonoscopist in a U.S. community practice setting. *J Interv Gastroenterol* 2012; **2**: 128-132 [PMID: 23805393 DOI: 10.4161/jig.23734]
- 38 **Leung JW**, Mann SK, Siao-Salera R, Canete W, Leung FW. The established and time-tested water exchange method in scheduled unsedated colonoscopy significantly enhanced patient-centered outcomes without prolonging procedural times - A randomized controlled trial. *J Interv Gastroenterol* 2013; **3**: 7-11 [DOI: 10.7178/jig.100]
- 39 **Bak AW**, Perini RF, Schroeder T, Leung FW. Experience with water-aided colonoscopy in a Canadian community population. *J Interv Gastroenterol* 2013; **3**: 49-52 [DOI: 10.7178/jig.122]
- 40 **Cadoni S**, Gallittu P, Sanna S, Fanari V, Porcedda ML, Erriu M, Leung FW. A two-center randomized controlled trial of water-aided colonoscopy versus air insufflation colonoscopy. *Endoscopy* 2014; **46**: 212-218 [PMID: 24218307 DOI: 10.1055/s-0033-1353604]

P- Reviewer: Hu H, Wei SC **S- Editor:** Qiu S **L- Editor:** A
E- Editor: Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 February 10; 8(3): 122-197





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Izuru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciaccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Rajiman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

Contents

Biweekly Volume 8 Number 3 February 10, 2016

TOPIC HIGHLIGHT

- 122 Use of water jet instruments in gastrointestinal endoscopy
Nakano T, Sato C, Sakurai T, Kamei T, Nakagawa A, Ohuchi N

REVIEW

- 128 Diagnostic and therapeutic biomarkers in pancreaticobiliary malignancy
Viterbo D, Gausman V, Gonda T
- 143 Biliary and pancreatic stenting: Devices and insertion techniques in therapeutic endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography
Mangiavillano B, Pagano N, Baron TH, Arena M, Iabichino G, Consolo P, Opocher E, Luigiano C

MINIREVIEWS

- 157 Review of current and evolving clinical indications for endoscopic ultrasound
Luthra AK, Evans JA
- 165 Treatment of gastric outlet obstruction that results from unresectable gastric cancer: Current evidence
Miyazaki Y, Takiguchi S, Takahashi T, Kurokawa Y, Makino T, Yamasaki M, Nakajima K, Mori M, Doki Y
- 173 Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection
Kim SJ, Choi CW, Kang DH, Kim HW, Park SB

ORIGINAL ARTICLE

Retrospective Cohort Study

- 180 Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis
Ito T, Sai JK, Okubo H, Saito H, Ishii S, Kanazawa R, Tomishima K, Watanabe S, Shiina S

Retrospective Study

- 186 Percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy: First clinical series
Imaeda H, Nakajima K, Hosoe N, Nakahara M, Zushi S, Kato M, Kashiwagi K, Matsumoto Y, Kimura K, Nakamura R, Wada N, Tsujii M, Yahagi N, Hibi T, Kanai T, Takehara T, Ogata H

CASE REPORT

- 192 Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review
Armellini E, Crinò SF, Ballarè M, Pallio S, Occhipinti P

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 3 February 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*,
Dimitrios Kapetanios, FEBG, PhD, Doctor, Gastroenterology Department, George
Papanikolaou Hospital, 55236 Thessaloniki, Greece

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
February 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

2016 Gastrointestinal Endoscopy: Global view

Use of water jet instruments in gastrointestinal endoscopy

Toru Nakano, Chiaki Sato, Tadashi Sakurai, Takashi Kamei, Atsuhiro Nakagawa, Noriaki Ohuchi

Toru Nakano, Chiaki Sato, Tadashi Sakurai, Takashi Kamei, Noriaki Ohuchi, Division of Advanced Surgical Science and Technology, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan

Atsuhiro Nakagawa, Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan

Author contributions: Nakano T performed the majority of the writing, prepared the figures; Sato C and Nakagawa A prepared the figures; Sakurai T, Kamei T and Ohuchi N coordinated the writing of the paper and reviewed the manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Toru Nakano, MD, PhD, Division of Advanced Surgical Science and Technology, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. torun@med.tohoku.ac.jp
Telephone: +81-22-7177214
Fax: +81-22-7177217

Received: April 28, 2015

Peer-review started: May 7, 2015

First decision: September 8, 2015

Revised: November 9, 2015

Accepted: December 1, 2015

Article in press: December 2, 2015

Published online: February 10, 2016

Abstract

In recent years, water jet instruments have been used

in the field of gastrointestinal endoscopy, mainly in two clinical situations: Investigation and treatment under endoscopic view. Injecting water jet into the gastrointestinal lumen is helpful for maintaining a clear endoscopic view, washing away blood or mucous in the lumen or on the surface of the tip of the endoscope. This contributes to reducing time and discomfort of examination. Water jet technology is an alternative method for dissecting soft tissue; this method does not harm the small vessels or cause mechanical or thermal damage. However, its use in clinical settings has been limited to the transmucosal injection of water into the submucosal layer that elevates the mucosa to prepare for endoscopic mucosal resection or endoscopic submucosal dissection, instead of tissue dissection, which may occur because of the continuous water jet. A preclinical study has been conducted using a pulsed water jet system as an alternative method for submucosal dissection by reducing intraoperative water consumption and maintenance of dissection capability. This review introduces recent studies pertaining to using a water jet in gastrointestinal endoscopy and discusses future prospects.

Key words: Endoscopy; Water jet; Endoscopic submucosal dissection; Endoscopic mucosal resection; Pulse

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This review provides an overview of recent clinical and preclinical studies of water jet instruments in gastrointestinal endoscopy. Water jets have been used to keep the endoscopic view clear which contributed to reduce time and discomfort of endoscopic examination, and the technology provides an alternative method for endoscopic tumor resection. However, continuous flow is used in the transmucosal injection of water into the submucosal layer for elevating the mucosa to prepare for endoscopic mucosal resection. A preclinical study has used a pulsed water jet system as an alternative method to achieve dissection of submucosal layer.

Nakano T, Sato C, Sakurai T, Kamei T, Nakagawa A, Ohuchi N. Use of water jet instruments in gastrointestinal endoscopy. *World J Gastrointest Endosc* 2016; 8(3): 122-127 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/122.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.122>

INTRODUCTION

Incidences of colorectal cancer are increasing in the developed world; in comparison with other types of examinations such as the stool occult blood test, barium enema, and computed tomography colonography, colonoscopy enables enhanced diagnostic specificity and sensitivity^[1]. The incidence of gastric cancer remains high in Asian countries, including Japan. The demand for upper gastrointestinal endoscopy has been increasing annually, especially in Asian countries^[2]. It requires highly advanced techniques and a learning curve exists for digestive endoscopy^[1,2]. When the endoscope first appeared, it was a struggle to maintain a clear endoscopic view. The introduction of the forceps hole into the endoscope has been useful for injecting water vigorously into the gastrointestinal lumen to keep the endoscopic view clear. Endoscopes with incorporated water jet systems have been developed and released for clinical practice and are in widespread use. Water jets have also been recently used for endoscopic treatment, *i.e.*, in endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). This review provides an overview of recent clinical and preclinical studies of water jet instrument in gastrointestinal endoscopy.

WATER JETS FOR MAINTAINING ENDOSCOPIC VIEW

Water jet instruments were initially used to facilitate endoscopic observation. During gastrointestinal endoscopy, blood, food residue, and bubbles can impede the endoscopic view. Specifically in colonoscopy, colonic cleaning with polyethylene glycol method (PEG) helps with finding small lesions^[3]. However, PEG can result in a lot of bubbles forming, hindering observation as much as the feces^[4]. It is necessary to wash these out to discover the minute lesions or to treat under a clear endoscopic view. During gastroendoscopy, premedication with mucolytic agents, such as pronase, N-acetylcysteine, or dimethylpolysiloxane before upper gastrointestinal endoscopy improves the mucosal visibility of the stomach^[5,6]. It is still necessary to wash away the bubbles caused by saliva or mucus (Figure 1). Recently, upper gastrointestinal endoscopy using nasal endoscope has rapidly become popular, as it is less painful and causes minimum vomiting reflux^[7-10]. However, problems to be solved with this technique

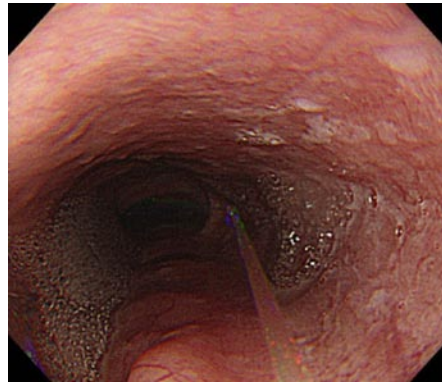


Figure 1 Endoscopic view of the esophagus shows that water jet flow washes away the bubbles caused by saliva or mucous in the esophagus.

include lower camera resolution, insufficient light intensity, and the longer duration of the procedure as compared with that of an oral endoscopy. Attempts to use fluids such as oolong tea to clean the lens surface have been reported^[11]. Manual water jet pumping prolongs inspection time^[12]; Takahashi *et al.*^[13] reported that the introduction of a water jet operated by a foot switch in the nasal gastrointestinal endoscopy reduced the average inspection time from 561 ± 123 s to 503 ± 98 s ($P = 0.0002$). Using a water jet to maintain a clear endoscopic view is useful for reducing time and the discomfort of examination. A water jet from an automatic lavage pump is useful to keep endoscopic view clear^[14]. This is currently supplied in products from several companies. Some models of upper gastrointestinal and colonic endoscope have separate water supply and forceps holes, which make it possible to inject water during endoscopic treatment such as hemostasis, EMR, or ESD (Figure 2). Hemostatic procedure is one of the important techniques during endoscopic treatment like EMR or ESD. So water jet systems are widely used to find the bleeding point and to make a view during hemostasis.

WATER JETS AS OPERATIVE INSTRUMENTS

Water jet technology was used in liver^[15] and cardiovascular^[16] surgeries, as well as in neurosurgery in the late 1980s^[17]. When used in liver surgery, this system reduces blood loss and parenchymal trauma better than both ultrasonic aspiration and blunt dissection^[18,19]. Using the water jet instrument as a surgical device provides energy using the kinetic energy of the water flowing from a nozzle at the tip of the delivery device. This energy is transmitted to the tissue surface where it ejects particles of tissue, making an incision through the organ or tissue. Mass reduction can also be achieved using water jets^[15,20]. Water jet has several features pertaining to dissection that are superior to conventional instruments, including selective tissue removal with vessel pre-

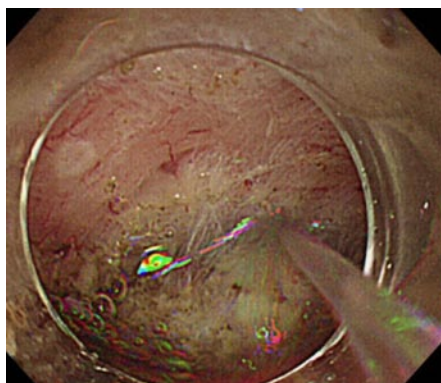


Figure 2 A water jet is useful to keep endoscopic view clear. Hemostatic procedure is one of the important techniques during endoscopic treatment like endoscopic mucosal resection or endoscopic submucosal dissection. So water jet systems are widely used to find the bleeding point and to make a view clean.

servation based on the different tensile strengths of the tissues. Water jet devices using a continuous water flow^[20] allow organ dissection while preserving vessels that are > 100-200 μm in diameter^[21,22]. Another notable advantage is that it helps avoid thermal damage to the surrounding parenchyma, which would otherwise be inevitable using an electric scalpel, electromagnetic, ultrasonic, and laser instruments^[23,24]. However, limitations have been reported to arise from the formation of air bubbles, which obscure the operative field, and the splashing of blood fluid, which could subject surgeons and nurses to cross infection^[16]. These limitations may be resolved when using the instrument in a luminal organ such as the gastrointestinal tract or in laparoscopic or thoracoscopic surgery. In addition, the development of a treatment instrument with lower water consumption would help address the limitations. Endoscopic treatment such as ESD in a narrow surgical field requires the application of highly advanced techniques by the operator. A lack of instruments that can aid this procedure preventing the risk of potential complications (thermal injury and vascular damage) is a drawback of the current ESD technique using an electric scalpel^[25]. Water jet technology, which is based on a conventional, pressure-driven continuous jet^[15,26] or a laser/electrically-induced pulsed pressure jet^[27-29], could provide an alternative method or novel procedure for the dissection of soft tissue without impairing small-diameter vessels or causing mechanical or thermal damage during endoscopic therapy.

WATER JET INSTRUMENTS FOR ENDOSCOPIC THERAPY FOR TUMOR RESECTION

Endoscopic resection has become the standard of care for the treatment of early stage gastrointestinal tumors. EMR is performed on relatively small lesions. ESD enables the resection of large lesions in a single piece, and has low local recurrence rates^[30,31]; how-

ever, operation time and the risk of complications are increased^[31,32]. Various knives such as the dual knife (Olympus Medical Systems Co., Tokyo, Japan), B-knife (Zeon Medical, Tokyo, Japan), IT-knife, or Hook knife (Olympus Medical Systems Co., Tokyo, Japan) are used in ESD^[33,34]; these are devised for safety and ease of use. As a preparation for safe EMR or ESD, it is useful either to inject fluids such as saline or hyaluronate or inject carbon dioxide into the submucosal layer to lift the lesion from the muscular layer^[35,36]. Various water jet dissectors have been developed, such as the Flush knife (Fujifilm Medical, Tokyo, Japan), Splash needle (Pentax Co., Tokyo, Japan), HybridKnife (ERBE, Tübingen, Germany), and the ENKI-2 water-jet system (NESTIS, Lyon, France)^[37-40]; these use continuous water flow to incise mucosa and inject fluid into the submucosal layer to lift the lesion. In contrast, the applying conventional pressure-driven continuous water jets endoscopically is limited to transmucosal injection of water into the submucosal layer for mucosal elevation prepare for EMR instead of tissue dissection^[40,41]. This may be because of the continuous water jet. An advantage of these water jet devices is that washing of the surgical field or additional submucosal injection can be performed by flushing water through the knife without changing the instrument; this results in marked improvements pertaining to the efficiency and safety of the procedure^[42]. Incision capability of these devices would be mostly due to the cooperation of water jet and electric cautery. Although Lesser *et al.*^[43] attempted to use a water jet dissector to cut polyp stalks clinically in the airway; the attempt to cut or dissect a submucosal layer under gastrointestinal endoscopy has been performed only in preclinical animal experiments. A continuous water jet flow of 30 kgf/cm² (Angiomat 3000, Liebel-Flarsheim, United States) was necessary to cut mucosa and mucosal muscle; however, injection fluid was spread in the submucosal layer in the swine stomach^[44]. Kaehler *et al.*^[41] reported that a continuous water jet dissector, the Helix Hydro-Jet (ERBE), is capable of penetrating the mucosa and creating highly selective fluid accumulation in the submucosal layer, using a water pressure of 50-70 bar and an application angle of 20°-90°^[41]. Lepilliez *et al.*^[45] reported a porcine gastric ESD where continuous jet dissection using a WJ medical system (Eschmann Equipment, West Sussex, England) *in vivo* was technically difficult due to the lack of visual control. Using continuous water jet also poses a potential risk of obscuring the narrow endoscopic operative view due to the large amounts of water. To date, there has been no report of continuous water flow being used to dissect the submucosal layer effectively. It has been reported that a pulsed water jet was feasible at 120 mL/min of water supply, but pulsed dissection was slower than IT knife dissection in the porcine stomach^[45]. That volume of water would interfere with the endoscope view in a narrow lumen such as the esophagus or large intestine. On the other hand, Sato *et al.*^[46] reported that laser-induced pulsed water jet dissection in the

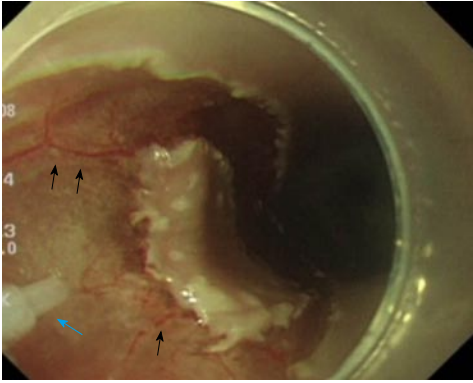


Figure 3 Preserved vessels using by pulsed water jet, which could be treated with pin-point ablation by hemostatic equipment would contribute to reliable hemostasis. Black arrows show small vessels preserved by the laser induced pulsed water jet. A blue arrow shows a nozzle of pulsed jet system.

porcine esophagus was performed safely and effectively, and the dissection rate was not different from hook knife dissection. Preservation of the vessels by water jet, which could be treated with pin-point ablation by hemostatic equipment would contribute to reliable hemostasis (Figure 3). They reported the feasibility of ESD of the esophagus with very small amounts of water (1.6 mL/min) and preserved micro-vessels. The optimal conditions for submucosal dissection are still unclear for both continuous and pulsed water jets, including the best size or shape of the nozzle, water pressure of the jet, pulse rate or volume of water supply. Since the required condition of the jet also depends on the physical properties of the tissue to be dissected^[47], the conditions may vary between the esophagus, stomach, and large intestine. Further study is needed to elucidate the optimal conditions for dissection by water jet.

CONCLUSION

In gastrointestinal endoscopy, using a water jet to maintain a clear endoscopic view is useful for reducing time and the discomfort of examination; furthermore, water jets contribute to endoscopic therapy such as ESD or EMR. Using the water jet as an operative instrument is a recent development. A continuous water jet is used to lift up the mucous layer to pretreat EMR or ESD. Hybrid products combining water jet and electric scalpel have also been developed, and their results reported. It may be difficult to dissect the submucosal layer directly using continuous flow due to its nature, but use of a pulsed water jet is feasible, with a lower volume of water consumption. Although the research reported is mostly based on animal studies limited, further research is expected in the future.

REFERENCES

- 1 Lee SH, Park YK, Lee DJ, Kim KM. Colonoscopy procedural skills and training for new beginners. *World J Gastroenterol* 2014; **20**:

- 16984-16995 [PMID: 25493011 DOI: 10.3748/wjg.v20.i45.16984]
- 2 Lee SH, Park YK, Cho SM, Kang JK, Lee DJ. Technical skills and training of upper gastrointestinal endoscopy for new beginners. *World J Gastroenterol* 2015; **21**: 759-785 [PMID: 25624710 DOI: 10.3748/wjg.v21.i3.759]
- 3 Davis GR, Santa Ana CA, Morawski SG, Fordtran JS. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. *Gastroenterology* 1980; **78**: 991-995 [PMID: 7380204]
- 4 Nagatani K, Mitsushima T, Yokouchi K, Nakamoto K, Abe Y, Arima N, Yokota T, Minamihara Y, Ikuma H, Tsuda S, Ohashi S. Evaluation of Colonic Lavage For The Screening Total Colonoscopy [in Japanese]. *Gastroenterological Endoscopy* 1989; **31**: 856-865 [DOI: 10.11280/gee1973b.31.856]
- 5 Bhandari P, Green S, Hamanaka H, Nakajima T, Matsuda T, Saito Y, Oda I, Gotoda T. Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: a prospective, randomized, controlled, blinded trial. *Scand J Gastroenterol* 2010; **45**: 357-361 [PMID: 20148732 DOI: 10.3109/00365520903483643]
- 6 Chang CC, Chen SH, Lin CP, Hsieh CR, Lou HY, Suk FM, Pan S, Wu MS, Chen JN, Chen YF. Premedication with pronase or N-acetylcysteine improves visibility during gastroendoscopy: an endoscopist-blinded, prospective, randomized study. *World J Gastroenterol* 2007; **13**: 444-447 [PMID: 17230616 DOI: 10.3748/wjg.v13.i3.444]
- 7 Campo R, Montserrat A, Brullet E. Transnasal gastroscopy compared to conventional gastroscopy: a randomized study of feasibility, safety, and tolerance. *Endoscopy* 1998; **30**: 448-452 [PMID: 9693891]
- 8 Christensen M, Achiam M, Trap R, Stöckel M, Rosenberg J, Schulze S. Transnasal gastroscopy. *Ugeskr Laeger* 2000; **162**: 3464-3467 [PMID: 10918831]
- 9 Dumortier J, Napoleon B, Hedelius F, Pellissier PE, Leprince E, Pujol B, Ponchon T. Unsedated transnasal EGD in daily practice: results with 1100 consecutive patients. *Gastrointest Endosc* 2003; **57**: 198-204 [PMID: 12556784 DOI: 10.1067/mge.2003.59]
- 10 Roy JF, Duforest D, Marek TA. Prospective comparison of nasal versus oral insertion of a thin video endoscope in healthy volunteers. *Endoscopy* 1996; **28**: 422-424 [PMID: 8858230]
- 11 Komazawa Y, Amano Y, Yuki M, Fukuhara H, Mishihiro T, Mishihiro T, Shizuku T, Kinoshita Y. Oolong tea is useful for lens cleansing in transnasal small-caliber esophagogastroduodenoscopy. *Endoscopy* 2010; **42**: 104-108 [PMID: 19967631 DOI: 10.1055/s-0029-1215380]
- 12 Abe K, Miyaoka M. Trial of Transnasal Esophagogastroduodenoscopy. *Digest Endosc* 2006; **18**: 212-217 [DOI: 10.1111/j.0915-5635.2006.00609.x]
- 13 Takahashi S, Nagata H, Kamata H, Takano T, Uchida J, Inada M, Asada M, Akabane A, Kon H, Wada R, Nagatani K, Shimamoto T, Mitsushima T. Usefulness of water jet cleaning for observation area transnasal upper gastrointestinal endoscopy: mechanize versus manual cleaning [in Japanese]. *Official Journal of Japan Society of Ningen Dock* 2012; **27**: 743-747 [DOI: 10.11320/ningendock.27.743]
- 14 Hosoi H, Sazaki N, Tokoi S, Endo S, Saito Y, Kajiura K, Yamanaka A, Fujiki K, Tamura K, Takashimizu I, Yamamoto N, Sasabe M, Nakamura R, Ohkusa T. An automatic lavage pump for cleaning colon on colonoscopy [in Japanese]. *Gastroenterological Endoscopy* 1992; **34**: 1101-1103 1099 [DOI: 10.11280/gee1973b.34.1101]
- 15 Papachristou DN, Barters R. Resection of the liver with a water jet. *Br J Surg* 1982; **69**: 93-94 [PMID: 7059775 DOI: 10.1002/bjs.1800690212]
- 16 Aroussi AA, Sami IM, Leguerrier A, Verhoye JP. The blower: a useful tool to complete thrombectomy of the mechanical prosthetic valve. *Ann Thorac Surg* 2006; **81**: 1911-1912 [PMID: 16631711 DOI: 10.1016/j.athoracsur.2005.02.070]
- 17 Terzis AJ, Nowak G, Rentzsch O, Arnold H, Diebold J, Baretton G. A new system for cutting brain tissue preserving vessels: water jet

- cutting. *Br J Neurosurg* 1989; **3**: 361-366 [PMID: 2789721]
- 18 **Izumi R**, Yabushita K, Shimizu K, Yagi M, Yamaguchi A, Konishi K, Nagakawa T, Miyazaki I. Hepatic resection using a water jet dissector. *Surg Today* 1993; **23**: 31-35 [PMID: 8384906]
- 19 **Rau HG**, Duessel AP, Wurzbacher S. The use of water-jet dissection in open and laparoscopic liver resection. *HPB (Oxford)* 2008; **10**: 275-280 [PMID: 18773110 DOI: 10.1080/13651820802167706]
- 20 **Oertel J**, Gaab MR, Knapp A, Essig H, Warzok R, Piek J. Water jet dissection in neurosurgery: experimental results in the porcine cadaveric brain. *Neurosurgery* 2003; **52**: 153-159; discussion 159 [PMID: 12493113 DOI: 10.1097/00006123-200301000-00020]
- 21 **Nakagawa A**, Hirano T, Jokura H, Uenohara H, Ohki T, Hashimoto T, Menezes V, Sato Y, Kusaka Y, Ohyama H, Saito T, Takayama K, Shirane R, Tominaga T. Pulsed holmium: yttrium-aluminum-garnet laser-induced liquid jet as a novel dissection device in neuroendoscopic surgery. *J Neurosurg* 2004; **101**: 145-150 [PMID: 15255265 DOI: 10.3171/jns.2004.101.1.0145]
- 22 **Ohki T**, Nakagawa A, Hirano T, Hashimoto T, Menezes V, Jokura H, Uenohara H, Sato Y, Saito T, Shirane R, Tominaga T, Takayama K. Experimental application of pulsed Ho: YAG laser-induced liquid jet as a novel rigid neuroendoscopic dissection device. *Lasers Surg Med* 2004; **34**: 227-234 [PMID: 1502249]
- 23 **Oertel J**, Gaab MR, Schiller T, Schroeder HW, Warzok R, Piek J. Towards waterjet dissection in neurosurgery: experimental in-vivo results with two different nozzle types. *Acta Neurochir (Wien)* 2004; **146**: 713-720 [PMID: 15197615]
- 24 **Schurr MO**, Wehrmann M, Kunert W, Melzer A, Lirici MM, Trapp R, Kanehira E, Buess G. Histologic effects of different technologies for dissection in endoscopic surgery: Nd: YAG laser, high frequency and water-jet. *Endosc Surg Allied Technol* 1994; **2**: 195-201 [PMID: 8000885]
- 25 **Oda I**, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, Bhandari P, Emura F, Saito D, Ono H. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005; **17**: 54-58 [DOI: 10.1111/j.1443-1661.2005.00459]
- 26 **Oertel J**, Gaab MR, Warzok R, Piek J. Waterjet dissection in the brain: review of the experimental and clinical data with special reference to meningioma surgery. *Neurosurg Rev* 2003; **26**: 168-174 [PMID: 12845544 DOI: 10.1007/s10143-002-0244-7]
- 27 **Hirano T**, Komatsu M, Saeki T, Uenohara H, Takahashi A, Takayama K, Yoshimoto T. Enhancement of fibrinolytics with a laser-induced liquid jet. *Lasers Surg Med* 2001; **29**: 360-368 [PMID: 11746114 DOI: 10.1002/lsm.1129]
- 28 **Miller JM**, Palanker DV, Vankov A, Marmor MF, Blumenkranz MS. Precision and safety of the pulsed electron avalanche knife in vitreoretinal surgery. *Arch Ophthalmol* 2003; **121**: 871-877 [PMID: 12796261 DOI: 10.1001/archophth.121.6.871]
- 29 **Ogawa Y**, Nakagawa A, Takayama K, Tominaga T. Pulsed laser-induced liquid jet for skull base tumor removal with vascular preservation through the transphenoidal approach: a clinical investigation. *Acta Neurochir (Wien)* 2011; **153**: 823-830 [PMID: 21229274]
- 30 **Hotta K**, Fujii T, Saito Y, Matsuda T. Local recurrence after endoscopic resection of colorectal tumors. *Int J Colorectal Dis* 2009; **24**: 225-230 [PMID: 18972121]
- 31 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
- 32 **Saito Y**, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2010; **72**: 1217-1225 [PMID: 21030017 DOI: 10.1016/j.gie.2010.08.004]
- 33 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002 DOI: 10.1016/S1542-3565(05)00291-0]
- 34 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973 [PMID: 17524403 DOI: 10.1016/j.gie.2007.02.053]
- 35 **Uraoka T**, Kawahara Y, Ohara N, Kato J, Hori K, Okada H, Yamamoto K. Carbon dioxide submucosal injection cushion: an innovative technique in endoscopic submucosal dissection. *Dig Endosc* 2011; **23**: 5-9 [PMID: 21198910 DOI: 10.1111/j.1443-1661.2010.01038.x]
- 36 **Yamamoto H**, Yube T, Isoda N, Sato Y, Sekine Y, Higashizawa T, Ido K, Kimura K, Kanai N. A novel method of endoscopic mucosal resection using sodium hyaluronate. *Gastrointest Endosc* 1999; **50**: 251-256 [PMID: 10425422 DOI: 10.1016/S0016-5107(99)70234-8]
- 37 **Ciocirlan M**, Pioche M, Lepilliez V, Gonon N, Roume R, Noel G, Pinset C, Ponchon T. The ENKI-2 water-jet system versus Dual Knife for endoscopic submucosal dissection of colorectal lesions: a randomized comparative animal study. *Endoscopy* 2014; **46**: 139-143 [DOI: 10.1055/s-0033-1344892]
- 38 **Fujishiro M**, Kodashima S, Goto O, Ono S, Muraki Y, Kakushima N, Omata M. Technical feasibility of endoscopic submucosal dissection of gastrointestinal epithelial neoplasms with a splash-needle. *Surg Laparosc Endosc Percutan Tech* 2008; **18**: 592-597 [PMID: 19098667 DOI: 10.1097/SLE.0b013e318187973f]
- 39 **Toyonaga T**, Man-I M, Morita Y, Sanuki T, Yoshida M, Kutsumi H, Inokuchi H, Azuma T. The new resources of treatment for early stage colorectal tumors: EMR with small incision and simplified endoscopic submucosal dissection. *Dig Endosc* 2009; **21** Suppl 1: S31-S37 [PMID: 19691730 DOI: 10.1111/j.1443-1661.2009.00872.x]
- 40 **Yahagi N**, Neuhaus H, Schumacher B, Neugebauer A, Kaehler GF, Schenk M, Fischer K, Fujishiro M, Enderle MD. Comparison of standard endoscopic submucosal dissection (ESD) versus an optimized ESD technique for the colon: an animal study. *Endoscopy* 2009; **41**: 340-345 [PMID: 19340739 DOI: 10.1055/s-0029-1214473]
- 41 **Kaehler GF**, Sold MG, Fischer K, Post S, Enderle M. Selective fluid cushion in the submucosal layer by water jet: advantage for endoscopic mucosal resection. *Eur Surg Res* 2007; **39**: 93-97 [PMID: 17299266 DOI: 10.1159/000099597]
- 42 **Nonaka K**, Kita H. Endoscopic Submucosal Dissection for Early Gastric Cancer. *J Cancer Ther* 2013; **4**: 26-32 [DOI: 10.4236/jct.2013.41A004]
- 43 **Lesser T**. Atypical lung parenchyma resection with the Hydro-Jet--initial experimental and clinical experiences. *Chirurg* 2000; **71**: 592 [PMID: 10875022]
- 44 **Nakamura N**, Hayashi T, Arai T, Tokonabe S, Ito H, Tajiri H, Makoto K. Experimental study on water jet incision of gastric mucosa to support the treatment for early gastric cancer. *JJMI* 1998; **68**: 369-374
- 45 **Lepilliez V**, Robles-Medrand C, Ciocirlan M, Lukashok H, Chemali M, Langonnet S, Chesnais S, Hervieu V, Ponchon T. Water-jet dissector for endoscopic submucosal dissection in an animal study: outcomes of the continuous and pulsed modes. *Surg Endosc* 2013; **27**: 2921-2927 [PMID: 23468330 DOI: 10.1007/s00464-013-2857-z]
- 46 **Sato C**, Nakano T, Nakagawa A, Yamada M, Yamamoto H, Kamei T, Miyata G, Sato A, Fujishima F, Nakai M, Niinomi M, Takayama K, Tominaga T, Satomi S. Experimental application of pulsed laser-induced water jet for endoscopic submucosal dissection: mechanical investigation and preliminary experiment in swine. *Dig Endosc* 2013; **25**: 255-263 [PMID: 23363046 DOI: 10.1111/j.1443-1661.2012.01375.x]
- 47 **Yamada M**, Nakano T, Sato C, Nakagawa A, Fujishima F, Kawagishi N, Nakanishi C, Sakurai T, Miyata G, Tominaga T, Ohuchi

N. The dissection profile and mechanism of tissue-selective dissection of the piezo actuator-driven pulsed water jet as a surgical

instrument: laboratory investigation using Swine liver. *Eur Surg Res* 2014; **53**: 61-72 [PMID: 25139450 DOI: 10.1159/000365288]

P- Reviewer: Iizuka T, Lee SH **S- Editor:** Ji FF **L- Editor:** A
E- Editor: Wu HL



Diagnostic and therapeutic biomarkers in pancreaticobiliary malignancy

Domenico Viterbo, Valerie Gausman, Tamas Gonda

Domenico Viterbo, Tamas Gonda, Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, NY 10032, United States

Valerie Gausman, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461, United States

Author contributions: Viterbo D, Gausman V and Gonda T contributed to the literature search, drafting of the manuscript, proof-reading and approval of the final version for submission; Viterbo D and Gausman V contributed equally to this work.

Conflict-of-interest statement: All authors declare that we have no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Tamas Gonda, MD, Assistant Professor of Medicine, Division of Digestive and Liver Diseases, Columbia University Medical Center, 161 Fort Washington Avenue, Suite 862, New York, NY 10032, United States. tg2214@cumc.columbia.edu
Telephone: +1-212-3051909
Fax: +1-212-3051081

Received: July 29, 2015
Peer-review started: July 29, 2015
First decision: October 13, 2015
Revised: October 17, 2015
Accepted: December 7, 2015
Article in press: December 8, 2015
Published online: February 10, 2016

Abstract

Pancreatic ductal adenocarcinoma (PDAC) and cholangio-

carcinoma (CCA) are two malignancies that carry significant morbidity and mortality. The poor prognoses of these cancers are strongly related to lack of effective screening modalities as well as few therapeutic options. In this review, we highlight novel biomarkers that have the potential to be used as diagnostic, prognostic and predictive markers. The focus of this review is biomarkers that can be evaluated on endoscopically-obtained biopsies or brush specimens in the pre-operative setting. We also provide an overview of novel serum based markers in the early diagnosis of both PDAC and CCA. In pancreatic cancer, the emphasis is placed on prognostic and theranostic markers, whereas in CCA the utility of molecular markers in diagnosis and prognosis are highlighted.

Key words: Biological markers; Pancreatic cancer; Cholangiocarcinoma; Diagnostic; Prognostic; Predictive; Brush specimens; Biopsies

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The poor prognoses of pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA) are strongly related to lack of effective screening modalities as well as few therapeutic options. Several novel biomarkers have been studied that have shown promise for early diagnosis and targeted therapy of these malignancies. These biomarkers provide a strong background for future clinical studies to screen for PDAC and CCA in the general population as well as to investigate molecularly targeted therapies.

Viterbo D, Gausman V, Gonda T. Diagnostic and therapeutic biomarkers in pancreaticobiliary malignancy. *World J Gastrointest Endosc* 2016; 8(3): 128-142 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/128.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.128>

INTRODUCTION

The focus of this review will serve to summarize diagnostic, prognostic and predictive tumor markers in pancreatic cancer and cholangiocarcinoma (CCA). Despite major advances in the therapies of many solid tumors, survival in pancreatic cancer has not improved^[1]. Delayed diagnosis, aggressive biology and marked chemoresistance have all contributed to this disappointing trend. Improving the sensitivity of diagnostic modalities, such as imaging or endoscopic tests and molecular markers, as well as innovation in surgical strategies and novel chemotherapeutic regimens had opened the possibility for significantly changing the status-quo. Although gemcitabine remains the back bone of chemotherapy in this disease, novel regimens have been introduced and some have demonstrated significantly better survival^[2,3].

CCA arises from the neoplastic proliferation of cholangiocytes, the epithelial cells in the biliary tree^[4]. It is an aggressive malignancy, characterized by early lymph node involvement and distant metastasis, with 5-year survival rates of 5%-10%^[5]. The identification of new biomarkers with diagnostic, prognostic or theranostic value is especially important as resection (by surgery or combined with a liver transplant) has shown promising results and novel therapies are emerging^[6]. However, the relatively low incidence of CCA, high frequency of co-existing cholestasis or cholangitis, and difficulties with obtaining adequate samples have complicated the search for accurate biomarkers.

DIAGNOSTIC SERUM MARKERS

Pancreatic cancer

Non-invasive blood-based biomarkers with high diagnostic accuracy would be ideal for the early diagnosis of pancreatic cancer. Current tumor markers [cancer antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), *etc.*] do not have adequate accuracy. The most commonly used marker, CA 19-9, has been reported to have sensitivity and specificity rates ranging from 60%-90% and 65%-92%. Both tumor size^[7], concurrent biliary or pancreatic obstruction and the presence of Lewis antigen has significant impact on CA 19-9 levels, making them even less useful as a diagnostic modality. Therefore novel molecular markers may fill an important void in non-invasive testing for early detection of pancreatic ductal adenocarcinoma (PDAC).

MicroRNAs (miRNAs) are highly stable 18-25 nucleotide single-stranded transcripts that function primarily as negative regulators of gene expression by inhibiting translation of their target messenger RNA. Emerging evidence suggests that initiation and progression of PDAC involves aberrant expression of miRNAs. Nearly 100 miRNAs are differentially expressed in pancreatic cancer. Many of these miRNAs are overexpressed and promote tumorigenesis by targeting tumor suppressor

genes^[8,9]. miRNAs have recently gained attention as potential diagnostic biomarkers and have been analyzed in human blood, bile, pancreatic juice, pancreatic cysts and stool. Relevant articles pertaining to miRNA and pancreatic cancer are summarized below.

Much of the research effort in this field was initially devoted to the characterization of miRNAs in pancreatic cancer. Bloomston *et al.*^[10] was one of the first to compare the global miRNA expression pattern of resected pancreatic cancer with healthy pancreatic tissue and chronic pancreatitis. He identified miRNAs miR-21, miR-155, miR-221 and miR-196a as key oncogenic miRNAs that correlated with aggressive tumors. In a similar fashion, miRNAs-221, -376a, -301, miR-93, -196a, -196b, -203, -205, -210, -221, -222 and -224 were found to be overexpressed in pancreatic cancer^[11,12]. A supportive study by Sadakari *et al.*^[13] showed the relative expression levels of microRNA-21 and microRNA-155 in pancreatic juice was significantly higher when compared to chronic pancreatitis. Elevated levels of miR-196a and miR-10b were subsequently discovered in pancreatic intraepithelial neoplasia (*PanIN*) lesions suggesting these molecular compounds may be important for early carcinogenesis^[14]. The prognostic significance of miRNA in pancreatic cancer was demonstrated by one study which associated elevated levels of miR-21 and miR-31 and low levels of miR-375 with poor clinical outcomes after surgical resection^[15].

Circulating miRNAs in whole blood have been investigated in patients with pancreatic cancer. Whole blood miRNA analysis is an attractive screening test because of its easy clinical application and minimal patient involvement. Table 1 summarizes the largest and most recent studies to analyze the utility of novel serum-based miRNAs in the diagnosis of PDAC.

Given the overall stability of miRNA and the large abundance of hepatobiliary juice in stool, analysis for miRNA biomarker expression in feces offers another noninvasive screening option to evaluate for pancreatic cancer. Fecal miRNA expression profiling by Link *et al.*^[16] showed that dysregulated miRNAs can be found in stool. They report miRNAs-196a, -216a, -143 and -155 are differentially expressed in patients with PDAC when compared to controls. The purpose of this study was to evaluate the feasibility of stool miRNAs as novel biomarker for PDAC screening^[17].

CCA

Acquisition of tumor tissue for histology or biomarker testing can be difficult and requires even more invasive and potentially risky procedures than diagnostic studies for PC. The most frequently used serologic markers of CCA are CA19-9 and possibly CEA. CEA has a sensitivity/specificity of 33%-84%/50%-87.8%^[18-20]. CA 19-9 not only has a wide variation of sensitivity/specificity: 38%-93%/67%-98%^[18-22], but can also be undetectable in 7% of the general population due to absence of the Lewis antigen^[23]. Although CA 19-9 may have a role in the diagnostic algorithm, especially in

Table 1 Diagnostic serum markers for pancreatic ductal adenocarcinoma and cholangiocarcinoma

	Diagnostic markers	Countries	CCA or PDAC patients, <i>n</i>	Sensitivity (%)	Specificity (%)
Pancreatic cancer	miRNA-10b, -30c, -106b, -155, and -212 ^[120] Index 1: (miR-145, miR-150, miR-223, miR-636) Index 2: (miR-26b, miR-34a, miR-122, miR-126, miR-145, miR-150, miR-223, miR-505, miR-636, miR-885.5p) ^[121]	United States Denmark	77 409	73-100 Index 1: 77 Index 2: 80	83-100 Index 1: 66 Index 2: 82
CCA	miR-21, miR-210, miR-155, and miR-196 ^[122] CYFRA 21-1 ^[18,24,30] MMP-7 ^[24,123,124] Combo (CEA, CA 19-9, MMP-7, CYFRA 21-1) ^[24] Combo (CYFRA 21-1, CA 19-9) ^[30] IL-6 ^[35,125-127] SSP411 ^[37] miR-21 ^[128] miR-150 ^[129] ¹ miR-192 ^[130] MUC5AC ^[131,132] Combo (AFP, CEA, CA 19-9, CA 125) ^[133]	United States United Kingdom, Italy Thailand, Italy Italy United Kingdom United States, Thailand China United States China Japan Thailand China	49 30 120 24 6 207 35 23 15 51 348 30	64 17-76 53-78 92 45 71.1-100 90 95 80.6 74 62.6-71 90	89 79-95 72.5-92 96 96 90-92 83.3 100 58.1 72 90-96.9 90

All markers identified with ELISA, except for ¹Western blot. All cases of cholangiocarcinoma are histologically-proven. Control patients for CCA include those with benign liver diseases, HCC and healthy controls. Combo: Combination; PDAC: Pancreatic ductal adenocarcinoma; CCA: Cholangiocarcinoma; CYFRA 21-1: Cytokeratin 19 fragment; MMP-7: Matrix metalloproteinase-7; CEA: Carcinoembryonic antigen; CA 19-9: Cancer antigen 19-9; IL-6: Interleukin-6; SSP411: Sperm-specific protein 411; MUC5AC: Mucin 5AC; AFP: Alpha-fetoprotein; ELISA: Enzyme-linked immunosorbent assay; HCC: Hepatocellular carcinoma.

patients with primary sclerosing cholangitis (PSC) in the absence of concurrent cholangitis or pancreatitis, the low accuracy of the test limits its role in screening and early diagnosis. Thus, novel biomarkers with potential diagnostic utility have been studied (Table 1).

In malignant epithelial cells, activated proteases release cytokeratin-19 fragments (CYFRA 21-1) into the bloodstream^[24]. CYFRA 21-1 levels have previously been shown to be a sensitive biomarker in non-small-cell lung cancer^[25], gastric cancer^[26], breast cancer^[27], bladder cancer^[28] and cervical carcinoma^[29]. Several studies have shown elevated CYFRA 21-1 expression in CCA, but sensitivity varied depending on the cut-off value^[18,24,30]. High matrix metalloproteinase-7 (MMP-7) expression has been found to be associated with cancer invasion in esophageal^[31], colon^[32] and pancreatic^[33] cancers. The elevation of CYFRA 21-1 and MMP-7 in various malignancies can preclude their use as CCA-specific diagnostic biomarkers. Thus, combinations of serum markers can be used to improve sensitivity without compromising specificity. Using CYFRA 21-1 and MMP-7 in a multi-marker panel along with CEA and CA 19-9 demonstrated the highest diagnostic accuracy of 93.9%^[24].

Interleukin-6 (IL-6) has been shown to be a growth factor for bile duct epithelium^[34] and has demonstrated sensitivity as high as 100% in diagnosing CCA^[35]. However, IL-6 is also elevated in many patients with hepatocellular carcinoma, benign biliary disease, and metastatic lesions, limiting its specificity^[36]. This reinforces the need for more serum-based CCA-specific proteins that are not normally expressed in healthy

liver tissue nor elevated in other malignancies. Sperm-specific protein 411 (SSP411) is one such protein which is elevated in the bile of CCA patients and recently found to successfully distinguish CCA from choledocholithiasis as a single serum-based biomarker^[37].

miRNAs are usually stable in the circulation when bound to proteins. When miRNAs are dysregulated in cancers, they enter the circulation in free form and can be detected as potential diagnostic markers^[38]. The utility of miRNAs lies in their tissue-specific patterns of expression. miRNAs commonly upregulated in other epithelial cancers (miR-192, 194 and 215 in colon, liver, pancreas and stomach cancer^[39]) are not altered in CCA, while CCA-specific miRNA expression profiles exist (miR-125a, -31, and -95 are downregulated, while multiple miRNAs are upregulated as compared to nonmalignant cholangiocytes)^[40,41]. The role of miRNAs in tumor invasion in CCA is supported by similar miRNA profiles between tumor tissue and adjacent non-tumor tissue as compared to normal tissue^[42,43]. The most commonly overexpressed miRNA in CCA is miR-21^[44-46]. However, it is also up-regulated in a variety of other cancers (gastric^[47], breast^[48] and colon^[49]), suggesting that the most effective use of miRNAs is likely as multi-marker panels specific for CCA. MicroRNA biomarker discovery has extended from serum and plasma samples to the utilization of bile vesicles, which have demonstrated high accuracy in PSC patients^[50].

The presence of circulating tumor cells (CTCs) in other solid cancers (including breast^[51], prostate^[52], colon^[53] and pancreatic^[54]) is associated with more aggressive disease and increased metastasis. Similarly,

CTCs in CCA were found to be prognostic of poor overall survival^[55,56]. Using a cut-off of 2 CTCs/7.5 mL of peripheral blood, the sensitivity of CTCs for CCA diagnosis is only 17%-23%^[55,56]. Despite their poor diagnostic utility, CTCs are potentially useful in detection and monitoring treatment of metastatic spread in real time.

DIAGNOSTIC BRUSH OR BIOPSY-BASED MARKERS

Pancreatic cancer

The diagnostic approach to pancreatic masses is dominated by endoscopic ultrasound-fine needle aspiration (EUS-FNA) and histologic or cytologic analysis. EUS-FNA is highly sensitive and specific for solid pancreatic lesions, with sensitivities as high as 85%-95% and specificities of 90%-95%^[57].

The two areas where reliance on cytology is not supported by sufficient diagnostic accuracy are cystic neoplasms and inflammatory masses that may mask an underlying neoplasm. EUS-FNA is critical for the evaluation of pancreatic cystic lesions. It is beyond the scope and focus of this review to provide a summary of the data available on the accuracy of cyst fluid based cancer markers and molecular markers. Overall, these markers generally perform well in distinguishing mucinous type lesions from non-mucinous lesions but have thus far shown limited accuracy in identifying high-risk lesions (high grade dysplasia or carcinoma) from lower risk lesions^[58-60]. Molecular analysis for DNA disruptions, *Kras* mutation and miRNAs has enhanced the diagnostic capability of EUS-FNA analysis of pancreatic cysts^[61-64]. Similarly, molecular markers are promising in the relatively infrequent setting when a pancreatic mass is noted concurrent with inflammation (either with autoimmune pancreatitis or in the setting of chronic pancreatitis). For example, the presence of *Kras* mutations in FNA specimens has been shown to be a highly sensitive marker^[65].

CCA

Despite advances in sampling techniques and visualization of the bile duct, obtaining representative tissue from the bile duct remains difficult. A single biliary stricture that occurs without associated suspicion of PSC has a different risk of being malignant than biliary strictures, even dominant strictures, identified in a patient with known PSC. Therefore, we consider the diagnostic tests used in these conditions separately.

PSC associated strictures: PSC is a chronic liver disease characterized by cholestasis, inflammation, multifocal biliary strictures and a 7%-12% lifetime risk of CCA^[66,67]. A minority of CCA patients are surgical candidates and resection carries a 5-year survival rate of only 18%-32.5%^[68-71]. The specialized protocol for PSC-associated CCA developed at the Mayo Clinic

(neoadjuvant radio- and chemo-therapy with liver transplantation), has the highest 5-year survival rate of 79%^[72]. Inclusion requires early-stage disease, thus excluding the majority of patients diagnosed by standard methods. Because the clinical presentation of CCA can mimic benign dominant biliary strictures, the major challenge lies in identifying potential biomarkers that detect early dysplasia and CCA (Table 2).

Conventional cytology has a low sensitivity due to inadequate cellular yield, but a near 100% specificity. Fluorescent *in situ* hybridization (FISH) trisomy/tetrasomy-positive results have a limited role in the detection of CCA in PSC because they were found to have a similar outcome to FISH negative patients^[73]. However, polysomy has been shown to increase the sensitivity of routine cytology. There may be some reduction in specificity with FISH as PSC patients may have benign strictures that manifest with chromosomal abnormalities. The importance of sampling the biliary tree at multiple locations, regardless of the location of the dominant stricture, was demonstrated in a recent study that found that multifocal polysomy carried a greater risk of CCA diagnosis than polysomy detected at a single location^[74]. Therefore, FISH should be part of the evaluation of PSC patients presenting with dominant strictures. In one retrospective study of PSC patients with polysomy on initial FISH testing but no signs of CCA, polysomy detected on repeat FISH was associated with increased incidence of CCA compared to patients with non-serial polysomy (polysomy present only on initial FISH)^[75]. Repeat sampling without ongoing symptoms or signs remains an area of uncertainty but may be the most effective way to survey patients.

Kirsten rat sarcoma viral oncogene homolog (*Kras*) is a GTPase downstream of the epidermal growth factor receptor (EGFR) receptor that activates proteins involved in cell growth and proliferation. The high specificity of *Kras* analysis in biliary strictures can be useful, but the low sensitivity precludes it from diagnostic use as a sole biomarker. When used in combination with cytology, sensitivity increased to 100%^[76].

Indeterminate biliary strictures: In certain series, up to a quarter of patients who undergo surgical resection for suspected CCA-related strictures turn out have benign etiology^[77]. The utility of a highly sensitive modality beyond cytology or histology may therefore reduce the number of unnecessary surgeries. Thus far, assessment of polysomy by FISH has shown the greatest accuracy in brush cytology specimens. Some studies have found that the inclusion of the 9p21/p16 deletion in FISH analysis of indeterminate strictures increased the sensitivity of FISH-polysomy for pancreaticobiliary tract cancers from 58% to 89% and from 70% to 76%^[73,78,79].

PROGNOSTIC MARKERS

General prognostic markers, not specific to a defined

Table 2 Tissue-based diagnostic biomarkers for cholangiocarcinoma

	Diagnostic marker	Countries	Total patients, <i>n</i>	CCA patients, <i>n</i>	Sensitivity (%)	Specificity (%)
PSC-associated strictures	Brush Cytology ^[21,76,134-140]	United States, The Netherlands, Sweden, Norway	828	138	7-73	89-100
	FISH polysomy ^[21,73,136,137,140]	United States	387	89	22-50	88-100
	FISH polysomy or trisomy ^[21,73,136,140]	United States	373	75	60-88	57-87
	Kras ^[141,142]	Norway, United States	180	74	29-47	96-100
	p53 ^[142]	Norway	48	33	31	100
	Cytology + CA19-9 ^[135]	United States	333	44	87.5	97.3
	Cytology + DNA aneuploidy + CA19-9 + CEA ^[138]	Sweden	20	7	88-100	80-85
	Cytology + p53 + KRAS ^[76]	The Netherlands	23	10	100	79
	FISH + KRAS ^[141]	United States	14	14	50-68	96
	Brush Cytology ^[75,78,79,136,140,143-150]	United States, Germany, France, Italy	640	199	5.8-80	92-100
Indeterminate strictures	FISH Polysomy ^[75,78,79,136,137,140]	United States, Italy	386	165	31-80	97-100.0
	FISH Polysomy or trisomy ^[75,136,140]	United States	147	88	49-64	79.6-100
	Biopsy ^[144,145,147,150-153]	United States, Japan, France	347	65	30-88	97-100
	FNA ^[145,154]	United States	133	30	25-61.6	100.0
	Cytology + biopsy ^[144,150]	France, Austria	258	28	63-86	97-100
	Cytology + FNA + biopsy ^[145]	United States	133	30	47-52	100
	Cytology + KRAS ^[155]	Belgium	142	12	55	100

Some studies included all biliary tract cancers (cholangiocarcinoma, gallbladder, pancreatic and ampullary), but sensitivity and specificity values were similar, so data is merged. Endobiliary sampling technique for cytology and FISH: ERCP or PTC brushing; Biopsy technique: Standard forceps, mini-forceps or transpapillary biopsy. FISH: Fluorescent *in situ* hybridization; PTC: Percutaneous transhepatic cholangiography; CCA: Cholangiocarcinoma; PSC: Primary sclerosing cholangitis; p53: Tumor protein p53; KRAS: Kirsten rat sarcoma viral oncogene homolog; CEA: Carcinoembryonic antigen; CA 19-9: Cancer antigen 19-9; FNA: Fine-needle aspiration.

therapeutic regimen, can be useful in distinguishing which patients are at higher risk of a poor outcome and should therefore be managed more aggressively. Table 3 summarizes the dysregulation of certain markers in PDAC and CCA and their effect on overall survival and/or rate of metastasis.

Pancreatic cancer

Secreted protein acidic and rich in cysteine: Secreted protein acidic and rich in cysteine (SPARC) is a matricellular glycoprotein with important implications in pancreatic cancer. SPARC undergoes epigenetic silencing in pancreatic adenocarcinoma, but is often strongly expressed at the interface between the tumor and stroma by stromal fibroblasts^[80]. Supporting data suggest this interaction is important for tumor progression, metastasis and protects against chemotherapeutic agents. Stromal SPARC expression is observed in all disease stages suggesting early expression is critical for tumor progression^[81].

Numerous studies have identified stromal SPARC as a negative prognostic marker in pancreatic cancer^[81]. Strong stromal SPARC expression in patients with well to moderately differentiated cancer who underwent surgical resection was associated with decreased overall survival when compared to patients with no SPARC expression^[81,82]. Furthermore, patients with diffuse stromal SPARC expression extending beyond the peritumoral region had a significantly worse prognosis^[83]. Interestingly, many report cytoplasmic SPARC expression

by malignant pancreatic cells to have no prognostication value^[81]. Others have revealed both stromal and cytoplasmic SPARC expression is associated with decreased overall survival in patients who were treated with gemcitabine^[84]. Similarly, elevated SPARC mRNA expression in pancreatic cancer is also associated with worse patient outcome^[85].

Human equilibrative nucleoside transporter 1:

Human equilibrative nucleoside transporter 1 (hENT1) plays a major role in the internalization of (transportation of) gemcitabine by cancer cells. Among patients who did not receive gemcitabine in one study, hENT1 levels did not have any prognostic or predictive value^[86]. Conversely, another study showed high hENT1 expression was a poor prognostic factor for early disease recurrence in the absence of gemcitabine therapy^[87].

miRNAs: A large supportive study analyzing miRNA levels in PDAC revealed high expression of miR-21 and miR-31 with low expression of miR-375 were associated with poor overall survival following surgical resection^[15].

CCA

miRNAs: Recent studies have been successful in establishing miRNA signatures that can discriminate between CCA and normal tissue as well as provide prognostic clues^[41,88]. As various miRNA expression patterns correlate with overall survival and rate of metastasis, the identification of accurate and predictive

Table 3 Prognostic markers in pancreatic ductal adenocarcinoma and cholangiocarcinoma

	Marker	Country	Total patients, <i>n</i>	Marker positive PDAC	Type of dysregulation	Prognostic value, OS months	HR or <i>P</i> value for OS
Pancreatic cancer	SPARC	United States ^[81]	299	200	Up-regulated	+SPARC: 15 -SPARC: 30	1.89
		Germany ^[83]	58	58	Up-regulated	+SPARC: 7.6 -SPARC: 10.2	2.23
		Germany ^[84]	160	95	Up-regulated	+SPARC: 17.9 -SPARC: 30.2	<i>P</i> = 0.006
		Japan ^[85]	104	104	Up-regulated	Decreased survival	2.92
		Sweden ^[82]	88	68	Up-regulated	+SPARC: 11.5 -SPARC: 25.3	2.12
CCA	Marker	Country	Total Patients, <i>n</i>	CCA patients, <i>n</i>	Type of dysregulation	Prognostic value	HR (95%CI) or <i>P</i> value for OS
	¹ miR-192 ^[130]	Japan	83	51	Up-regulated	Increased LN mets; shorter survival	2.076 (1.004-4.291) <i>P</i> < 0.05 mets
	miR-675-5p ^[88]	China	72	63	Up-regulated	Shorter survival	2.562 (1.295-4.929)
	miR-652-3p, miR-338-3p ^[88]	China	72	63	Down-regulated	Increased survival	0.477 (0.247-0.922); 0.498 (0.257-0.966)
	miR-151-3p and miR-126 ^[156]	United States	32	32	Up-regulated and down-regulated, respectively	Increased survival	0.201 (0.043-0.928)
	¹ miR-21 ^[46]	Thailand, China	41	32	Up-regulated	Increased LN mets; shorter survival	<i>P</i> < 0.05 OS <i>P</i> = 0.037 mets
	miR-214 ^[157]	China	14	14	Down-regulated	Increased mets	<i>P</i> < 0.05 mets
	miR-373 ^[90]	China	48	48	Down-regulated	Shorter survival	<i>P</i> < 0.05 OS
	Group 1: miR-21, miR-31, miR-223	Greece	179	21	Group 1: Up-regulated	None	-
	Group 2: miR-122, miR-145, miR-146a, miR-200c, miR-221, and miR-222 ^[44]				Group 2: Down-regulated		
	CYFRA 21-1 ^[18,30]	United Kingdom, Japan	195	137	Up-regulated	Shorter survival	<i>P</i> = 0.001 ^[30] <i>P</i> < 0.01 ^[18]
	EGFR ^[93,94]	Japan	373	338	Up-regulated	Shorter survival	5.655 (2.72-11.74) ^[93] 2.67 (1.52-4.69) ^[94]

¹Liver fluke-associated CCA. PDAC: Pancreatic ductal adenocarcinoma; CCA: Cholangiocarcinoma; mets: Metastases; OS: Overall survival; SPARC: Secreted protein acidic and rich in cysteine; CYFRA 21-1: Cytokeratin 19 fragment; EGFR: Epidermal growth factor receptor; LN: Lymph node.

multi-marker panels can identify patients in need of more aggressive management earlier (Table 3). However, the majority of these studies analyzed histologic samples from tumor resections, and therefore their utility from samples obtained at time of ERCP has not yet been demonstrated^[44,88-92].

EGFR and CYFRA 21-1: Over-expression of EGFR^[93,94] and CYFRA 21-1 values above 2.7-3 ng/mL^[18,30] were each prognostic of decreased overall survival.

THERANOSTIC MARKERS

The goal of theranostic markers is to predict response to a specific therapy. In many other cancers, the role of targeted therapy has changed the approach to treatment. Various genetic mutations have been identified in PDAC and CCA (Table 4) that can be used to guide a personalized approach to therapy.

Pancreatic cancer

SPARC: One the most interesting clinical features of SPARC is its potential role as a predictive marker for

response to therapy with nab-paclitaxel. Von hoff *et al*^[2] identified stromal SPARC to be an important therapeutic marker in patients treated with combination nab-paclitaxel and gemcitabine chemotherapy. Specifically, patients with high SPARC expression treated with combination therapy had increased overall survival when compared to combination therapy in patients with low SPARC or absence of SPARC. This finding is thought to be due to nab-paclitaxel targeting stromal SPARC and is thought to facilitate delivery of gemcitabine by depleting tumor stroma. Contradictory results by Sinn *et al*^[84] revealed high stromal SPARC expression in patients with pancreatic cancer treated solely with gemcitabine resulted in decreased overall survival. Such studies suggest the theranostic impact of SPARC is restricted to patients who receive therapy with nab-paclitaxel.

hENT1: A great deal of enthusiasm surrounds hENT1 because of its potential to remodel chemotherapy regimens in pancreatic cancer. There is overwhelming data to support its use as a first line test in pancreatic cancer. hENT1 plays a major role in the internalization

Table 4 Theranostic markers in pancreatic ductal adenocarcinoma and cholangiocarcinoma

	Marker (drug)	Countries	Patients with + marker	Staining	Median survival (mo)	HR
Pancreatic cancer	SPARC ^[2]	United States	67	36	+SPARC: 17.8 -SPARC: 8.1	$P = 0.0431$
	(nab-paclitaxel/ gemcitabine)	Canada ^[96]	21	Low hENT1: 12 High hENT1: 9	Low: 4 High: 13	¹
	hENT1 (Gemcitabine)	Italy ^[158]	83	Low hENT1: 27 Inter: 28 High hENT1: 26	Low: 8.5 Inter: 15.7 High: 25.7	4.21
		United States ^[97]	91	Low hENT1: 39 High hENT1: 34	²	0.51
		Belgium ^[98]	45	Low hENT1: 26 High hENT1: 19	Low: 13.3 High: 18.7	4.31 (HR for death)
		Japan ^[159]	40	Low hENT1: 26 High hENT1: 14	Low: 8 High: 25	$P = 0.0001$ (OS) $P = 0.011$ (OS)
		Japan ^[160]	55	Low hENT1: 16 High hENT1: 39	Low: 11.8 High: 24.9	3.15 (OS)
		Belgium France ^[86]	243	Low hENT1: 142 High hENT1: 92	²	0.34
		Worldwide multicenter ^[99]	177	Low hENT1: 118 High hENT1: 59	Low: 6.1 High: 5.2	1.147
		England ^[161]	176	Low hENT1: 77 High hENT1: 99	Low: 17.1 High: 26.2	0.6
	Marker	Countries	CCA patients	% mutated	Type of mutation	Potential theranostic value
CCA	EGFR ^[94,105,109,112]	United States, South Korea, Japan, Italy	400	1-81	G719S kinase activation	EGFR inhibitors
	VEGF ^[108,162]	South Korea	272	41.7-56.8	Up-regulation	Anti-VEGF therapies
	Kras ^[109,111,142,163-166]	United States, Germany, China, Norway, Japan	197	7.4-45	Substitution	U0126 (MEK inhibitor)
	BRAF ^[109,110,164,167]	United States, Germany, China	222	0-22	Activating missense	BRAF inhibitors
	ErbB2 (HER2/neu) ^[94,112]	South Korea, Italy	284	4-5.1	Up-regulation	Anti-ErbB2 therapies
	IDH1/2 ^[109,114,115,168]	United States	576	10-22.3 ¹	Gain of function	α -KG-mimics reverse methylation
	miR-21, miR-200b ^[40] , miR-29b, miR-205, miR-221 ^[117] miR-494 ^[92]	United States, Japan	¹	¹	Up-regulated	Increased sensitivity to gemcitabine
		United States	43	¹	Down-regulated	Up-regulation decreases tumor growth
	Panel: CDO1, DCLK1, ZSCAN18 and SFRP1 ^[169]	Norway	39	87	Promoter methylation	Anti-methylation therapy
	Panel: CDO1, CNRIP1, SEPT9, and VIM ^[170] SFRP1 ^[169,171-173]	Norway, United Kingdom, South Korea, Thailand	30 255	85 59-83.6	Promoter methylation	Tumor suppression with gene therapy (RNAi)

¹Not reported; ²Results graphed. OS: Overall survival; PDAC: Pancreatic ductal adenocarcinoma; CCA: Cholangiocarcinoma; Kras: Kirsten rat sarcoma viral oncogene homolog; MEK: Mitogen-activated protein kinase/ERK kinase; EGFR: Epidermal growth factor receptor; ErbB2: Erythroblastosis oncogene B 2; VEGF: Vascular endothelial growth factor; CDO1: Cysteine dioxygenase type 1; DCLK1: Doublecortin-like kinase 1; ZSCAN18: Zinc finger and SCAN domain containing 18; SFRP1: Secreted frizzled-related protein 1; CNRIP1: Cannabinoid receptor interacting protein 1; SEPT9: Septin 9; VIM: Vimentin; IDH1/2: Isocitrate dehydrogenase 1/2; α -KG: Alpha-ketoglutarate.

of gemcitabine by pancreatic cancer cells^[95] and is an important prognostic and predictive biomarker for gemcitabine efficacy in patients with pancreatic cancer. Its value as a biomarker is supported by an abundance of clinical studies. Acceptance of its clinical use is limited by a lack of large prospective validation studies. Supportive data is reviewed in this review.

Clinical studies have demonstrated response to gemcitabine parallels hENT1 expression. Namely, patients with tumors that test positive for hENT1 have longer median survival with gemcitabine therapy than those for whom hENT1 was absent. Spratlin *et al.*^[96] revealed strong hENT1 expression in patients with pancreatic adenocarcinoma was associated with a 3 fold increase

in overall survival after treatment with gemcitabine. Subsequently, a range of studies have reinforced the positive relationship observed with hENT1 expression and gemcitabine efficacy. Interestingly, this positive finding was not observed with other chemotherapy agents^[97]. Additionally, several groups have reported a synergistic survival effect with hENT1 and other tumor markers including hCNT3 and deoxycytidine kinase (dCK) in subjects treated with adjuvant gemcitabine after curative resection^[98].

Interestingly, Poplin *et al.*^[99] discovered that hENT1 expression did not predict gemcitabine sensitivity in patients with metastatic pancreatic cancer. This may be due to increased tumor heterogeneity in select patients. Acquired resistance to gemcitabine is bound to happen and may be due to altered gene expression involving important transport proteins including dCK, ribonucleotide reductase M1 (RRM1), RRM2, and hENT1^[100]. Additionally, favorable single nucleotide polymorphisms (SNPs) of enzymes involved in the transportation or metabolism of gemcitabine have been identified and may be absent with an unfavorable phenotype^[101,102].

Implementing pretreatment analysis for hENT1 expression is feasible, requiring a small tissue sample which can easily be obtained by EUS-FNA. Quantitative mRNA analysis of HENT1 or protein analysis with immunohistochemistry are both useful approaches that are presently limited by a lack of large validation trials.

CCA

Small-molecule inhibitors have demonstrated a good response rate in lung carcinoma harboring a mutation in the tyrosine kinase domain of the *EGFR* gene^[103]. *EGFR* mutations can be unique to CCA^[104] or identical to those in non-small cell lung cancer^[105], highlighting the significance of genotyping in guiding therapy. A phase II study of single agent erlotinib in patients with advanced biliary cancer demonstrated disease stabilization in 17%^[106]. Upregulation of vascular endothelial growth factor (VEGF) is associated with an *EGFR* inhibitor-resistant phenotype^[107]. Vandetanib, a dual inhibitor of VEGF and *EGFR*, has shown prolonged time to metastasis in CCA tumors that harbor both mutations^[108].

Genes that function downstream of *EGFR* can also be important therapeutic targets. *Kras* is one of the most frequently mutated genes in CCA. *BRAF* mutations are most commonly associated with malignant melanoma, but have also been identified in up to 22% of CCAs^[109,110]. Several studies suggest the potential application for targeted therapy with vemurafenib in this population, while avoiding *EGFR*-inhibitors^[109,111]. There are no studies evaluating the response of *BRAF*-mutated CCA to vemurafenib therapy. However, there is an on-going phase II "basket" study of vemurafenib in non-melanoma solid tumors harboring *BRAF* mutations that demonstrated stable disease at 8 wk in 4/7 CCA patients, partial response in 2/7 at 24 wk and the

remaining 1/7 with disease progression (clinical trial# NCT01524978).

The small minority (4%-5%) of CCA cases that overexpress erythroblastosis oncogene B2 (ErbB2 or HER2)^[94,112] may benefit from targeted anti-HER2 therapy. One case study demonstrated a dramatic regression of metastatic CCA in a HER2-positive patient who was started on trastuzumab after failing third-line chemotherapy^[113].

A gain-of-function mutation in isocitrate dehydrogenase 1 (IDH1), leading to inhibition of α -ketoglutarate, has been seen in 23% of intrahepatic CCA cases^[114], and a minority (0%-7%) of extrahepatic CCA tumors^[114-116]. In-vivo studies have suggested that drugs mimicking α -ketoglutarate alone or in combination with inhibitors of mutant IDH1 can reverse the increased histone methylation^[116]. Additionally, IDH enzymes are stable therapeutic targets because the mutation appears early in oncogenesis and is maintained throughout progression to high-grade lesions^[115].

The increased expression of some miRNAs predicts a favorable response to gemcitabine treatment^[40,117]. The potential of miRNAs lies not only in their theranostic utility, but also as therapeutic agents. Treatment of cholangiocytes with miR-494, which is down-regulated in CCA, induced cell-cycle arrest in tumor cells while sparing normal cells^[92]. MicroRNA replacement therapy has seen success in phase I clinical trials for ovarian^[118] and hepatocellular carcinoma^[119] and appears promising as a therapeutic modality in CCA.

Another benefit of these genes and miRNAs as markers is that they can be identified by mutational analysis on DNA or RNA and are commercially available.

CONCLUSION

Our review focused on PDAC- and CCA-specific biomarkers that may help in the early diagnosis of cancer or guide therapeutic decisions in the case of inoperable malignancy. The general population will benefit from a non-invasive serologic screening test with a high sensitivity, with multi-marker panels appearing advantageous. Despite the more invasive nature of tissue markers, high-risk patients would benefit from their high specificity. Additionally, the utility of predictive biomarkers will soon pave the way for individualized biliary and pancreatic cancer therapeutics.

REFERENCES

- 1 **Yadav D**, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; **144**: 1252-1261 [PMID: 23622135 DOI: 10.1053/j.gastro.2013.01.068]
- 2 **Von Hoff DD**, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 2011; **29**: 4548-4554 [PMID: 21969517 DOI: 10.1200/JCO.2011.36.5742]
- 3 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn

- Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
- 4 **Alvaro D**, Cardinale V. Molecular profiling. In: Herman JM, Pawlik TM, Thomas Jr. CR, editors. Biliary Tract and Gallbladder Cancer: A Multidisciplinary Approach. 2nd ed. Springer, 2014: 99-117
- 5 **Reddy SB**, Patel T. Current approaches to the diagnosis and treatment of cholangiocarcinoma. *Curr Gastroenterol Rep* 2006; **8**: 30-37 [PMID: 16510032]
- 6 **Blechacz B**, Gores GJ. Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. *Hepatology* 2008; **48**: 308-321 [PMID: 18536057 DOI: 10.1002/hep.22310]
- 7 **Tian F**, Appert HE, Myles J, Howard JM. Prognostic value of serum CA 19-9 levels in pancreatic adenocarcinoma. *Ann Surg* 1992; **215**: 350-355 [PMID: 1348409]
- 8 **Bhatti I**, Lee A, James V, Hall RI, Lund JN, Tufarelli C, Lobo DN, Larvin M. Knockdown of microRNA-21 inhibits proliferation and increases cell death by targeting programmed cell death 4 (PDCD4) in pancreatic ductal adenocarcinoma. *J Gastrointest Surg* 2011; **15**: 199-208 [PMID: 21088996 DOI: 10.1007/s11605-010-1381-x]
- 9 **Park JK**, Lee EJ, Esau C, Schmittgen TD. Antisense inhibition of microRNA-21 or -221 arrests cell cycle, induces apoptosis, and sensitizes the effects of gemcitabine in pancreatic adenocarcinoma. *Pancreas* 2009; **38**: e190-e199 [PMID: 19730150 DOI: 10.1097/MPA.0b013e3181ba82e1]
- 10 **Bloomston M**, Frankel WL, Petrocca F, Volinia S, Alder H, Hagan JP, Liu CG, Bhatt D, Taccioli C, Croce CM. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA* 2007; **297**: 1901-1908 [PMID: 17473300 DOI: 10.1001/jama.297.17.1901]
- 11 **Lee EJ**, Gusev Y, Jiang J, Nuovo GJ, Lerner MR, Frankel WL, Morgan DL, Postier RG, Brackett DJ, Schmittgen TD. Expression profiling identifies microRNA signature in pancreatic cancer. *Int J Cancer* 2007; **120**: 1046-1054 [PMID: 17149698 DOI: 10.1002/ijc.22394]
- 12 **Szafranska AE**, Davison TS, John J, Cannon T, Sipos B, Maghnouj A, Labourier E, Hahn SA. MicroRNA expression alterations are linked to tumorigenesis and non-neoplastic processes in pancreatic ductal adenocarcinoma. *Oncogene* 2007; **26**: 4442-4452 [PMID: 17237814 DOI: 10.1038/sj.onc.1210228]
- 13 **Sadakari Y**, Ohtsuka T, Ohuchida K, Tsutsumi K, Takahata S, Nakamura M, Mizumoto K, Tanaka M. MicroRNA expression analyses in preoperative pancreatic juice samples of pancreatic ductal adenocarcinoma. *JOP* 2010; **11**: 587-592 [PMID: 21068491]
- 14 **Xue Y**, Abou Tayoun AN, Abo KM, Pipas JM, Gordon SR, Gardner TB, Barth RJ, Suriawinata AA, Tsongalis GJ. MicroRNAs as diagnostic markers for pancreatic ductal adenocarcinoma and its precursor, pancreatic intraepithelial neoplasm. *Cancer Genet* 2013; **206**: 217-221 [PMID: 23933230 DOI: 10.1016/j.cancergen.2013.05.020]
- 15 **Ma MZ**, Kong X, Weng MZ, Cheng K, Gong W, Quan ZW, Peng CH. Candidate microRNA biomarkers of pancreatic ductal adenocarcinoma: meta-analysis, experimental validation and clinical significance. *J Exp Clin Cancer Res* 2013; **32**: 71 [PMID: 24289824 DOI: 10.1186/1756-9966-32-71]
- 16 **Link A**, Becker V, Goel A, Wex T, Malferteiner P. Feasibility of fecal microRNAs as novel biomarkers for pancreatic cancer. *PLoS One* 2012; **7**: e42933 [PMID: 22905187 DOI: 10.1371/journal.pone.0042933]
- 17 **Yang JY**, Sun YW, Liu DJ, Zhang JF, Li J, Hua R. MicroRNAs in stool samples as potential screening biomarkers for pancreatic ductal adenocarcinoma cancer. *Am J Cancer Res* 2014; **4**: 663-673 [PMID: 25520858]
- 18 **Uenishi T**, Yamazaki O, Tanaka H, Takemura S, Yamamoto T, Tanaka S, Nishiguchi S, Kubo S. Serum cytokeratin 19 fragment (CYFRA21-1) as a prognostic factor in intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2008; **15**: 583-589 [PMID: 17955299 DOI: 10.1245/s10434-007-9650-y]
- 19 **Björnsson E**, Kilander A, Olsson R. CA 19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Liver* 1999; **19**: 501-508 [PMID: 10661684]
- 20 **Qin XL**, Wang ZR, Shi JS, Lu M, Wang L, He QR. Utility of serum CA19-9 in diagnosis of cholangiocarcinoma: in comparison with CEA. *World J Gastroenterol* 2004; **10**: 427-432 [PMID: 14760772]
- 21 **Charatcharoenwittaya P**, Enders FB, Halling KC, Lindor KD. Utility of serum tumor markers, imaging, and biliary cytology for detecting cholangiocarcinoma in primary sclerosing cholangitis. *Hepatology* 2008; **48**: 1106-1117 [PMID: 18785620 DOI: 10.1002/hep.22441]
- 22 **Patel AH**, Harnois DM, Klee GG, LaRusso NF, Gores GJ. The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. *Am J Gastroenterol* 2000; **95**: 204-207 [PMID: 10638584 DOI: 10.1111/j.1572-0241.2000.01685.x]
- 23 **Nehls O**, Gregor M, Klump B. Serum and bile markers for cholangiocarcinoma. *Semin Liver Dis* 2004; **24**: 139-154 [PMID: 15192787 DOI: 10.1055/s-2004-828891]
- 24 **Lumachi F**, Lo Re G, Tozzoli R, D'Aurizio F, Facomer F, Chiara GB, Basso SM. Measurement of serum carcinoembryonic antigen, carbohydrate antigen 19-9, cytokeratin-19 fragment and matrix metalloproteinase-7 for detecting cholangiocarcinoma: a preliminary case-control study. *Anticancer Res* 2014; **34**: 6663-6667 [PMID: 25368272]
- 25 **Takada M**, Masuda N, Matsuura E, Kusunoki Y, Matui K, Nakagawa K, Yana T, Tuyuguchi I, Oohata I, Fukuoka M. Measurement of cytokeratin 19 fragments as a marker of lung cancer by CYFRA 21-1 enzyme immunoassay. *Br J Cancer* 1995; **71**: 160-165 [PMID: 7529525]
- 26 **Nakata B**, Chung YS, Kato Y, Ogawa M, Ogawa Y, Inui A, Maeda K, Sawada T, Sowa M. Clinical significance of serum CYFRA 21-1 in gastric cancer. *Br J Cancer* 1996; **73**: 1529-1532 [PMID: 8664124]
- 27 **Nakata B**, Takashima T, Ogawa Y, Ishikawa T, Hirakawa K. Serum CYFRA 21-1 (cytokeratin-19 fragments) is a useful tumour marker for detecting disease relapse and assessing treatment efficacy in breast cancer. *Br J Cancer* 2004; **91**: 873-878 [PMID: 15280913 DOI: 10.1038/sj.bjc.6602074]
- 28 **Andreadis C**, Touloupidis S, Galaktidou G, Kortsaris AH, Boutis A, Mouratidou D. Serum CYFRA 21-1 in patients with invasive bladder cancer and its relevance as a tumor marker during chemotherapy. *J Urol* 2005; **174**: 1771-1775; discussion 1775-1776 [PMID: 16217281 DOI: 10.1097/01.ju.0000176742.53556.25]
- 29 **Yuan CC**, Huang TS, Ng HT, Liu RS, Hung MW, Tsai LC. Elevated cytokeratin-19 expression associated with apoptotic resistance and malignant progression of human cervical carcinoma. *Apoptosis* 1998; **3**: 161-169 [PMID: 14646497]
- 30 **Chapman MH**, Sandanayake NS, Andreola F, Dhar DK, Webster GJ, Dooley JS, Pereira SP. Circulating CYFRA 21-1 is a Specific Diagnostic and Prognostic Biomarker in Biliary Tract Cancer. *J Clin Exp Hepatol* 2011; **1**: 6-12 [PMID: 22228935 DOI: 10.1016/S0973-6883(11)60110-2]
- 31 **Adachi Y**, Itoh F, Yamamoto H, Matsuno K, Arimura Y, Kusano M, Endoh T, Hinoda Y, Oohara M, Hosokawa M, Imai K. Matrix metalloproteinase matrilysin (MMP-7) participates in the progression of human gastric and esophageal cancers. *Int J Oncol* 1998; **13**: 1031-1035 [PMID: 9772296]
- 32 **Adachi Y**, Yamamoto H, Itoh F, Hinoda Y, Okada Y, Imai K. Contribution of matrilysin (MMP-7) to the metastatic pathway of human colorectal cancers. *Gut* 1999; **45**: 252-258 [PMID: 10403738]
- 33 **Crawford HC**, Scoggins CR, Washington MK, Matrisian LM, Leach SD. Matrix metalloproteinase-7 is expressed by pancreatic cancer precursors and regulates acinar-to-ductal metaplasia in exocrine pancreas. *J Clin Invest* 2002; **109**: 1437-1444 [PMID: 12045257 DOI: 10.1172/JCI15051]
- 34 **Matsumoto K**, Fujii H, Michalopoulos G, Fung JJ, Demetris AJ. Human biliary epithelial cells secrete and respond to cytokines and hepatocyte growth factors in vitro: interleukin-6, hepatocyte growth

- factor and epidermal growth factor promote DNA synthesis in vitro. *Hepatology* 1994; **20**: 376-382 [PMID: 8045498]
- 35 **Goydos JS**, Brumfield AM, Frezza E, Booth A, Lotze MT, Carty SE. Marked elevation of serum interleukin-6 in patients with cholangiocarcinoma: validation of utility as a clinical marker. *Ann Surg* 1998; **227**: 398-404 [PMID: 9527063]
 - 36 **Bonney GK**, Craven RA, Prasad R, Melcher AF, Selby PJ, Banks RE. Circulating markers of biliary malignancy: opportunities in proteomics? *Lancet Oncol* 2008; **9**: 149-158 [PMID: 18237849 DOI: 10.1016/S1470-2045(08)70027-5]
 - 37 **Shen J**, Wang W, Wu J, Feng B, Chen W, Wang M, Tang J, Wang F, Cheng F, Pu L, Tang Q, Wang X, Li X. Comparative proteomic profiling of human bile reveals SSP411 as a novel biomarker of cholangiocarcinoma. *PLoS One* 2012; **7**: e47476 [PMID: 23118872 DOI: 10.1371/journal.pone.0047476]
 - 38 **Mitchell PS**, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Brian KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci USA* 2008; **105**: 10513-10518 [PMID: 18663219 DOI: 10.1073/pnas.0804549105]
 - 39 **Lu J**, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. *Nature* 2005; **435**: 834-838 [PMID: 15944708 DOI: 10.1038/nature03702]
 - 40 **Meng F**, Henson R, Lang M, Wehbe H, Maheshwari S, Mendell JT, Jiang J, Schmittgen TD, Patel T. Involvement of human micro-RNA in growth and response to chemotherapy in human cholangiocarcinoma cell lines. *Gastroenterology* 2006; **130**: 2113-2129 [PMID: 16762633 DOI: 10.1053/j.gastro.2006.02.057]
 - 41 **Chen L**, Yan HX, Yang W, Hu L, Yu LX, Liu Q, Li L, Huang DD, Ding J, Shen F, Zhou WP, Wu MC, Wang HY. The role of microRNA expression pattern in human intrahepatic cholangiocarcinoma. *J Hepatol* 2009; **50**: 358-369 [PMID: 19070389 DOI: 10.1016/j.jhep.2008.09.015]
 - 42 **Plieskatt JL**, Rinaldi G, Feng Y, Peng J, Yonglithipagon P, Easley S, Laha T, Pairajkul C, Bhudhisawasdi V, Srija B, Brindley PJ, Mulvenna JP, Bethony JM. Distinct miRNA signatures associate with subtypes of cholangiocarcinoma from infection with the tumorigenic liver fluke *Opisthorchis viverrini*. *J Hepatol* 2014; **61**: 850-858 [PMID: 25017828 DOI: 10.1016/j.jhep.2014.05.035]
 - 43 **Plieskatt J**, Rinaldi G, Feng Y, Peng J, Easley S, Jia X, Potriquet J, Pairajkul C, Bhudhisawasdi V, Srija B, Brindley PJ, Bethony J, Mulvenna J. A microRNA profile associated with *Opisthorchis viverrini*-induced cholangiocarcinoma in tissue and plasma. *BMC Cancer* 2015; **15**: 309 [PMID: 25903557 DOI: 10.1186/s12885-015-1270-5]
 - 44 **Karakatsanis A**, Papaconstantinou I, Gazouli M, Lyberopoulou A, Polymeneas G, Voros D. Expression of microRNAs, miR-21, miR-31, miR-122, miR-145, miR-146a, miR-200c, miR-221, miR-222, and miR-223 in patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma and its prognostic significance. *Mol Carcinog* 2013; **52**: 297-303 [PMID: 22213236 DOI: 10.1002/mc.21864]
 - 45 **Liu CZ**, Liu W, Zheng Y, Su JM, Li JJ, Yu L, He XD, Chen SS. PTEN and PDCD4 are bona fide targets of microRNA-21 in human cholangiocarcinoma. *Chin Med Sci J* 2012; **27**: 65-72 [PMID: 22770403]
 - 46 **Chusorn P**, Namwat N, Loilome W, Techasen A, Pairajkul C, Khuntikeo N, Dechakhamphu A, Talabnin C, Chan-On W, Ong CK, Teh BT, Yongvanit P. Overexpression of microRNA-21 regulating PDCD4 during tumorigenesis of liver fluke-associated cholangiocarcinoma contributes to tumor growth and metastasis. *Tumour Biol* 2013; **34**: 1579-1588 [PMID: 23417858 DOI: 10.1007/s13277-013-0688-0]
 - 47 **Wu J**, Li G, Wang Z, Yao Y, Chen R, Pu X, Wang J. Circulating MicroRNA-21 Is a Potential Diagnostic Biomarker in Gastric Cancer. *Dis Markers* 2015; **2015**: 435656 [PMID: 26063956 DOI: 10.1155/2015/435656]
 - 48 **Yan LX**, Huang XF, Shao Q, Huang MY, Deng L, Wu QL, Zeng YX, Shao JY. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. *RNA* 2008; **14**: 2348-2360 [PMID: 18812439 DOI: 10.1261/rna.1034808]
 - 49 **Yamada A**, Horimatsu T, Okugawa Y, Nishida N, Honjo H, Ida H, Kou T, Kusaka T, Sasaki Y, Yagi M, Higurashi T, Yukawa N, Amanuma Y, Kikuchi O, Muto M, Ueno Y, Nakajima A, Chiba T, Boland CR, Goel A. Serum miR-21, miR-29a, and miR-125b Are Promising Biomarkers for the Early Detection of Colorectal Neoplasia. *Clin Cancer Res* 2015; **21**: 4234-4242 [PMID: 26038573 DOI: 10.1158/1078-0432.CCR-14-2793]
 - 50 **Li L**, Masica D, Ishida M, Tomuleasa C, Umegaki S, Kalloo AN, Georgiades C, Singh VK, Khashab M, Amateau S, Li Z, Okolo P, Lennon AM, Saxena P, Geschwind JF, Schlachter T, Hong K, Pawlik TM, Canto M, Law J, Sharaiha R, Weiss CR, Thuluvath P, Goggins M, Shin EJ, Peng H, Kumbhari V, Hutfless S, Zhou L, Mezey E, Meltzer SJ, Karchin R, Selaru FM. Human bile contains microRNA-laden extracellular vesicles that can be used for cholangiocarcinoma diagnosis. *Hepatology* 2014; **60**: 896-907 [PMID: 24497320 DOI: 10.1002/hep.27050]
 - 51 **Cristofanilli M**, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, Reuben JM, Doyle GV, Allard WJ, Terstappen LW, Hayes DF. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 2004; **351**: 781-791 [PMID: 15317891 DOI: 10.1056/NEJMoa040766]
 - 52 **de Bono JS**, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, Doyle GV, Terstappen LW, Pienta KJ, Raghavan D. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2008; **14**: 6302-6309 [PMID: 18829513 DOI: 10.1158/1078-0432.CCR-08-0872]
 - 53 **Cohen SJ**, Punt CJ, Iannotti N, Saidman BH, Sabbath KD, Gabrail NY, Picus J, Morse M, Mitchell E, Miller MC, Doyle GV, Tissing H, Terstappen LW, Meropol NJ. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 3213-3221 [PMID: 18591556 DOI: 10.1200/JCO.2007.15.8923]
 - 54 **Bidard FC**, Huguet F, Louvet C, Mineur L, Bouché O, Chibaudel B, Artru P, Desseigne F, Bachet JB, Mathiot C, Pierga JY, Hammel P. Circulating tumor cells in locally advanced pancreatic adenocarcinoma: the ancillary CirCe 07 study to the LAP 07 trial. *Ann Oncol* 2013; **24**: 2057-2061 [PMID: 23676420 DOI: 10.1093/annonc/mdt176]
 - 55 **Yang JD**, Campion MB, Liu MC, Chaiteerakij R, Giana NH, Ahmed Mohammed H, Zhang X, Hu C, Campion VL, Jen J, Venkatesh SK, Halling KC, Kipp BR, Roberts LR. Circulating tumor cells are associated with poor overall survival in patients with cholangiocarcinoma. *Hepatology* 2016; **63**: 148-158 [PMID: 26096702 DOI: 10.1002/hep.27944]
 - 56 **Al Ustwani O**, Iancu D, Yacoub R, Iyer R. Detection of circulating tumor cells in cancers of biliary origin. *J Gastrointest Oncol* 2012; **3**: 97-104 [PMID: 22811877 DOI: 10.3978/j.issn.2078-6891.2011.047]
 - 57 **Chen J**, Yang R, Lu Y, Xia Y, Zhou H. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol* 2012; **138**: 1433-1441 [PMID: 22752601 DOI: 10.1007/s00432-012-1268-1]
 - 58 **Okasha HH**, Ashry M, Imam HM, Ezzat R, Naguib M, Farag AH, Gemeie EH, Khattab HM. Role of endoscopic ultrasound-guided fine needle aspiration and ultrasound-guided fine-needle aspiration in diagnosis of cystic pancreatic lesions. *Endosc Ultrasound* 2015; **4**: 132-136 [PMID: 26020048 DOI: 10.4103/2303-9027.156742]
 - 59 **van der Waaij LA**, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest Endosc* 2005; **62**: 383-389 [PMID: 16111956]
 - 60 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlowski T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic

- cyst study. *Gastroenterology* 2004; **126**: 1330-1336 [PMID: 15131794]
- 61 **Winner M**, Sethi A, Poneris JM, Stavropoulos SN, Francisco P, Lightdale CJ, Allendorf JD, Stevens PD, Gonda TA. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. *JOP* 2015; **16**: 143-149 [PMID: 25791547]
- 62 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102 [PMID: 19152896 DOI: 10.1016/j.gie.2008.07.033]
- 63 **Shen J**, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer* 2009; **117**: 217-227 [PMID: 19415731 DOI: 10.1002/cncy.20027]
- 64 **Singhi AD**, Nikiforova MN, Fasanella KE, McGrath KM, Pai RK, Ohori NP, Bartholow TL, Brand RE, Chennat JS, Lu X, Papachristou GI, Slivka A, Zeh HJ, Zureikat AH, Lee KK, Tsung A, Mantha GS, Khalid A. Preoperative GNAS and KRAS testing in the diagnosis of pancreatic mucinous cysts. *Clin Cancer Res* 2014; **20**: 4381-4389 [PMID: 24938521 DOI: 10.1158/1078-0432.CCR-14-0513]
- 65 **Bournet B**, Souque A, Senesse P, Assenat E, Barthet M, Lesavre N, Aubert A, O'Toole D, Hammel P, Levy P, Ruzsiewicz P, Bouisson M, Escourrou J, Cordelier P, Buscail L. Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with KRAS mutation assay to distinguish pancreatic cancer from pseudotumoral chronic pancreatitis. *Endoscopy* 2009; **41**: 552-557 [PMID: 19533561 DOI: 10.1055/s-0029-1214717]
- 66 **Bergquist A**, Ekblom A, Olsson R, Kornfeldt D, Lööf L, Danielsson A, Hultcrantz R, Lindgren S, Prytz H, Sandberg-Gertzén H, Almer S, Granath F, Broomé U. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002; **36**: 321-327 [PMID: 11867174]
- 67 **Burak K**, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2004; **99**: 523-526 [PMID: 15056096 DOI: 10.1111/j.1572-0241.2004.04067.x]
- 68 **Rea DJ**, Munoz-Juarez M, Farnell MB, Donohue JH, Que FG, Crownhart B, Larson D, Nagorney DM. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. *Arch Surg* 2004; **139**: 514-523; discussion 523-525 [PMID: 15136352 DOI: 10.1001/archsurg.139.5.514]
- 69 **Jang JY**, Kim SW, Park DJ, Ahn YJ, Yoon YS, Choi MG, Suh KS, Lee KU, Park YH. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. *Ann Surg* 2005; **241**: 77-84 [PMID: 15621994]
- 70 **Jarnagin WR**, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, Youssef BA M, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; **234**: 507-517; discussion 517-519 [PMID: 11573044]
- 71 **DeOliveira ML**, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schulick RD. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; **245**: 755-762 [PMID: 17457168 DOI: 10.1097/01.sla.0000251366.62632.d3]
- 72 **Rosen CB**, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int* 2010; **23**: 692-697 [PMID: 20497401 DOI: 10.1111/j.1432-2277.2010.01108.x]
- 73 **Bangarulingam SY**, Björnsson E, Enders F, Barr Fritcher EG, Gores G, Halling KC, Lindor KD. Long-term outcomes of positive fluorescence in situ hybridization tests in primary sclerosing cholangitis. *Hepatology* 2010; **51**: 174-180 [PMID: 19877179 DOI: 10.1002/hep.23277]
- 74 **Eaton JE**, Barr Fritcher EG, Gores GJ, Atkinson EJ, Tabibian JH, Topazian MD, Gossard AA, Halling KC, Kipp BR, Lazaridis KN. Biliary multifocal chromosomal polysomy and cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2015; **110**: 299-309 [PMID: 25623660 DOI: 10.1038/ajg.2014.433]
- 75 **Barr Fritcher EG**, Kipp BR, Voss JS, Clayton AC, Lindor KD, Halling KC, Gores GJ. Primary sclerosing cholangitis patients with serial polysomy fluorescence in situ hybridization results are at increased risk of cholangiocarcinoma. *Am J Gastroenterol* 2011; **106**: 2023-2028 [PMID: 21844920 DOI: 10.1038/ajg.2011.272]
- 76 **Ponsioen CY**, Vrouenraets SM, van Milligen de Wit AW, Sturm P, Tascilar M, Offerhaus GJ, Prins M, Huibregtse K, Tytgat GN. Value of brush cytology for dominant strictures in primary sclerosing cholangitis. *Endoscopy* 1999; **31**: 305-309 [PMID: 10376457 DOI: 10.1055/s-1999-18]
- 77 **Clayton RA**, Clarke DL, Currie EJ, Madhavan KK, Parks RW, Garden OJ. Incidence of benign pathology in patients undergoing hepatic resection for suspected malignancy. *Surgeon* 2003; **1**: 32-38 [PMID: 15568422]
- 78 **Gonda TA**, Glick MP, Sethi A, Poneris JM, Palmas W, Iqbal S, Gonzalez S, Nandula SV, Emond JC, Brown RS, Murty VV, Stevens PD. Polysomy and p16 deletion by fluorescence in situ hybridization in the diagnosis of indeterminate biliary strictures. *Gastrointest Endosc* 2012; **75**: 74-79 [PMID: 22100297 DOI: 10.1016/j.gie.2011.08.022]
- 79 **Boldorini R**, Paganotti A, Andorno S, Orlando S, Mercalli F, Orsello M, Ballarè M, Magnani C, Sartori M. A multistep cytological approach for patients with jaundice and biliary strictures of indeterminate origin. *J Clin Pathol* 2015; **68**: 283-287 [PMID: 25681513 DOI: 10.1136/jclinpath-2014-202731]
- 80 **Sato N**, Fukushima N, Maehara N, Matsubayashi H, Koopmann J, Su GH, Hruban RH, Goggins M. SPARC/osteonectin is a frequent target for aberrant methylation in pancreatic adenocarcinoma and a mediator of tumor-stromal interactions. *Oncogene* 2003; **22**: 5021-5030 [PMID: 12902985 DOI: 10.1038/sj.onc.1206807]
- 81 **Infante JR**, Matsubayashi H, Sato N, Tonascia J, Klein AP, Riall TA, Yeo C, Iacobuzio-Donahue C, Goggins M. Peritumoral fibroblast SPARC expression and patient outcome with resectable pancreatic adenocarcinoma. *J Clin Oncol* 2007; **25**: 319-325 [PMID: 17235047 DOI: 10.1200/JCO.2006.07.8824]
- 82 **Gundewar C**, Sasor A, Hilmersson KS, Andersson R, Ansari D. The role of SPARC expression in pancreatic cancer progression and patient survival. *Scand J Gastroenterol* 2015; **50**: 1170-1174 [PMID: 25765175 DOI: 10.3109/00365521.2015.1024281]
- 83 **Mantoni TS**, Schendel RR, Rödel F, Niedobitek G, Al-Assar O, Masamune A, Brunner TB. Stromal SPARC expression and patient survival after chemoradiation for non-resectable pancreatic adenocarcinoma. *Cancer Biol Ther* 2008; **7**: 1806-1815 [PMID: 18787407]
- 84 **Sinn M**, Sinn BV, Striefler JK, Lindner JL, Stieler JM, Lohneis P, Bischoff S, Bläker H, Pelzer U, Bahra M, Dietel M, Dörken B, Oettle H, Riess H, Denkert C. SPARC expression in resected pancreatic cancer patients treated with gemcitabine: results from the CONKO-001 study. *Ann Oncol* 2014; **25**: 1025-1032 [PMID: 24562449 DOI: 10.1093/annonc/mdl084]
- 85 **Miyoshi K**, Sato N, Ohuchida K, Mizumoto K, Tanaka M. SPARC mRNA expression as a prognostic marker for pancreatic adenocarcinoma patients. *Anticancer Res* 2010; **30**: 867-871 [PMID: 20393008]
- 86 **Maréchal R**, Bachet JB, Mackey JR, Dalban C, Demetter P, Graham K, Couvelard A, Svrcek M, Bardier-Dupas A, Hammel P, Sauvanet A, Louvet C, Paye F, Rougier P, Penna C, André T, Dumontet C, Cass CE, Jordheim LP, Matera EL, Closset J, Salmon I, Devière J, Emile JF, Van Laethem JL. Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. *Gastroenterology* 2012; **143**: 664-674.e1-6 [PMID: 22705007 DOI: 10.1053/j.gastro.2012.06.006]
- 87 **Fisher SB**, Patel SH, Bagci P, Kooby DA, El-Rayes BF, Staley CA, Adsay NV, Maithel SK. An analysis of human equilibrative nucleoside transporter-1, ribonucleoside reductase subunit M1, ribonucleoside reductase subunit M2, and excision repair cross-complementing gene-1 expression in patients with resected pancreas adenocarcinoma: implications for adjuvant treatment. *Cancer* 2013; **119**: 445-453 [PMID: 22569992 DOI: 10.1002/cncr.27619]

- 88 **Zhang MY**, Li SH, Huang GL, Lin GH, Shuang ZY, Lao XM, Xu L, Lin XJ, Wang HY, Li SP. Identification of a novel microRNA signature associated with intrahepatic cholangiocarcinoma (ICC) patient prognosis. *BMC Cancer* 2015; **15**: 64 [PMID: 25880914 DOI: 10.1186/s12885-015-1067-6]
- 89 **Namwat N**, Chusorn P, Loilome W, Techasen A, Puetkasichonpasutha J, Pairojkul C, Khuntikeo N, Yongvanit P. Expression profiles of oncomir miR-21 and tumor suppressor let-7a in the progression of opisthorchiasis-associated cholangiocarcinoma. *Asian Pac J Cancer Prev* 2012; **13** Suppl: 65-69 [PMID: 23480766]
- 90 **Chen YJ**, Luo J, Yang GY, Yang K, Wen SQ, Zou SQ. Mutual regulation between microRNA-373 and methyl-CpG-binding domain protein 2 in hilar cholangiocarcinoma. *World J Gastroenterol* 2012; **18**: 3849-3861 [PMID: 22876037 DOI: 10.3748/wjg.v18.i29.3849]
- 91 **Zhang J**, Han C, Wu T. MicroRNA-26a promotes cholangiocarcinoma growth by activating β -catenin. *Gastroenterology* 2012; **143**: 246-56. e8 [PMID: 22484120 DOI: 10.1053/j.gastro.2012.03.045]
- 92 **Olaru AV**, Ghiaur G, Yamanaka S, Luvsanjav D, An F, Popescu I, Alexandrescu S, Allen S, Pawlik TM, Torbenson M, Georgiades C, Roberts LR, Gores GJ, Ferguson-Smith A, Almeida MI, Calin GA, Mezey E, Selaru FM. MicroRNA down-regulated in human cholangiocarcinoma control cell cycle through multiple targets involved in the G1/S checkpoint. *Hepatology* 2011; **54**: 2089-2098 [PMID: 21809359 DOI: 10.1002/hep.24591]
- 93 **Chang YT**, Chang MC, Huang KW, Tung CC, Hsu C, Wong JM. Clinicopathological and prognostic significances of EGFR, KRAS and BRAF mutations in biliary tract carcinomas in Taiwan. *J Gastroenterol Hepatol* 2014; **29**: 1119-1125 [PMID: 24372748 DOI: 10.1111/jgh.12505]
- 94 **Yoshikawa D**, Ojima H, Iwasaki M, Hiraoka N, Kosuge T, Kasai S, Hirohashi S, Shibata T. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. *Br J Cancer* 2008; **98**: 418-425 [PMID: 18087285 DOI: 10.1038/sj.bjc.6604129]
- 95 **Mackey JR**, Mani RS, Selner M, Mowles D, Young JD, Belt JA, Crawford CR, Cass CE. Functional nucleoside transporters are required for gemcitabine influx and manifestation of toxicity in cancer cell lines. *Cancer Res* 1998; **58**: 4349-4357 [PMID: 9766663]
- 96 **Spratlin J**, Sangha R, Glubrecht D, Dabbagh L, Young JD, Dumontet C, Cass C, Lai R, Mackey JR. The absence of human equilibrative nucleoside transporter 1 is associated with reduced survival in patients with gemcitabine-treated pancreas adenocarcinoma. *Clin Cancer Res* 2004; **10**: 6956-6961 [PMID: 15501974 DOI: 10.1158/1078-0432.CCR-04-0224]
- 97 **Farrell JJ**, Elsaleh H, Garcia M, Lai R, Ammar A, Regine WF, Abrams R, Benson AB, Macdonald J, Cass CE, Dicker AP, Mackey JR. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. *Gastroenterology* 2009; **136**: 187-195 [PMID: 18992248 DOI: 10.1053/j.gastro.2008.09.067]
- 98 **Maréchal R**, Mackey JR, Lai R, Demetter P, Peeters M, Polus M, Cass CE, Young J, Salmon I, Devière J, Van Laethem JL. Human equilibrative nucleoside transporter 1 and human concentrative nucleoside transporter 3 predict survival after adjuvant gemcitabine therapy in resected pancreatic adenocarcinoma. *Clin Cancer Res* 2009; **15**: 2913-2919 [PMID: 19318496 DOI: 10.1158/1078-0432.CCR-08-2080]
- 99 **Poplin E**, Wasan H, Rolfe L, Raponi M, Ikdaht T, Bondarenko I, Davidenko I, Bondar V, Garin A, Boeck S, Ormanns S, Heinemann V, Bassi C, Evans TR, Andersson R, Hahn H, Picozzi V, Dicker A, Mann E, Voong C, Kaur P, Isaacson J, Allen A. Randomized, multicenter, phase II study of CO-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma: including a prospective evaluation of the role of hENT1 in gemcitabine or CO-101 sensitivity. *J Clin Oncol* 2013; **31**: 4453-4461 [PMID: 24220555 DOI: 10.1200/JCO.2013.51.0826]
- 100 **Nakano Y**, Tanno S, Koizumi K, Nishikawa T, Nakamura K, Minoguchi M, Izawa T, Mizukami Y, Okumura T, Kohgo Y. Gemcitabine chemoresistance and molecular markers associated with gemcitabine transport and metabolism in human pancreatic cancer cells. *Br J Cancer* 2007; **96**: 457-463 [PMID: 17224927 DOI: 10.1038/sj.bjc.6603559]
- 101 **Tanaka M**, Javle M, Dong X, Eng C, Abbruzzese JL, Li D. Gemcitabine metabolic and transporter gene polymorphisms are associated with drug toxicity and efficacy in patients with locally advanced pancreatic cancer. *Cancer* 2010; **116**: 5325-5335 [PMID: 20665488 DOI: 10.1002/cncr.25282]
- 102 **Myers SN**, Goyal RK, Roy JD, Fairfull LD, Wilson JW, Ferrell RE. Functional single nucleotide polymorphism haplotypes in the human equilibrative nucleoside transporter 1. *Pharmacogenet Genomics* 2006; **16**: 315-320 [PMID: 16609362 DOI: 10.1097/01.fpc.0000189804.41962.15]
- 103 **Chou TY**, Chiu CH, Li LH, Hsiao CY, Tzen CY, Chang KT, Chen YM, Perng RP, Tsai SF, Tsai CM. Mutation in the tyrosine kinase domain of epidermal growth factor receptor is a predictive and prognostic factor for gefitinib treatment in patients with non-small cell lung cancer. *Clin Cancer Res* 2005; **11**: 3750-3757 [PMID: 15897572 DOI: 10.1158/1078-0432.CCR-04-1981]
- 104 **Leone F**, Cavalloni G, Pignochino Y, Sarotto I, Ferraris R, Piacibello W, Venesio T, Capussotti L, Risio M, Aglietta M. Somatic mutations of epidermal growth factor receptor in bile duct and gallbladder carcinoma. *Clin Cancer Res* 2006; **12**: 1680-1685 [PMID: 16551849 DOI: 10.1158/1078-0432.CCR-05-1692]
- 105 **Gwak GY**, Yoon JH, Shin CM, Ahn YJ, Chung JK, Kim YA, Kim TY, Lee HS. Detection of response-predicting mutations in the kinase domain of the epidermal growth factor receptor gene in cholangiocarcinomas. *J Cancer Res Clin Oncol* 2005; **131**: 649-652 [PMID: 16032426 DOI: 10.1007/s00432-005-0016-1]
- 106 **Philip PA**, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, Donehower RC, Fitch T, Picus J, Erlichman C. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol* 2006; **24**: 3069-3074 [PMID: 16809731 DOI: 10.1200/JCO.2005.05.3579]
- 107 **Viloria-Petit A**, Crombet T, Jothy S, Hicklin D, Bohlen P, Schlaeppli JM, Rak J, Kerbel RS. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. *Cancer Res* 2001; **61**: 5090-5101 [PMID: 11431346]
- 108 **Yoshikawa D**, Ojima H, Kokubu A, Ochiya T, Kasai S, Hirohashi S, Shibata T. Vandetanib (ZD6474), an inhibitor of VEGFR and EGFR signalling, as a novel molecular-targeted therapy against cholangiocarcinoma. *Br J Cancer* 2009; **100**: 1257-1266 [PMID: 19319137 DOI: 10.1038/sj.bjc.6604988]
- 109 **Voss JS**, Holtegaard LM, Kerr SE, Fritcher EG, Roberts LR, Gores GJ, Zhang J, Highsmith WE, Halling KC, Kipp BR. Molecular profiling of cholangiocarcinoma shows potential for targeted therapy treatment decisions. *Hum Pathol* 2013; **44**: 1216-1222 [PMID: 23391413 DOI: 10.1016/j.humpath.2012.11.006]
- 110 **Tannapel A**, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, Hauss J, Wittekind C. Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. *Gut* 2003; **52**: 706-712 [PMID: 12692057]
- 111 **Robertson S**, Hyder O, Dodson R, Nayar SK, Poling J, Beierl K, Eshleman JR, Lin MT, Pawlik TM, Anders RA. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. *Hum Pathol* 2013; **44**: 2768-2773 [PMID: 24139215 DOI: 10.1016/j.humpath.2013.07.026]
- 112 **Altamari A**, Fiorentino M, Gabusi E, Gruppioni E, Corti B, D'Errico A, Grigioni WF. Investigation of ErbB1 and ErbB2 expression for therapeutic targeting in primary liver tumours. *Dig Liver Dis* 2003; **35**: 332-338 [PMID: 12846405]
- 113 **Law LY**. Dramatic response to trastuzumab and paclitaxel in a patient with human epidermal growth factor receptor 2-positive metastatic cholangiocarcinoma. *J Clin Oncol* 2012; **30**: e271-e273 [PMID: 22851567 DOI: 10.1200/JCO.2012.42.3061]
- 114 **Borger DR**, Tanabe KK, Fan KC, Lopez HU, Fantin VR, Straley KS, Schenkein DP, Hezel AF, Ancukiewicz M, Liebman HM, Kwak EL, Clark JW, Ryan DP, Deshpande V, Dias-Santagata D, Ellisen LW, Zhu AX, Iafrate AJ. Frequent mutation of isocitrate

- dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. *Oncologist* 2012; **17**: 72-79 [PMID: 22180306 DOI: 10.1634/theoncologist.2011-0386]
- 115 **Kipp BR**, Voss JS, Kerr SE, Barr Fritcher EG, Graham RP, Zhang L, Highsmith WE, Zhang J, Roberts LR, Gores GJ, Halling KC. Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. *Hum Pathol* 2012; **43**: 1552-1558 [PMID: 22503487 DOI: 10.1016/j.humpath.2011.12.007]
 - 116 **Xu W**, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Wang P, Xiao MT, Liu LX, Jiang WQ, Liu J, Zhang JY, Wang B, Frye S, Zhang Y, Xu YH, Lei QY, Guan KL, Zhao SM, Xiong Y. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α -ketoglutarate-dependent dioxygenases. *Cancer Cell* 2011; **19**: 17-30 [PMID: 21251613 DOI: 10.1016/j.ccr.2010.12.014]
 - 117 **Okamoto K**, Miyoshi K, Murawaki Y. miR-29b, miR-205 and miR-221 enhance chemosensitivity to gemcitabine in HuH28 human cholangiocarcinoma cells. *PLoS One* 2013; **8**: e77623 [PMID: 24147037 DOI: 10.1371/journal.pone.0077623]
 - 118 **Banno K**, Yanokura M, Iida M, Adachi M, Nakamura K, Nogami Y, Umene K, Masuda K, Kisu I, Nomura H, Kataoka F, Tominaga E, Aoki D. Application of microRNA in diagnosis and treatment of ovarian cancer. *Biomed Res Int* 2014; **2014**: 232817 [PMID: 24822185 DOI: 10.1155/2014/232817]
 - 119 **Nagaraj AB**, Joseph P, DiFeo A. miRNAs as prognostic and therapeutic tools in epithelial ovarian cancer. *Biomark Med* 2015; **9**: 241-257 [PMID: 25731210 DOI: 10.2217/bmm.14.108]
 - 120 **Cote GA**, Gore AJ, McElyea SD, Heathers LE, Xu H, Sherman S, Korc M. A pilot study to develop a diagnostic test for pancreatic ductal adenocarcinoma based on differential expression of select miRNA in plasma and bile. *Am J Gastroenterol* 2014; **109**: 1942-1952 [PMID: 25350767 DOI: 10.1038/ajg.2014.331]
 - 121 **Schultz NA**, Dehlendorf C, Jensen BV, Bjerregaard JK, Nielsen KR, Bojesen SE, Calatayud D, Nielsen SE, Yilmaz M, Holländer NH, Andersen KK, Johansen JS. MicroRNA biomarkers in whole blood for detection of pancreatic cancer. *JAMA* 2014; **311**: 392-404 [PMID: 24449318 DOI: 10.1001/jama.2013.284664]
 - 122 **Wang J**, Chen J, Chang P, LeBlanc A, Li D, Abbruzzese JL, Frazier ML, Killary AM, Sen S. MicroRNAs in plasma of pancreatic ductal adenocarcinoma patients as novel blood-based biomarkers of disease. *Cancer Prev Res (Phila)* 2009; **2**: 807-813 [PMID: 19723895 DOI: 10.1158/1940-6207.CAPR-09-0094]
 - 123 **Leelawat K**, Narong S, Wannaprasert J, Ratanashu-ek T. Prospective study of MMP7 serum levels in the diagnosis of cholangiocarcinoma. *World J Gastroenterol* 2010; **16**: 4697-4703 [PMID: 20872971]
 - 124 **Prakobwong S**, Charoensuk L, Hiraku Y, Pinlaor P, Pairojkul C, Mairiang E, Sithithaworn P, Yongvanit P, Khuntikeo N, Pinlaor S. Plasma hydroxyproline, MMP-7 and collagen I as novel predictive risk markers of hepatobiliary disease-associated cholangiocarcinoma. *Int J Cancer* 2012; **131**: E416-E424 [PMID: 21935919 DOI: 10.1002/ijc.26443]
 - 125 **Cheon YK**, Cho YD, Moon JH, Jang JY, Kim YS, Kim YS, Lee MS, Lee JS, Shim CS. Diagnostic utility of interleukin-6 (IL-6) for primary bile duct cancer and changes in serum IL-6 levels following photodynamic therapy. *Am J Gastroenterol* 2007; **102**: 2164-2170 [PMID: 17617204 DOI: 10.1111/j.1572-0241.2007.01403.x]
 - 126 **Sripa B**, Thinkhamrop B, Mairiang E, Laha T, Kaewkes S, Sithithaworn P, Periago MV, Bhudhisawasdi V, Yonglithipagon P, Mulvenna J, Brindley PJ, Loukas A, Bethony JM. Elevated plasma IL-6 associates with increased risk of advanced fibrosis and cholangiocarcinoma in individuals infected by *Opisthorchis viverrini*. *PLoS Negl Trop Dis* 2012; **6**: e1654 [PMID: 22629477 DOI: 10.1371/journal.pntd.0001654]
 - 127 **Tangkijvanich P**, Thong-ngam D, Theamboonlers A, Hanvivatvong O, Kullavanijaya P, Poovorawan Y. Diagnostic role of serum interleukin 6 and CA 19-9 in patients with cholangiocarcinoma. *Hepatogastroenterology* 2004; **51**: 15-19 [PMID: 15011822]
 - 128 **Selaru FM**, Olaru AV, Kan T, David S, Cheng Y, Mori Y, Yang J, Paun B, Jin Z, Agarwal R, Hamilton JP, Abraham J, Georgiades C, Alvarez H, Vivekanandan P, Yu W, Maitra A, Torbenson M, Thuluvath PJ, Gores GJ, LaRusso NF, Hruban R, Meltzer SJ. MicroRNA-21 is overexpressed in human cholangiocarcinoma and regulates programmed cell death 4 and tissue inhibitor of metalloproteinase 3. *Hepatology* 2009; **49**: 1595-1601 [PMID: 19296468 DOI: 10.1002/hep.22838]
 - 129 **Wang S**, Yin J, Li T, Yuan L, Wang D, He J, Du X, Lu J. Upregulated circulating miR-150 is associated with the risk of intrahepatic cholangiocarcinoma. *Oncol Rep* 2015; **33**: 819-825 [PMID: 25482320 DOI: 10.3892/or.2014.3641]
 - 130 **Silakit R**, Loilome W, Yongvanit P, Chusorn P, Techasen A, Boonmars T, Khuntikeo N, Chamadol N, Pairojkul C, Namwat N. Circulating miR-192 in liver fluke-associated cholangiocarcinoma patients: a prospective prognostic indicator. *J Hepatobiliary Pancreat Sci* 2014; **21**: 864-872 [PMID: 25131257 DOI: 10.1002/jhbp.145]
 - 131 **Wongkham S**, Sheehan JK, Boonla C, Patrakitkomjorn S, Howard M, Kirkham S, Sripa B, Wongkham C, Bhudhisawasdi V. Serum MUC5AC mucin as a potential marker for cholangiocarcinoma. *Cancer Lett* 2003; **195**: 93-99 [PMID: 12767517]
 - 132 **Bamrungphon W**, Prempracha N, Bunchu N, Rangdaeng S, Sandhu T, Srisukho S, Boonla C, Wongkham S. A new mucin antibody/enzyme-linked lectin-sandwich assay of serum MUC5AC mucin for the diagnosis of cholangiocarcinoma. *Cancer Lett* 2007; **247**: 301-308 [PMID: 16793202 DOI: 10.1016/j.canlet.2006.05.007]
 - 133 **Li Y**, Li DJ, Chen J, Liu W, Li JW, Jiang P, Zhao X, Guo F, Li XW, Wang SG. Application of Joint Detection of AFP, CA19-9, CA125 and CEA in Identification and Diagnosis of Cholangiocarcinoma. *Asian Pac J Cancer Prev* 2015; **16**: 3451-3455 [PMID: 25921161]
 - 134 **Furmanczyk PS**, Grieco VS, Agoff SN. Biliary brush cytology and the detection of cholangiocarcinoma in primary sclerosing cholangitis: evaluation of specific cytomorphologic features and CA19-9 levels. *Am J Clin Pathol* 2005; **124**: 355-360 [PMID: 16191503 DOI: 10.1309/J030-JYPW-KQTH-CLNJ]
 - 135 **Siqueira E**, Schoen RE, Silverman W, Martin J, Rabinovitz M, Weissfeld JL, Abu-Elmagd K, Madariaga JR, Slivka A. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2002; **56**: 40-47 [PMID: 12085033]
 - 136 **Moreno Luna LE**, Kipp B, Halling KC, Sebo TJ, Kremers WK, Roberts LR, Barr Fritcher EG, Levy MJ, Gores GJ. Advanced cytologic techniques for the detection of malignant pancreaticobiliary strictures. *Gastroenterology* 2006; **131**: 1064-1072 [PMID: 17030177 DOI: 10.1053/j.gastro.2006.08.021]
 - 137 **Kipp BR**, Stadheim LM, Halling SA, Pochron NL, Harmsen S, Nagorney DM, Sebo TJ, Therneau TM, Gores GJ, de Groen PC, Baron TH, Levy MJ, Halling KC, Roberts LR. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. *Am J Gastroenterol* 2004; **99**: 1675-1681 [PMID: 15330900 DOI: 10.1111/j.1572-0241.2004.30281.x]
 - 138 **Lindberg B**, Arnemo U, Bergquist A, Thörne A, Hjerpe A, Granqvist S, Hansson LO, Tribukait B, Persson B, Broomé U. Diagnosis of biliary strictures in conjunction with endoscopic retrograde cholangiopancreatography, with special reference to patients with primary sclerosing cholangitis. *Endoscopy* 2002; **34**: 909-916 [PMID: 12430077 DOI: 10.1055/s-2002-35298]
 - 139 **Boberg KM**, Jebsen P, Clausen OP, Foss A, Aabakken L, Schrumpf E. Diagnostic benefit of biliary brush cytology in cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2006; **45**: 568-574 [PMID: 16879890 DOI: 10.1016/j.jhep.2006.05.010]
 - 140 **Levy MJ**, Baron TH, Clayton AC, Enders FB, Gostout CJ, Halling KC, Kipp BR, Petersen BT, Roberts LR, Rumalla A, Sebo TJ, Topazian MD, Wiersma MJ, Gores GJ. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. *Am J Gastroenterol* 2008; **103**: 1263-1273 [PMID: 18477350 DOI: 10.1111/j.1572-0241.2007.01776.x]
 - 141 **Kipp BR**, Fritcher EG, Clayton AC, Gores GJ, Roberts LR, Zhang J, Levy MJ, Halling KC. Comparison of KRAS mutation analysis and FISH for detecting pancreaticobiliary tract cancer in cytology specimens collected during endoscopic retrograde

- cholangiopancreatography. *J Mol Diagn* 2010; **12**: 780-786 [PMID: 20864634 DOI: 10.2353/jmoldx.2010.100016]
- 142 **Boberg KM**, Schrupp E, Bergquist A, Broomé U, Pares A, Remotti H, Schjölberg A, Spurkland A, Clausen OP. Cholangiocarcinoma in primary sclerosing cholangitis: K-ras mutations and Tp53 dysfunction are implicated in the neoplastic development. *J Hepatol* 2000; **32**: 374-380 [PMID: 10735605]
 - 143 **Glasbrenner B**, Ardan M, Boeck W, Preclik G, Möller P, Adler G. Prospective evaluation of brush cytology of biliary strictures during endoscopic retrograde cholangiopancreatography. *Endoscopy* 1999; **31**: 712-717 [PMID: 10604612 DOI: 10.1055/s-1999-73]
 - 144 **Ponchon T**, Gagnon P, Berger F, Labadie M, Liaras A, Chavaillon A, Bory R. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. *Gastrointest Endosc* 1995; **42**: 565-572 [PMID: 8674929]
 - 145 **Jailwala J**, Fogel EL, Sherman S, Gottlieb K, Flueckiger J, Bucksot LG, Lehman GA. Triple-tissue sampling at ERCP in malignant biliary obstruction. *Gastrointest Endosc* 2000; **51**: 383-390 [PMID: 10744806]
 - 146 **Baron TH**, Harewood GC, Rumalla A, Pochron NL, Stadheim LM, Gores GJ, Therneau TM, De Groen PC, Sebo TJ, Salomao DR, Kipp BR. A prospective comparison of digital image analysis and routine cytology for the identification of malignancy in biliary tract strictures. *Clin Gastroenterol Hepatol* 2004; **2**: 214-219 [PMID: 15017605]
 - 147 **Draganov PV**, Chauhan S, Wagh MS, Gupte AR, Lin T, Hou W, Forsmark CE. Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. *Gastrointest Endosc* 2012; **75**: 347-353 [PMID: 22248602 DOI: 10.1016/j.gie.2011.09.020]
 - 148 **Ryan ME**, Baldauf MC. Comparison of flow cytometry for DNA content and brush cytology for detection of malignancy in pancreaticobiliary strictures. *Gastrointest Endosc* 1994; **40**: 133-139 [PMID: 8013809]
 - 149 **Macken E**, Drijkoningen M, Van Aken E, Van Steenberghe W. Brush cytology of ductal strictures during ERCP. *Acta Gastroenterol Belg* 2000; **63**: 254-259 [PMID: 11189981]
 - 150 **Schoeffl R**, Haefner M, Wrba F, Pfeffel F, Stain C, Poetzi R, Gangl A. Forceps biopsy and brush cytology during endoscopic retrograde cholangiopancreatography for the diagnosis of biliary stenoses. *Scand J Gastroenterol* 1997; **32**: 363-368 [PMID: 9140159]
 - 151 **Sugiyama M**, Atomi Y, Wada N, Kuroda A, Muto T. Endoscopic transpapillary bile duct biopsy without sphincterotomy for diagnosing biliary strictures: a prospective comparative study with bile and brush cytology. *Am J Gastroenterol* 1996; **91**: 465-467 [PMID: 8633492]
 - 152 **Kubota Y**, Takaoka M, Tani K, Ogura M, Kin H, Fujimura K, Mizuno T, Inoue K. Endoscopic transpapillary biopsy for diagnosis of patients with pancreaticobiliary ductal strictures. *Am J Gastroenterol* 1993; **88**: 1700-1704 [PMID: 8213710]
 - 153 **Kim HJ**, Kim MH, Lee SK, Yoo KS, Seo DW, Min YI. Tumor vessel: a valuable cholangioscopic clue of malignant biliary stricture. *Gastrointest Endosc* 2000; **52**: 635-638 [PMID: 11060188 DOI: 10.1067/mge.2000.108969]
 - 154 **Howell DA**, Beveridge RP, Bosco J, Jones M. Endoscopic needle aspiration biopsy at ERCP in the diagnosis of biliary strictures. *Gastrointest Endosc* 1992; **38**: 531-535 [PMID: 1327937]
 - 155 **Van Laethem JL**, Bourgeois V, Parma J, Delhaye M, Cochaux P, Velu T, Devière J, Cremer M. Relative contribution of K-ras gene analysis and brush cytology during ERCP for the diagnosis of biliary and pancreatic diseases. *Gastrointest Endosc* 1998; **47**: 479-485 [PMID: 9647372]
 - 156 **McNally ME**, Collins A, Wojcik SE, Liu J, Henry JC, Jiang J, Schmittgen T, Bloomston M. Concomitant dysregulation of microRNAs miR-151-3p and miR-126 correlates with improved survival in resected cholangiocarcinoma. *HPB (Oxford)* 2013; **15**: 260-264 [PMID: 23458262 DOI: 10.1111/j.1477-2574.2012.00523.x]
 - 157 **Li B**, Han Q, Zhu Y, Yu Y, Wang J, Jiang X. Down-regulation of miR-214 contributes to intrahepatic cholangiocarcinoma metastasis by targeting Twist. *FEBS J* 2012; **279**: 2393-2398 [PMID: 22540680 DOI: 10.1111/j.1742-4658.2012.08618.x]
 - 158 **Giovannetti E**, Del Tacca M, Mey V, Funel N, Nannizzi S, Ricci S, Orlandini C, Boggi U, Campani D, Del Chiaro M, Iannopollo M, Bevilacqua G, Mosca F, Danesi R. Transcription analysis of human equilibrative nucleoside transporter-1 predicts survival in pancreas cancer patients treated with gemcitabine. *Cancer Res* 2006; **66**: 3928-3935 [PMID: 16585222 DOI: 10.1158/0008-5472.CAN-05-4203]
 - 159 **Fujita H**, Ohuchida K, Mizumoto K, Itaba S, Ito T, Nakata K, Yu J, Kayashima T, Souzaki R, Tajiri T, Manabe T, Ohtsuka T, Tanaka M. Gene expression levels as predictive markers of outcome in pancreatic cancer after gemcitabine-based adjuvant chemotherapy. *Neoplasia* 2010; **12**: 807-817 [PMID: 20927319]
 - 160 **Murata Y**, Hamada T, Kishiwa M, Ohsawa I, Mizuno S, Usui M, Sakurai H, Tabata M, Ii N, Inoue H, Shiraishi T, Isaji S. Human equilibrative nucleoside transporter 1 expression is a strong independent prognostic factor in UICC T3-T4 pancreatic cancer patients treated with preoperative gemcitabine-based chemoradiotherapy. *J Hepatobiliary Pancreat Sci* 2012; **19**: 413-425 [PMID: 21898089 DOI: 10.1007/s00534-011-0440-3]
 - 161 **Greenhalf W**, Ghaneh P, Neoptolemos JP, Palmer DH, Cox TF, Lamb RF, Garner E, Campbell F, Mackey JR, Costello E, Moore MJ, Valle JW, McDonald AC, Carter R, Tebbutt NC, Goldstein D, Shannon J, Derveniz C, Glimelius B, Deakin M, Charnley RM, Lacaine F, Scarfe AG, Middleton MR, Anthony A, Halloran CM, Mayerle J, Oláh A, Jackson R, Rawcliffe CL, Scarpa A, Bassi C, Büchler MW. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. *J Natl Cancer Inst* 2014; **106**: djt347 [PMID: 24301456 DOI: 10.1093/jnci/djt347]
 - 162 **Park BK**, Paik YH, Park JY, Park KH, Bang S, Park SW, Chung JB, Park YN, Song SY. The clinicopathologic significance of the expression of vascular endothelial growth factor-C in intrahepatic cholangiocarcinoma. *Am J Clin Oncol* 2006; **29**: 138-142 [PMID: 16601431 DOI: 10.1097/01.coc.0000204402.29830.08]
 - 163 **Tannapfel A**, Benicke M, Katalinic A, Uhlmann D, Köckerling F, Hauss J, Wittekind C. Frequency of p16(INK4A) alterations and K-ras mutations in intrahepatic cholangiocarcinoma of the liver. *Gut* 2000; **47**: 721-727 [PMID: 11034592]
 - 164 **Xu RF**, Sun JP, Zhang SR, Zhu GS, Li LB, Liao YL, Xie JM, Liao WJ. KRAS and PIK3CA but not BRAF genes are frequently mutated in Chinese cholangiocarcinoma patients. *Biomed Pharmacother* 2011; **65**: 22-26 [PMID: 21051183 DOI: 10.1016/j.biopha.2010.06.009]
 - 165 **Zou S**, Li J, Zhou H, Frech C, Jiang X, Chu JS, Zhao X, Li Y, Li Q, Wang H, Hu J, Kong G, Wu M, Ding C, Chen N, Hu H. Mutational landscape of intrahepatic cholangiocarcinoma. *Nat Commun* 2014; **5**: 5696 [PMID: 25526346 DOI: 10.1038/ncomms5696]
 - 166 **Isa T**, Tomita S, Nakachi A, Miyazato H, Shimoi H, Kusano T, Muto Y, Furukawa M. Analysis of microsatellite instability, K-ras gene mutation and p53 protein overexpression in intrahepatic cholangiocarcinoma. *Hepatogastroenterology* 2002; **49**: 604-608 [PMID: 12063950]
 - 167 **Goldenberg D**, Rosenbaum E, Argani P, Wistuba II, Sidransky D, Thuluvath PJ, Hidalgo M, Califano J, Maitra A. The V599E BRAF mutation is uncommon in biliary tract cancers. *Mod Pathol* 2004; **17**: 1386-1391 [PMID: 15181454 DOI: 10.1038/modpathol.3800204]
 - 168 **Wang P**, Dong Q, Zhang C, Kuan PF, Liu Y, Jeck WR, Andersen JB, Jiang W, Savich GL, Tan TX, Auman JT, Hoskins JM, Misher AD, Moser CD, Yourstone SM, Kim JW, Cibulskis K, Getz G, Hunt HV, Thorgerisson SS, Roberts LR, Ye D, Guan KL, Xiong Y, Qin LX, Chiang DY. Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. *Oncogene* 2013; **32**: 3091-3100 [PMID: 22824796 DOI: 10.1038/onc.2012.315]
 - 169 **Andresen K**, Boberg KM, Vedeld HM, Honne H, Hektoen M, Wadsworth CA, Clausen OP, Karlsen TH, Foss A, Mathisen O, Schrupp E, Lothe RA, Lind GE. Novel target genes and a valid biomarker panel identified for cholangiocarcinoma. *Epigenetics* 2012; **7**: 1249-1257 [PMID: 22983262 DOI: 10.4161/epi.22191]
 - 170 **Andresen K**, Boberg KM, Vedeld HM, Honne H, Jebsen P,

- Hektoen M, Wadsworth CA, Clausen OP, Lundin KE, Paulsen V, Foss A, Mathisen Ø, Aabakken L, Schrumpf E, Lothe RA, Lind GE. Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma. *Hepatology* 2015; **61**: 1651-1659 [PMID: 25644509 DOI: 10.1002/hep.27707]
- 171 **Sriraksa R**, Zeller C, El-Bahrawy MA, Dai W, Daduang J, Jearanaikoon P, Chau-In S, Brown R, Limpaiboon T. CpG-island methylation study of liver fluke-related cholangiocarcinoma. *Br J Cancer* 2011; **104**: 1313-1318 [PMID: 21448164 DOI: 10.1038/bjc.2011.102]
- 172 **Uhm KO**, Lee ES, Lee YM, Kim HS, Park YN, Park SH. Aberrant promoter CpG islands methylation of tumor suppressor genes in cholangiocarcinoma. *Oncol Res* 2008; **17**: 151-157 [PMID: 18773859]
- 173 **Amornpisutt R**, Proungvitaya S, Jearanaikoon P, Limpaiboon T. DNA methylation level of OPCML and SFRP1: a potential diagnostic biomarker of cholangiocarcinoma. *Tumour Biol* 2015; **36**: 4973-4978 [PMID: 25652468 DOI: 10.1007/s13277-015-3147-2]

P-Reviewer: Lee CL, Yu B **S-Editor:** Ji FF **L-Editor:** A
E-Editor: Wu HL



Biliary and pancreatic stenting: Devices and insertion techniques in therapeutic endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography

Benedetto Mangiavillano, Nico Pagano, Todd H Baron, Monica Arena, Giuseppe Iabichino, Pierluigi Consolo, Enrico Opocher, Carmelo Luigiano

Benedetto Mangiavillano, Unit of Gastroenterology and Digestive Endoscopy, General Hospital of Sanremo, 18038 Sanremo, Italy

Nico Pagano, Unit of Gastroenterology, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, 40138 Bologna, Italy

Todd H Baron, Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC 27599, United States

Monica Arena, Giuseppe Iabichino, Carmelo Luigiano, Unit of Digestive Endoscopy, San Paolo Hospital, 20142 Milano, Italy

Pierluigi Consolo, Endoscopy Unit, University Hospital "G. Martino", 98125 Messina, Italy

Enrico Opocher, Department of Surgery, Unit of Hepatobilio-pancreatic and Digestive Surgery, San Paolo Hospital, University of Milan, 20142 Milano, Italy

Author contributions: Mangiavillano B, Pagano N and Luigiano C designed research and wrote, edited and finalized the text; Arena M, Iabichino G and Consolo P performed literature search and analyzed the data; Baron TH and Opocher E reviewed the paper for important intellectual content.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Benedetto Mangiavillano, MD, Unit of

Gastroenterology and Digestive Endoscopy, General Hospital of Sanremo, Via G. Borea 56, 18038 Sanremo, Italy. b_mangiavillano@hotmail.com
Telephone: +39-0184-536870
Fax: +39-0184-536875

Received: July 30, 2015

Peer-review started: July 31, 2015

First decision: September 29, 2015

Revised: October 7, 2015

Accepted: November 23, 2015

Article in press: November 25, 2015

Published online: February 10, 2016

Abstract

Stents are tubular devices made of plastic or metal. Endoscopic stenting is the most common treatment for obstruction of the common bile duct or of the main pancreatic duct, but also employed for the treatment of bilio-pancreatic leakages, for preventing post- endoscopic retrograde cholangiopancreatography pancreatitis and to drain the gallbladder and pancreatic fluid collections. Recent progresses in techniques of stent insertion and metal stent design are represented by new, fully-covered lumen apposing metal stents. These stents are specifically designed for transmural drainage, with a saddle-shape design and bilateral flanges, to provide lumen-to-lumen anchoring, reducing the risk of migration and leakage. This review is an update of the technique of stent insertion and metal stent deployment, of the most recent data available on stent types and characteristics and the new applications for biliopancreatic stents.

Key words: Biliary stent; Pancreatic stent; Endoscopic retrograde cholangiopancreatography; Self-expandable

metal stent; Endoscopic ultrasonography

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Biliary and pancreatic stents have become one of the major advances made in therapeutic endoscopy and the endoscopic placement of these devices has a universally recognized role in the management of numerous pancreatobiliary diseases. This review is an update of the technical considerations and available devices for biliary and pancreatic stenting.

Mangiavillano B, Pagano N, Baron TH, Arena M, Iabichino G, Consolo P, Opocher E, Luigiano C. Biliary and pancreatic stenting: Devices and insertion techniques in therapeutic endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography. *World J Gastrointest Endosc* 2016; 8(3): 143-156 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/143.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.143>

INTRODUCTION

In 1980 the first case of biliary stent placement for drainage of malignant obstructive jaundice was published^[1]. A single-pigtail stent was fashioned using the cut end of an angiography catheter. The procedure was technically successful, but ultimately, the stent migrated upstream.

Cotton^[2] reported the use of a stent made with a double-pigtail design to prevent upward migration and Huibregtse *et al.*^[3] described the creation of side flaps in the wall of a straight stent instead of pigtails to prevent migration.

Today a variety of plastic stents (PSs) with different designs, diameters, lengths and plastic materials have been investigated and available in the market. At the end of the 80s, some authors described the insertion of a self-expandable metal stent (SEMS) across biliary stenosis^[4,5]. Early SEMS had relatively poor stent patency because of over and ingrowth of tissue. Because of their non-removability partially covered (PC) and then fully covered (FC) SEMSs were developed. Such stents are covered by a biocompatible polymer resistant to organic degradation. Despite various original articles and reviews about the types and techniques of stenting for different bilio-pancreatic disorders^[6-9], the majority are focused only on one or more than one pathology or focused to pancreatic or biliary disease. The aim of our review is to emphasize the update of the technique of stent insertion and metal stent deployment, considering the most recent data available on stent types and characteristics and the new applications for bilio-pancreatic stents, both for endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS), considering also the gallbladder drainage and pancreatic fluid collections (PFC).

TECHNIQUES OF BILIARY AND GALLBLADDER STENTING AND TYPES OF STENTS

Plastic biliary stents

Ideally PSs should be technically easy to insert, should effectively relieve biliary obstruction, should not occlude, and should not cause injury to the bile duct or duodenal wall. Several different materials, sizes, and shapes have been used to optimize these aspects (Table 1 and Figure 1).

Plastic biliary stents are composed of polyethylene, polyurethane, polytetrafluoroethylene (Teflon) and other plastic polymers. The diameters of PSs are measured in French (Fr), corresponding to 0.33 mm, and diameters range from 5 Fr to 12 Fr.

PS with a diameter of 10 Fr require a 3.7 mm operative endoscope channel, and, when the diameter is larger (≥ 11.5 Fr) a 4.2 mm operative channel is needed.

PSs have lengths ranging from 1 to 18 cm, and custom-made models may be requested from some manufacturers. A given stent length represents the entire length of the stent, although for some it is the distance between the end flaps. The length of a PS is generally selected to allow the shortest length possible while simultaneously ensuring adequate drainage. The length of plastic stents chosen is that which allows the ends to extend one to two cm over the proximal edge of the biliary lesion and 1 cm inside the duodenum.

Different types of PSs are commercially available. Plastic pig-tail stents are coiled at their proximal and distal extremities, or only at the distal (double pig-tail or single pig-tail, respectively). Side hole are generally placed at the coiled end. PSs may be straight or curved, with a flap on the proximal and the distal end and a side hole or with 4 flaps at both ends, without side holes (Tannenbaum stent). The role of side holes is to maintain biliary or pancreatic flow if the ends of the stent became occluded by bile or food impaction.

However, it has been hypothesized that side-holes can contribute to the formation of sludge. Moreover, the Tannenbaum stent (with multiple flap at its extremities but without side-holes) was designed to prevent migration. The aim of the development in biliary stenting in the recent years has been to increase the patency of the stents, improving the materials used for coating, a double-layer design, and a star-shaped stent winged stent without a central lumen. Finally, PSs are visualized radiographically, and some stents contain radiopaque markers at the proximal and/or distal ends. Introducing kits can be included in the stent package or available individually.

Biliary SEMS

The first widely used SEMS were made of stainless steel, whereas today most SEMS are made of nitinol. SEMS are available as uncovered, partially (PC-SEMS) or fully covered (FC-SEMS) (Figure 2, Tables 2 and 3). Different

Table 1 Technical characteristics of the most commonly used biliary plastic stents

Producer	Model	Diameter (Fr)	Length (cm)	Shape	Material
Boston Scientific	Advanix	7, 8.5, 10	5-18	Duodenal bend, centre bend, double pigtail	Polyethylene
ConMed	Hydroduct	7, 10, 12	4-15	Straight, angled, curved, double pigtail	Polyurethane with hydrophilic hydromer coating
Cook Endoscopy	Compass BDS	7	5, 10, 15	Double pigtail	Polyethylene
Cook Endoscopy	Cotton-Huibregtse	7, 8.5, 10, 11.5	5-18	Angled	Polyethylene
Cook Endoscopy	Cotton-Leung	7, 8.5, 10, 11.5	5-18	Curved	Polyethylene
Cook Endoscopy	Cotton-Leung Sof-Flex	7, 10	5-15	Curved	Polyethylene and polyurethane blend
Cook Endoscopy	Fusion Marathon	10	5-12	Curved	Polyethylene with teflon sleeve
Cook Endoscopy	Antireflux Soehendra-Tannenbaum	8.5, 10, 11.5	5-15	Curved	Teflon
Cook Endoscopy	Solus	10	1-15	Double pigtail	Polyethylene and polyurethane blend
Cook Endoscopy	Zimmon	5, 6, 7, 10	4, 7, 10	Double pigtail	Polyethylene
Endo-Flex	PE-Soft	7, 8.5, 10, 11.5	3-15	Bended, straight, curved, double pigtail, single pigtail	Polyethylene
Endo-Flex	PTFE-Strong	7, 8.5, 10, 11.5	5-15	Bended, straight, curved	Polytetrafluoroethylene
GI Supply	ViaDuct	7, 10	5-15	Winged straight	Polyurethane
Hobbs Medical	Biliary stent	7, 10	4-15	Curved, Double pigtail	Soft polymer blend
Indus Medical	CIBIDI	7, 10	5-15	Straight, curved, double pigtail	Polyurethane and teflon
Olympus	Double Layer	10	4-15	Duodenal bend, centre bend	Inner layer: Perfluoro; middle layer: Stainless steel; outer layer: Polyamide elastomer
Olympus	Biliary EVA	7, 8.5, 10, 12	5-18	Straight, proximal bend, centre bend, double pigtail	Ethylene vinyl acetate copolymers
Olympus	Biliary FEP	7, 8.5, 10, 12	3-15	Straight, proximal bend	Fluorinated ethylene propylene
Olympus	Biliary PE	7, 8.5, 10, 12	3-15	Straight, proximal bend, centre bend, double pigtail	Polyethylene
Pauldrach Medical	Gallengangs	7, 8.4, 10	9	Curved	Polyethylene

**Figure 1** A display of different types of biliary plastic stents available.

materials contribute to the cover of the PFC-SEMS and of the FC-SEMS such as polytetrafluoroethylene, silicone and polyurethane, present on the exterior or interior of the SEMS.

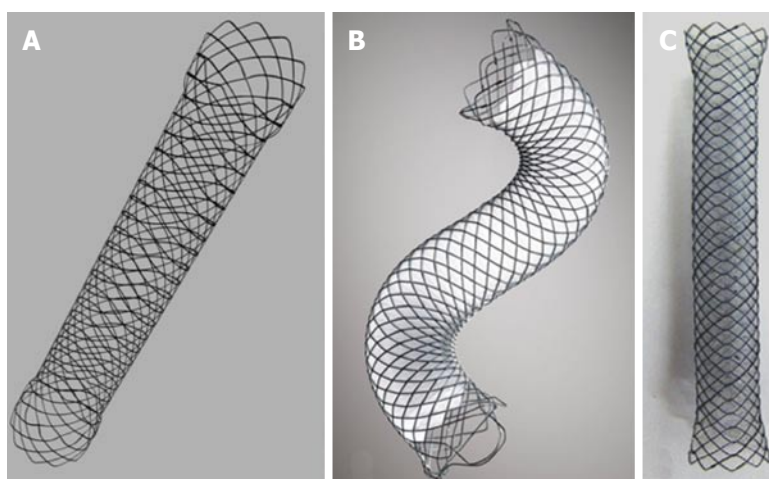
Mechanical properties of SEMS are related to the stent design, type of wire, and covering materials. As

a result of combinations of these variables, radial force and axial force were proposed as major mechanical properties that affect clinical outcomes. Radial force is well known as an expanding force, while axial force is a straightening or recovery force when SEMS are bent.

Radial force affects stent patency in that dilation of

Table 2 Technical characteristics of the most commonly used uncovered self-expandable metal stents

Producer	Model	Material	Diameter (mm)	Length (cm)	Shortening	Reconstrain	Characteristics
Boston Scientific	Wallflex®	Platinol	8, 10	4, 6, 8, 10	Yes	Yes	-----
ConMed	Flexxus	Nitinol	8, 10	4, 6, 8, 10	Yes	No	Pistol delivery system
Cook Endoscopy	Zilver®	Nitinol	6, 8, 10	4, 6, 8	No	No	-----
Cook Endoscopy	Evolution®	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	Pistol delivery system
Ella-CS	SX-ELLA®	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	-----
	Nitinella Plus						
Endochoice	Bonastent®	Nitinol	8, 10	4, 5, 6, 8, 10, 12	Yes	Yes	-----
Endo-Flex	BIL-stent	Nitinol	10	6, 8, 10	Yes	No	-----
Endo-Technik	NIT-BIL-1010®	Nitinol	10	4, 6, 8, 10	Yes	Yes	-----
Leufen Medical	Aixstent®	Nitinol	8, 10	4, 6, 8	Yes	No	-----
Leufen Medical	Gallengang Aixstent®	Nitinol	8, 10	4, 6, 8, 10, 12	Yes	No	The open cell design allows for Y stenting at the hilar region
Leufen Medical	Gallengang BDL - BDH						
Merit Endotek	Alimaxx-B®	Nitinol	8, 10	4, 6, 8	Yes	No	The open cell design allows for Y stenting at the hilar region
M.I. Tech	Hanarostent®	Nitinol	8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	Yes	-----
M.I. Tech	Hanarostent® Hilar	Nitinol	10	8	Yes	No	The large cell design allows for Y stenting at the hilar region
Micro-Tech	BD stents Classic or Platinum-Line	Nitinol	10	4, 6, 8, 10	Yes	No	-----
Olympus	NIRflex	Nitinol	8, 10	4, 6, 8, 10	Yes	No	-----
S and G Biotech	EGIS® Biliary DC Stent	Nitinol	8, 10, 12	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	Single or double bare
TaeWoong Medical	LCD®	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	The large cell design allows for Y stenting at the hilar region
TaeWoong Medical	Niti-S® D-type	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	-----
TaeWoong Medical	Niti-S® S-type	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	-----

**Figure 2** A display of different types of biliary self-expandable metal stents available. The Evolution (A) uncovered stent, Cook Endoscopy, the Wallflex (B) partially covered stent, Boston Scientific, and the SHC (C) fully covered stent, Hanaro MI Tech.

a biliary stricture and maintenance of luminal patency depend on the expanding force of the SEMS. Two factors in radial force exist in terms of time course. Immediate stent expansion at the time of stent deployment affects short-term outcomes, and chronic resistant force against tissue compression affects long-term outcomes. In general, the chronic resistant radial force is higher than the immediate stent expanding force because SEMS are made of a type of shape-memory alloy. This characteristic

means that SEMS partially expand immediately after deployment and then gradually expand to their full extent, even though the radial force may be high. Axial force is considered to define conformability of SEMS in the bile duct and may have a greater relationship with clinical outcomes than radial force. After deployment in the bile duct, SEMS are fixed at the stricture by the tissue and axial force causes compression to the bile duct at both stent ends. As axial force increases, so does the

Table 3 Technical characteristics of the most commonly used partially and fully-covered self-expandable metal stents

Producer	Model	Material	Diameter (mm)	Length (cm)	Shortening	Reconstrain	Shape	Covering
Allium Medical	Allium BIS®	Nitinol	8, 10	6, 8, 10, 12	No	No	Straight with anchoring segment	FC in polyurethane
Boston Scientific	Wallflex®	Platinol	8, 10	4, 6, 8, 10	Yes	Yes	Two flanges	PC and FC in permalume
Cook Endoscopy	Evolution®	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	Two flanges	PC and FC in silicone
Ella-CS	SX-ELLA® Nitinella Plus	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	Two flanges	PC and FC in silicone
Endochoice	Bonastent®	Nitinol	8, 10	4, 5, 6, 8, 10, 12	Yes	Yes	Two flanges	FC in silicone
Endo-Flex	BIL-stent	Nitinol	10	6, 8	Yes	No	Straight	FC in silicone
Endo-Technik	NIT-BIL-1010®	Nitinol	10	4, 6, 8, 10	Yes	No	Straight	PC in silicone
Gore Medical	Viabil®	Nitinol	8, 10	4, 6, 8, 10	No	No	Straightwith anchoring fins	FC in PTFE with/without drainage holes
Leufen Medical	Aixstent® Gallengang	Nitinol	8, 10	4, 6, 8	Yes	No	Two flanges	PC and FC in polyurethane
M.I. Tech	Hanarostent® BCT	Nitinol	10	4, 6, 8, 10	Yes	Yes	One flange with flaps and lasso	FC in silicone
M.I. Tech	Hanarostent® BCS	Nitinol	10	4, 6, 8, 10, 12	Yes	No	One flange and with flaps	FC in silicone
M.I. Tech	Hanarostent® BPE	Nitinol	8, 10	8, 10	Yes	No	One flange and with flaps	PC in silicone
Micro-Tech	BD stents	Nitinol	10	4, 6, 8, 10	Yes	No	Two flanges	PC and FC in silicone
S and G	EGIS® Biliary DC	Nitinol	8, 10, 12	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	Two flanges	PC in PTFE
Biotech	Stent	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 10, 12	Yes	No	Two flanges	FC in silicone
TaeWoong Medical	Niti-S® S-type covered	Nitinol	6, 8, 10	4, 5, 6, 7, 8	Yes	No	Two flanges	FC in silicone
TaeWoong Medical	Niti-S® Kaffes	Nitinol	6, 8, 10	4, 5, 6, 7, 8	Yes	No	Tapered with long lasso	FC in silicone
TaeWoong Medical	Niti-S® Bumpy	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 10, 12	Yes	No	Two flanges	FC in silicone and PTFE
TaeWoong Medical	Niti-S® Giobor	Nitinol	8, 10	8, 10	Yes	No	One flange	PC in silicone
TaeWoong Medical	Niti-S® ComVi	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 10, 12	Yes	No	Straight	FC in PTFE

PC: Partially covered; FC: Fully-covered; PTFE: Polytetrafluoroethylene.

compression of the bile duct or cystic duct or pancreatic duct orifice. Clinically, this situation may cause kinking of the bile duct with resultant cholecystitis or pancreatitis. In addition, less conformability of SEMS in the bile duct leads to stent migration. In general, axial force affects clinical outcomes such as stent migration and pancreatitis more than radial force.

SEMS have lengths ranging from 4 to 12 cm and diameters from 6 to 10 mm. The stents are mounted on a delivery system accepting a wire of 0.035 diameter, and the newest models can be also used with a single operator system. The diameters of the delivery systems range between 5.0 and 10.5 Fr. The smaller the catheter the easier it is to cross the stenosis without mechanical or pneumatic dilation. The same can be said for patients with Klatskin neoplasia.

The majority of the delivery kits are resistant, avoiding kinking during insertion, allowing correct placement; the outer sheath of the kit is transparent for the visualization of the distal stent extremity during SEMS release. During stent placement, the outer sheath is gently pulled inside the operative endoscope channel to allow the release and expansion of the SEMS. Rarely, the stent is constrained by a thread that, when removed, allows SEMS expansion.

Generally, SEMS can be recaptured, until 80% of their opening and all metal stents are visible fluoroscopically. The majority of SEMS have a marker at both extremities and, in some models, one at the middle. Some models of FC-SEMS have anti-migration flaps or flared ends to avoid distal or proximal migration (Figure 3).

Recently, a new type of FC-SEMS is produced with the intent to diminish proximal and distal migration (Figure 4). The Hanaro, M.I. Tech, Seoul, South Korea has an "anchoring-flap" system made of four flaps in the proximal end, flared ends and one proximal and one distal lasso for retrieval. TaeWoong produces the Bumpy®-Niti-S stent, with a membrane of silicone (distal extremity) and polytetrafluoroethylene (body of the stent). This stent has both flared ends and a string for the removal, at the distal extremity. The characteristic of this FC-SEMS are the irregular meshes; it contributes to a different radial force in every point of the stent, conferring conformability and adaptability in the lumen of the duct, preventing migration.

Technique of transpapillary biliary stenting

Before stent placement a cholangiogram is performed to confirm successful biliary cannulation and to evaluate the

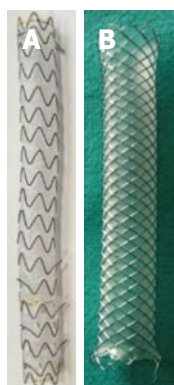


Figure 3 The Viabil (A) fully covered stent, Gore Medical, and the Wallflex (B) fully covered stent, Boston Scientific.

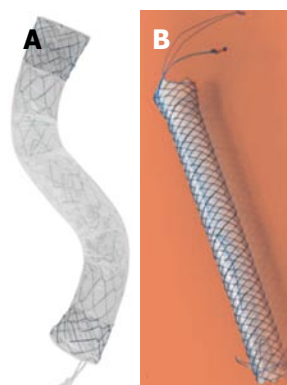


Figure 4 The Bumpy Niti-S stent (A), Taewoong Medical and The BCT stent (B), Hanaro MI Tech.

location and length of the stricture or leak^[10-12].

The correct choice of PS length is often based on operator's experience. Alternatively after bile duct contrast medium injection, or using a centimeter guidewire. An alternative way to measure the length of the strictures for the choice of the stent is to gently withdrawing the catheter from the proximal to the distal end of the strictures, measuring with a ruler the centimeters of the device out of the operating channel.

Endoscopic sphincterotomy (ES) is not necessary for inserting a single PS, while is indispensable for multiple plastic stenting. If the stricture is tight, dilation with a balloon or a bougie before stenting may be useful. Balloon dilatation of strictures is usually helpful for placement of hilar PSs, particularly when bilateral stenting is attempted. Moreover, in these strictures, there is still a role for stents of smaller diameter and the tapered pigtail stent design. For example, if bilateral stenting is required in patients with hilar obstruction, it is often easier to place two 7 Fr stents initially to gradually dilate the bile duct and then replace them later with 10 Fr stents. Tapered pigtail stents are sometimes helpful to allow passage across very tight strictures.

The PS stent is loaded on a guide-catheter, over the guidewire, with the pusher-catheter. The guide-catheter and guidewire need to be made wet using a saline solution because they are hydrophilic. The entire stent insertion loaded kit is introduced inside the operative channel. When the PS is placed across the stricture, moving the endoscope in anti-clockwise rotation and with alternately moving the elevator up and down, the guide-catheter is pulled back, pushing the stent inside the CBD with the pusher-tube. When the guide-catheter is completely pulled back, the pusher-catheter can be removed from the channel.

During stent placement, maintaining the endoscope close to the Vater's papilla facilitates tent insertion because it avoids looping of the delivery system in the duodenal lumen.

If the guide-catheter is inadvertently withdrawn from the inside of the PS, it may be possible to readvance it, continuing the stent placement. When stent insertion is

challenging, the "long position" of the endoscope might be useful. This position allows to the operator to then use the straightening maneuver and, maintaining the elevator in up position, insert the stent into the duct. If the PS is damaged during insertion in the bile duct it can be removed over-the-wire, by passing a dilation balloon inside the PS or by using the Soehendra retriever, leaving the wire in place, and replacing the a new PS delivery system.

A final radiographic image should be obtained to verify if contrast medium drains through the stent. For implantation of a SEMS an ES is often performed, though is not mandatory. Then, under fluoroscopic examination (for biliary strictures), the length, presence or absence of a gallbladder and the relationship of the cystic duct with the CBD is determined for the correct choice of the type of the SEMS (length, diameter and covered vs uncovered).

Because of a potential risk of cholecystitis, some endoscopists prefer to use uncovered SEMS in the presence of a gallbladder, to avoid the cystic duct occlusion, or to place a FCSEMS, when indicated and a small diameter plastic stent inside the cystic duct. Before their insertion into the duct, the uncovered SEMS and the FC-SEMS are generally wet with saline solution in the guidewire channel and inside the outer sheath.

The release of the SEMS is performed under X-ray control, withdrawing the outer sheath of the device, pulling down the elevator, maintaining the stent in the correct position during the release, pulling back the device as it tends to move away from the operator and proximally into the duct. Most of the stent can be recaptured until 80% of the complete release. At the end of the procedure, after metal stent release a cholangiography is required to confirm the correct position of the SEMS and flow of contrast medium flow into the duodenal lumen. If the SEMS is released too proximally, it can be withdrawn distally grasping the distal extremity, or the distal thread, with a rat-tooth forceps. If these attempts fail, a second stent can be deployed, with the distal extremity inside the proximal one of the previous stent. Contrariwise, if the SEMS is released too distally into the duodenum, it can be

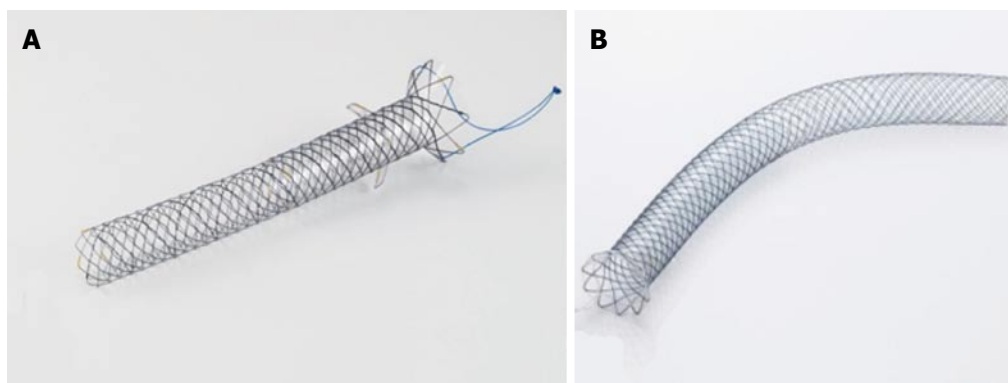


Figure 5 The BPE stent (A), Hanaro MI Tech, and the Giobor Niti-S stent (B), Taewoong Medical.

completely removed by a rat-tooth forceps or the excess stent cut using argon plasma coagulation.

Different techniques are utilized for the drainage of the hepatic hilum. Preoperative magnetic resonance cholangiopancreatography or high-resolution CT should be performed in all patients with suspected proximal biliary stenosis to delineate the anatomy before the procedure. SEMS insertion can be performed using the "side-by-side" (SBS) or the "stent-in-stent" (SIS -"Y") technique.

When SBS technique is performed, two or more guidewires are placed inside different biliary ducts to be drained. After the release of the first metal stent, the insertion of the delivery system of the second SEMS can be difficult because of the impaction of the distal ends of the first SEMS with the delivery of the second one. A way to overcome this difficulty is the insertion of a temporary plastic stent to maintain an accessory space between the first SEMS and the duct wall. In SBS technique the first lobe to drain is the left because the SEMS insertion in the right lobe is easier.

With the SIS technique, the second stent is deployed inside the meshes of the first stent. Balloon dilation of the first SEMS meshes might be helpful to facilitate positioning of the second SEMS device. Some SEMS are designed with large diameter meshes of the middle part to facilitate the deployment of the second one (Y-shaped stent).

Endoscopic ultrasound-guided biliary drainage

In recent years, EUS has evolved from a diagnostic to a therapeutic procedure, and is now increasingly used to guide biliary drainage (BD) after failed ERCP. For therapeutic EUS, the use of a linear-array endoscope with a 3.8 mm operative channel is preferable to allow the passage of large diameter accessories. There are two possible puncture routes for EUS-BD; transgastric for the intra-hepatic bile duct drainage or transduodenal (bulb) for extrahepatic bile duct drainage. During therapeutic EUS Color Doppler is mandatory, to prevent damage to interposed vessels between the endoscope and the ducts. The puncture of the duct to drain can be performed with a fine needle aspiration (FNA) needle of 19- or 22-gauge (G). The 19 G needle is generally used because the capability of support a 0.035-inch guidewire, which provides more

stiffness. The 22 G needle accommodates only a 0.018-inch guidewire, which carries a greater risk of dislodgement of the guidewire during the procedure. After duct access with the EUS needle, contrast medium injection from the needle is required to perform cholangiography for the confirmation of the correct position of the needle inside the biliary tree. After that, under fluoroscopic guidance, the guidewire can be placed into the duct, advancing it inside the needle^[13-16].

If the drainage is performed transmurally from the stomach, only intrahepatic ducts can be drained [hepaticogastrostomy (HPG)], and if performed from the duodenal bulb the extrahepatic bile duct are more accessible [choledochoduodenostomy (CLD)]. If the guidewire exits the papilla, the drainage can be integrated by ERCP, using the *rendezvous* technique. When the deployment of the stent is performed through the puncture route or deployed across the stricture or the ampulla in an antegrade fashion, different devices can be used for dilation of the site, such as bougie (6 or 7 Fr), pneumatic dilation balloon (4 or 6 mm) or a cystotome (8.5 Fr). Both plastic and metal stents are used for HPG or CLD although PC and FC SEMS are most often used to prevent stent migration and bile leakage. Uncovered SEMS should not be used for HPG or CLD. Recently two new SEMS have emerged specifically designed for EUS-BD (Figure 5).

The Giobor Niti-S, Taewoong, is a PC-SEMS with the inner part (intra-biliary) uncovered to prevent intrahepatic bile duct obstruction and migration, and covered in the trans and intragastric part to prevent bile leakage; it also has a single lasso for possible retrieval. The BPE, Hanaro MI Tech, is a PC-SEMS, the proximal portion, which is 15 to 55 mm in length, is uncovered for the prevention of duct obstruction, while the distal end, 35 mm in length, has a silicone cover for the prevention of bile leakage. The BPE stent has anti-migration flaps at both extremities, for prevention of stent migration.

Technique of transpapillary gallbladder stenting

Cystic duct negotiation is the most challenging part of transpapillary gallbladder stenting. Methods to reach the cystic duct are cholangiography and fluoroscopy arm longitudinal and transversal axis rotation to allow for identification of the level of its insertion into the CBD^[17,18].

Table 4 Technical characteristics of the most commonly used pancreatic plastic stents

Producer	Model	Diameter (Fr)	Length (cm)	Shape	Material
Boston scientific	Advanix	3, 4, 5, 7, 10	2-18	Straight or single pigtail with or without internal flap	Polyethylene
Cook endoscopy	Geenan Sof-Flex	5	3-12	Curved with or without internal flap	Polyethylene and polyurethane blend
Cook endoscopy	Geenan	3, 5, 7	3-15	Curved	Polyethylene
Cook endoscopy	Johlin Wedge	8.5, 10	8-22	Wedge	Polyethylene and polyurethane blend
Cook endoscopy	Zimmon	3, 5, 7	2-12	Single pigtail with or without internal flap	Polyethylene
Endo-Flex	PTFE-Strong	5, 7	3-9	Curved	Polytetrafluoroethylene
GI supply	ViaDuct	5, 7	3-12	Winged straight or single pigtail with or without internal flap	Polyurethane
Hobbs medical	Freeman Flexi-Stents	3, 4, 5, 7	2-18	Straight or single pigtail with or without internal flap	Soft polymer
Olympus	Pancreatic PE	7, 8.5, 10	3-15	Straight, S-shaped	Polyethylene

For a left-side cystic duct take-off, a flexible-tip catheter or a rotatable sphincterotome may be used, while for a right-sided take-off, a standard sphincterotome may be used because it usually bows toward the cystic duct when it takes off on the right side. A 0.035" or 0.025" guidewire (stiff or hydrophilic) is used to enter into the cystic duct orifice. The angled tip guidewires are preferable to enter and pass through the spiral valves of Heister while minimizing the risk of perforation. In difficult cannulation of the cystic duct, an inflated Fogarty balloon up to the cystic duct insertion, with an angled-tip guidewire passed alongside may be useful for its negotiation. After cystic duct negotiation, the guidewire is advanced and coiled within the gallbladder lumen and an accurate study of the course and diameter of the duct must be performed for the correct choice of the stent. The catheter is then removed and the stent placed over the wire. Double pigtail 6 to 10 Fr PSs are preferable because of their superior anchorage into the gallbladder lumen compared with straight stents. The length of the stent is chosen based upon the distance between the major duodenal papilla and the gallbladder (usually 12-15 cm long stents are used) and the stent size according to the diameter of the cystic duct and common bile duct. When 10 Fr stents are placed, an ES should be performed to minimize the risk of post-ERCP pancreatitis caused by the fulcrum effect.

EUS guided gallbladder drainage

EUS guided gallbladder drainage (EUS-GD) is performed using a large channel (3.7 or 3.8 mm) echoendoscope with fluoroscopic guidance^[19-22].

The best way to visualize the gallbladder is the prepyloric area, in the stomach, or from the duodenal bulb. The puncture is performed in the site in which gallbladder is in contact with the bowel. The more stable the echoendoscope position the easier the procedure. Color Doppler is mandatory, before gallbladder puncture, to avoid puncture of interposed blood vessels.

A 19 G FNA needle is usually used to obtain gallbladder access. After gallbladder puncture and removal of the stylet, cholecystography is performed by injecting contrast medium through the needle. After cholecystography, a

guidewire is inserted and coiled inside the gallbladder. After the removal of the needle, the access-site can be enlarged using either a mechanical (6 or 7 Fr bougie or balloon catheters) or electrocautery (6 or 10 Fr cystotome or needle-knife) device. After dilation, the stent is advanced over the wire and into the gallbladder.

Recently, a single-step device allowing access, dilation and plastic stent placement has been developed for EUS-GD (Giovannini Needle Wire Oasis, Cook Ireland Ltd, Limerick, Ireland).

Plastic stents, standard or modified tubular covered SEMSs and lumen apposing metal stents (LAMSs) are used. Plastic stents were used for EUS-GD in early studies. However, the PSs can become occluded and may not allow complete sealing between the gallbladder and duodenal or gastric wall with a relative risk of bile leak in the abdomen.

To circumvent the limitations of plastic stents tubular FCSEMS were used for EUS-GD. Metal stents, with their high radial force and covering can reduce this risk. The larger diameters may facilitate draining of thick or necrotic debris, pus or sludge reducing the risk of stent clogging.

However when metal and plastic stents designed for ERCP are used migration remains an important risk. Recently LAMS have been developed to obtain better anchorage between the gallbladder or bile ducts and the bowel wall, reducing the risk of stent migration and bile leakage. These include the Axios stent (Boston Scientific, Natick, MA, United States) (Figure 6A) and Spaxus Niti-S stent (Taewoong Medical, Seoul, South Korea) (Figure 6B).

TECHNIQUES OF PANCREATIC DUCT AND PERI-PANCREATIC FLUID COLLECTION DRAINAGE AND TYPES OF STENTS

Pancreatic plastic stents

Pancreatic stents (Table 4 and Figure 7) are made of

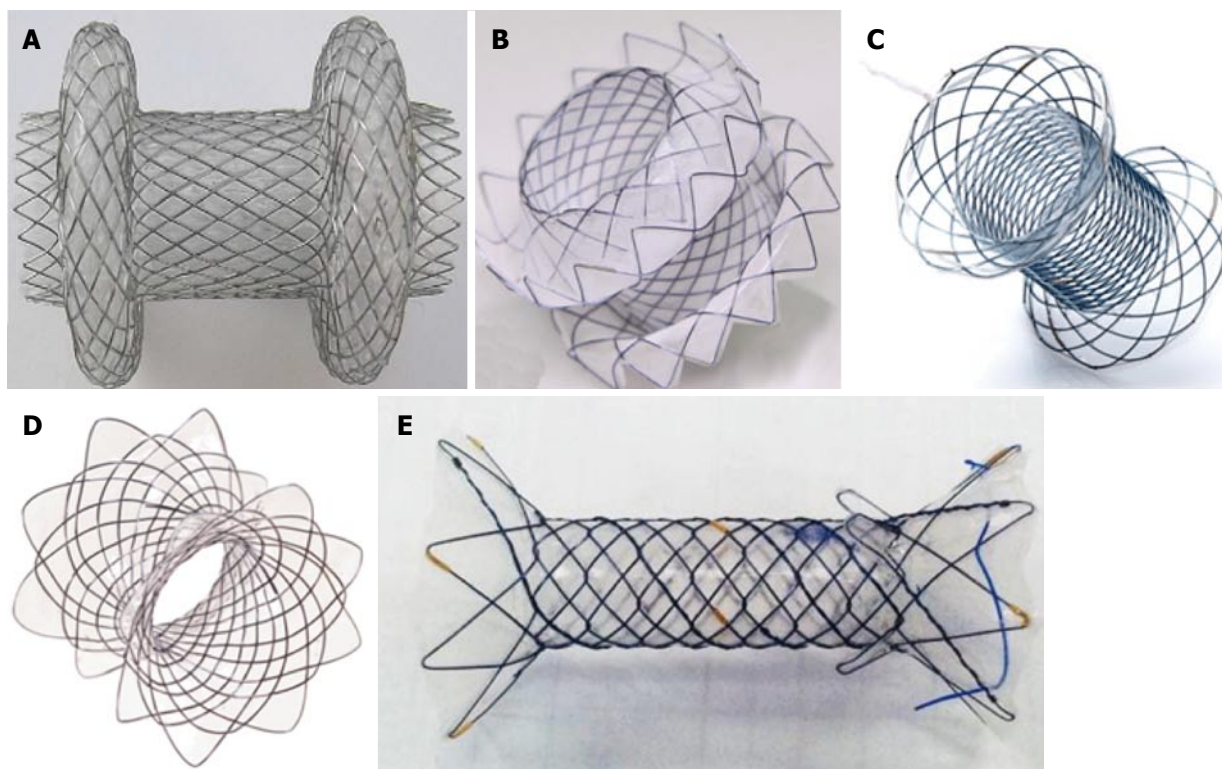


Figure 6 A display of different types of lumen apposing metal stents available: The AXIOS (A) stent, Boston Scientific, the Spaxus (B) and NAGI (C) Niti-S stents, Taewoong Medical, the Aix (D) stent, Leufen Medical, and the BCF (E) stent, Hanaro MI Tech.

polyethylene; the shape and design resemble those of biliary stents, save for the presence of side holes along the length of the stent. The side holes allow draining of pancreatic juice from side branches.

Pancreatic stents have lengths between 2 and 25 cm and diameters between 3 and 11.5 Fr. Different types of stents are now commercially available, with different shapes as straight, winged or with curved distal end or wedged proximal end. Some of these have a "J" or single pigtail shape to prevent migration into the pancreatic duct. There is also an S-shaped stent with many side holes and made in ethylene-vinyl-acetate (EVA). EVA has more flexibility compared to polyethylene.

Pancreatic stents with S-shape are made for a better adapting to the profile of the main pancreatic duct. A winged stent (Via-Duct stent, GI Supply) is made to allow pancreatic juice to flow through the wings of the stent.

Pancreatic PSs without a proximal flap are designed to allow spontaneous distal migration, when the stent are only to be used for a short time. Pancreatic PSs with a distal end pig-tail are designed for avoidance of proximal migration.

The majority of pancreatic PSs are deployed over-the-wire, only with the push-catheter, without the use of the guide-catheter, because of their small diameter. Pancreatic plastic stent with a diameter more than 8.5 Fr requires the use of a guide-catheter.

Pancreatic self-expandable metal stents

The only self-expandable stent designed for drainage

of the main pancreatic duct (MPD) is the TaeWoong Bumpy® - Niti-S, that presents a non-regular cell mesh. It results in a different radial force in every part of the stent, avoiding compression of the side branches of the pancreatic duct.

However, other FC-SEMS are used off-label with good outcomes in selected situations, such as the WallFlex (Boston Scientific) and the Viabil (Gore Medical). The Viabil stent is fully covered and available with side holes designed to allow cystic duct drainage and which may allow drainage of some pancreatic duct side branches.

Technique of transpapillary pancreatic duct stenting

The pancreatic PSs placement technique is the same as used for the biliary tree. After MPD cannulation, the stent is inserted inside the duct over the wire; hydrophilic guidewire of 0.035" is used for placement of PSs from 5 to 10 Fr; 0.018" guidewires are used for 3 Fr PSs, generally reserved for cases of minor pancreatic duct stenting and temporary placement for prevention of post-ERCP pancreatitis. Pancreatic sphincterotomy is not always necessary for placement of PSs. In case of bilio-pancreatic sphincterotomy, pancreatic sphincterotomy is generally performed after biliary sphincterotomy^[23].

The PSs diameter must not be greater than the maximum diameter of the pancreatic duct. Five and 7 Fr PSs are generally implanted in absence of duct dilation; 10 Fr PSs, or more than 10 Fr, are instead used when MPD stenosis with upstream duct dilation occurs. When very tight strictures are present, the placement of a PSs

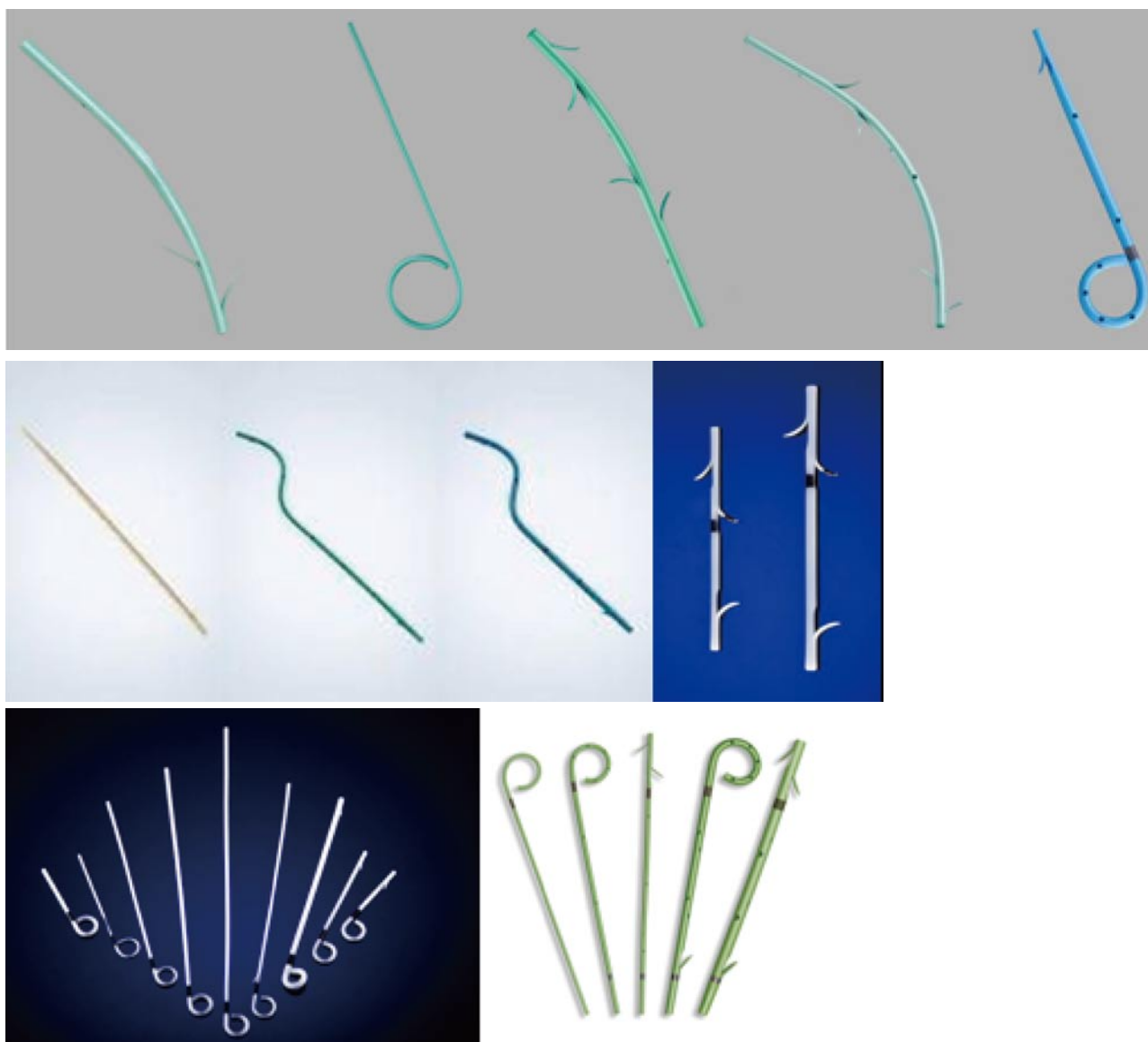


Figure 7 A display of different types of pancreatic plastic stents available.

can be challenging. In this situation balloon dilation or a bougienage dilation are often helpful to, allow stent placement.

For implantation of a SEMS a pancreatic sphincterotomy is typically performed (often also with biliary sphincterotomy). The metal stent diameter and length are determined on the basis of a combination of location of lesion (stricture or leak), ductal configuration and in cases of stricture the diameter of dilated upstream duct proximal to the lesion.

For MPD strictures dilation is typically performed before SEMS placement and the stent is deployed through the ductal lesion. The distal portion of the SEMS is left in the duodenum for prevention of proximal migration and easy removal.

EUS-guided pancreatic duct drainage

To perform EUS-guided drainage of the pancreatic duct (PDD) a large channel echoendoscope (3.7 or 3.8 mm)

is required. The most common site for pancreatic duct (PD) access is the stomach (gastric body), usually the most straightforward and stable, but also transbulbar access is used (impossible in those with prior pancreatoduodenectomy)^[24-28].

However, the route is selected on the basis of the pancreatic anatomical site to be treated. The aim of the drainage is to gain access the shortest way between the echoendoscope and the PD. The shorter the distance the easier the procedure, considering over-the-wire exchanges of devices. Pancreatic duct access may be performed with a 19-G FNA needle followed by either 0.035" or 0.025" guidewire placement *via* the needle or with a 22-G FNA needle that allows only the passage of an 0.018" guidewire.

After PD access, the wire is placed inside the duct, advancing it into the duodenal lumen, through the Vater's papilla, or into the jejunal lumen in presence of a pancreatico-jejunal anastomosis. During guidewire

placement and device exchanges, the use of fluoroscopy is helpful.

After guidewire placement, PD stenting can be performed in retrograde fashion, with EUS-guided PD rendezvous technique, with a side-viewing duodenoscope or with a frontal-viewing endoscope, in patients with postoperative anatomy, or in antegrade fashion, from the stomach or from the duodenal bulb, with EUS-guidance.

For antegrade stenting, dilation of the gastric wall or duodenal bulb wall and dilation of pancreatic parenchyma with a balloon is helpful before stent placement. In many cases a cystotome is used to gain access to the PD, after wire placement, creating an "electrocautery-tunnel", to allow subsequent stent deployment. During EUS-guided PDD, a plastic stent is generally preferred to a metallic one, considering the risk of leakage if uncovered SEMS are used. Finally, when PSs are used, to avoid leakage and migration, the diameter of the stent should not be less than the diameter of the dilated tract.

Endoscopic drainage of pancreatic fluid collections

Endoscopic drainage of PFCs are performed with different approaches as the trans-papillary (*i.e.*, using endoscopic retrograde pancreatography), or transmural (cystoenterostomy), or both^[29-35].

For transpapillary drainage, before implantation of the stent, a major or minor papilla pancreatic sphincterotomy is typically performed. Following this, a large-bore stent is placed. When the stent is placed, its proximal part can be placed inside the PFC or, in case of leakage, across the disruption of the PD. If a stricture of the PD is present downstream to the PFC, judicious dilation by bougie or dilation balloons needs to be performed before application of the stent.

PFC drainage can be performed or through the stomach (transgastric) or through the duodenum (trans-duodenal). More rarely drainage is performed through the esophageal wall (transesophageal). The drainage can be undertaken with or without EUS guidance.

When non-EUS-guided techniques are performed a large channel gastroscope or duodenoscope with a 4.2-mm working channel is used.

The side-viewing endoscope is most often used because it permits better visualization of the posterior wall of the gastric body, allowing placement of large diameter accessories (deployment of 10 Fr stents) with assistance of the elevator.

The initial PFC puncture for transmural drainage is generally performed at level of visible bulging on the gastric or duodenal wall. To obtain good endoscope stability, the short position, when possible, is recommended, and the angle between the needle and the gastric/duodenal wall needs to be closer to 90°. The closer to 90° results in shorter distance to traverse.

To access a PFC with the side-viewing endoscope, diathermic puncture technique or the Seldinger technique are used. The diathermic puncture technique involves the use of a needle-knife sphincterotome (double or triple-

lumen), or a 10-Fr cystotome that is a catheter with a diathermic ring and a 5-Fr inner catheter housing a low-profile, 0.38" needle knife to facilitate close apposition of the PFC to the enteral lumen. A pure cutting current is recommended and the electrocautery should be discontinued immediately upon entry of the needle into the PFC cavity to avoid thermal injury to surrounding structures.

Following this, aspiration of fluid (which can be sent for analysis) and gentle injection of contrast under fluoroscopic guidance confirm position within the cavity. The needle is exchanged for a standard catheter. After that, the guidewire is placed inside the PFC, and coiled for 2-3 times.

Following deep access with a guidewire, the catheter is exchanged for an 8 or 10 mm pneumatic balloon, to dilate the tract. After dilation, the balloon is removed and a plastic or metallic stent is deployed over the guidewire. Alternatively, a cystotome can be used for single-step drainage, avoiding balloon dilation.

When the Seldinger technique is used, a 19-G aspirating needle is used for initial puncture of the PFC. After fluid aspiration contrast is injected inside the PFC for the confirmation of the correct position of the needle. Through the needle a guidewire is passed, coiling it inside the fluid collection. Leaving the wire in place, the needle is withdrawn and a cystotome or a dilation balloon is passed over the wire. Finally the cystotome (or the dilating balloon) is removed and a stent is placed over the guidewire. Moreover balloon dilation can be performed after the creation of the fistula with the cystotome.

There are two techniques for EUS-guided drainage (EUS-GD) of PFC: The 2-step approach and the 1-step approach. For 2-step approach larger (3.7 or 3.8 mm) and smaller (2.8 or 3.2 mm) mm working channel echoendoscopes can be used.

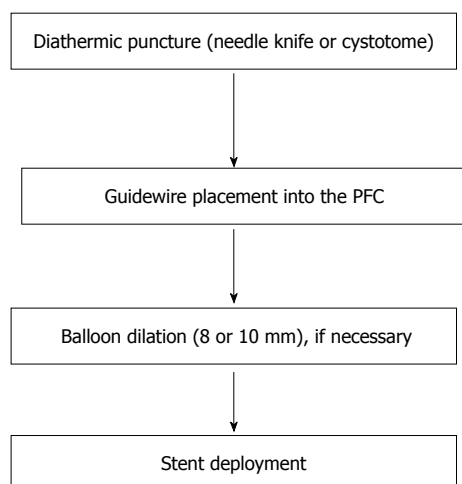
The PFC is located and studied by EUS, identifying the best site for drainage of the collection which is closest to the transducer. Color Doppler helps to avoid puncture of interposed vessels during drainage. This site can be marked with a biopsy forceps, with a metal clip or with India ink and the echoendoscope withdrawn and replaced with a side-viewing duodenoscope to perform the drainage. Otherwise, the PFC puncture is directly performed with a 19 G needle and, after puncture, a guidewire is placed inside the collection. After wire placement, the echoendoscope can be withdrawn, leaving the guidewire in place inside the PFC, and replaced with a side-viewing endoscope over the guidewire, and the drainage can be performed using this endoscope. These exchange of endoscope approaches are now used infrequently.

With the 1-step approach the echoendoscope is used for the entire procedure. An echoendoscope with a large operative channel is required. It allows the use large diameter accessories (deployment of 10 Fr stents) with the assistance of an elevator.

The PFC puncture is usually performed using a

Table 5 Technical characteristics of the lumen apposing metal stents

Producer	Model	Internal diameter (mm)	Length (mm)	Flange diameter (mm)
Boston Scientific	Axios	10, 15	10	21, 24
Leufen Medical	Aix	10, 14	20	14/16, 18/20
M.I. Tech	Hanarostent BCF	10, 12	30, 40	25
TaeWoong Medical	Spaxus	8, 10, 16	20	25
TaeWoong Medical	Nagi	10, 12, 14, 16	10, 20, 30	22, 24, 26, 28

**Figure 8** Traditional transmural endoscopic drainage of pancreatic fluid collections. PFC: Pancreatic fluid collections.

19-G needle under endosonographic view. The collection contents can be aspirated for biochemical analysis, gram stain, culture and cytology. Through the lumen of the needle a 0.025" or 0.035" guidewire is advanced until it coils in the PFC which adds stabilisation of the position and access by forming anchoring extra loops in the cavity.

Fistula dilation is achieved by balloon dilatation over the guidewire, or using a cystostome and diathermy needle. Finally the stent is placed over the guidewire.

The 1-step approach PFC drainage avoids guidewire displacement during the exchange of the echoendoscope with the side-viewing endoscope. When more than one stent, or an additional naso-cystic drainage (NCD) are placed, two guidewires can be inserted inside the same catheter to avoid recannulation of the PFC. Recently, a 3-layer puncture kit, allowing synchronous placement of two guidewires has been described. This kit is composed of a 6 Fr catheter made of Teflon, inside an outer catheter of 8.5 Fr and a 22G FNA needle inside the 6 Fr catheter. Puncture of the collection is performed with a 22 G needle using electrocautery, under EUS-guidance. After puncture the 6 Fr inner catheter and the 8.5 French outer catheter are advanced inside the PFC. When the entire kit is inside the PFC, both needle and inner catheter are removed, and two guidewires can be inserted into the PFC through the outer catheter. Then, two stents, or one stent and one NCD, are placed.

After initial puncture and dilation some endoscopists described the use of the Soehendra dilator or a cystotome 10 Fr outer catheter for passage of two guidewires.

The "Navix-access-device" (Boston Scientific, Natick, MA, United States) consists of a 19-gauge trocar with a short extendable side blade. The retractable blade creates a cystoenterostomy without the use of cautery. It has an anchoring and dilating balloon (10 mm), as well as 2 guidewire ports to permit double wire advancement with the same puncture for sequential stent placement.

Traditionally, more than one plastic pigtail stent is used for PFC transmurial drainage. The fistula tract between the gastrointestinal wall and the PFC is maintained by placement of double pigtail plastic stents for preventing dislocation and migration. When 7 Fr stents are used the occlusion rates are higher. To further improve transmural drainage of PFCs, tubular FCSEMS (available for the treatment of biliary strictures) have recently been used as an alternative for the traditionally used plastic double-pigtail stents. Fully covered SEMS have larger diameters (10 mm) and placement of a single stent can provide a wide drainage opening. Furthermore, due to the larger diameter, there is a reduced risk of occlusion, especially for collections containing a significant amount of solid debris.

However, these stents are designed for drainage related to a luminal stricture and not to a transmural route. When a bile duct stent is used for PFC drainage, protrusion of the ends of the stent both into the GI tract and inside the PFC can increase the risk of stent migration or bleeding, caused by a contact ulceration of the stent within the wall. They are not ideal in cases when the PFC is not firmly attached to the gastrointestinal wall because they do not apply any anchorage force and resultant leakage may occur.

To overcome limitations associated with the use of tubular biliary SEMS for transmural drainage, novel drainage stents have been developed.

These new lumen apposing metal stents (Table 5), are specifically designed for transmural drainage (Figure 6). These stent are fully-covered for preventing ingrowth of tissue and have large flanges at the distal ends, with a length from 10 to 40 mm. The flanges are designed to provide lumen-to-lumen anchoring and a low migration and leakage risk. The diameter of the stents, 10 and 15 mm, enable direct necrosectomy through the lumen of the stent. A flow-chart for the traditional transmural endoscopic drainage of PFC is summarized in Figure 8.

CONCLUSION

Biliary and pancreatic stents are important advancements

in therapeutic endoscopy and have revolutionized the approach to pancreaticobiliary disorders. The new designs of plastic and metal stents have allowed an increased use in a large, broad range of biliary and pancreatic benign and malignant conditions, replacing interventional radiologic approaches and surgery in most cases.

REFERENCES

- 1 Soehendra N, Reynders-Frederix V. Palliative bile duct drainage - a new endoscopic method of introducing a transpapillary drain. *Endoscopy* 1980; **12**: 8-11 [PMID: 7353562 DOI: 10.1055/s-2007-1021702]
- 2 Cotton PB. Duodenoscopic placement of biliary prostheses to relieve malignant obstructive jaundice. *Br J Surg* 1982; **69**: 501-503 [PMID: 6179561]
- 3 Huibregtse K, Haverkamp HJ, Tytgat GN. Transpapillary positioning of a large 3.2 mm biliary endoprosthesis. *Endoscopy* 1981; **13**: 217-219 [PMID: 7274173 DOI: 10.1055/s-2007-1021688]
- 4 Neuhaus H, Hagenmüller F, Classen M. Self-expanding biliary stents: preliminary clinical experience. *Endoscopy* 1989; **21**: 225-228 [PMID: 2792016 DOI: 10.1055/s-2007-1012954]
- 5 Huibregtse K, Cheng J, Coene PP, Fockens P, Tytgat GN. Endoscopic placement of expandable metal stents for biliary strictures--a preliminary report on experience with 33 patients. *Endoscopy* 1989; **21**: 280-282 [PMID: 2482170 DOI: 10.1055/s-2007-1012969]
- 6 Uppal DS, Wang AY. Advances in endoscopic retrograde cholangiopancreatography for the treatment of cholangiocarcinoma. *World J Gastrointest Endosc* 2015; **7**: 675-687 [PMID: 26140095 DOI: 10.4253/wjge.v7.i7.675]
- 7 Bang JY, Hawes R, Bartolucci A, Varadarajulu S. Efficacy of metal and plastic stents for transmural drainage of pancreatic fluid collections: a systematic review. *Dig Endosc* 2015; **27**: 486-498 [PMID: 25515976 DOI: 10.1111/den.12418]
- 8 Kawakami H, Itoi T, Sakamoto N. Endoscopic ultrasound-guided transluminal drainage for peripancreatic fluid collections: where are we now? *Gut Liver* 2014; **8**: 341-355 [PMID: 25071899]
- 9 Baron TH. Best endoscopic stents for the biliary tree and pancreas. *Curr Opin Gastroenterol* 2014; **30**: 453-456 [PMID: 25010683 DOI: 10.1097/MOG.0000000000000100]
- 10 Dumonceau JM, Heresbach D, Devière J, Costamagna G, Beilenhoff U, Riphaus A. Biliary stents: models and methods for endoscopic stenting. *Endoscopy* 2011; **43**: 617-626 [PMID: 21614754 DOI: 10.1055/s-0030-1256315]
- 11 Lee JH. Self-expandable metal stents for malignant distal biliary strictures. *Gastrointest Endosc Clin N Am* 2011; **21**: 463-480, viii-ix [PMID: 21684465 DOI: 10.1016/j.giec.2011.04.009]
- 12 Srinivasan I, Kahaleh M. Metal stents for hilar lesions. *Gastrointest Endosc Clin N Am* 2012; **22**: 555-565 [PMID: 22748248 DOI: 10.1016/j.giec.2012.05.009]
- 13 Binmoeller KF, Nguyen-Tang T. Endoscopic ultrasound-guided anterograde cholangiopancreatography. *J Hepatobiliary Pancreat Sci* 2011; **18**: 319-331 [PMID: 21190119 DOI: 10.1007/s00534-010-0358-1]
- 14 Itoi T, Isayama H, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Tsuji S, Ishii K, Ikeuchi N, Tanaka R, Umeda J, Moriyasu F, Kawakami H. Stent selection and tips on placement technique of EUS-guided biliary drainage: transduodenal and transgastric stenting. *J Hepatobiliary Pancreat Sci* 2011; **18**: 664-672 [PMID: 21688214 DOI: 10.1007/s00534-011-0410-9]
- 15 Perez-Miranda M, Barclay RL, Kahaleh M. Endoscopic ultrasound-guided endoscopic retrograde cholangiopancreatography: endosonographic cholangiopancreatography. *Gastrointest Endosc Clin N Am* 2012; **22**: 491-509 [PMID: 22748245 DOI: 10.1016/j.giec.2012.05.004]
- 16 Kahaleh M, Artifon EL, Perez-Miranda M, Gupta K, Itoi T, Binmoeller KF, Giovannini M. Endoscopic ultrasonography guided biliary drainage: summary of consortium meeting, May 7th, 2011, Chicago. *World J Gastroenterol* 2013; **19**: 1372-1379 [PMID: 23538784 DOI: 10.3748/wjg.v19.i9.1372]
- 17 Itoi T, Coelho-Prabhu N, Baron TH. Endoscopic gallbladder drainage for management of acute cholecystitis. *Gastrointest Endosc* 2010; **71**: 1038-1045 [PMID: 20438890 DOI: 10.1016/j.gie.2010.01.026]
- 18 Hasan MK, Itoi T, Varadarajulu S. Endoscopic management of acute cholecystitis. *Gastrointest Endosc Clin N Am* 2013; **23**: 453-459 [PMID: 23540969 DOI: 10.1016/j.giec.2012.12.010]
- 19 Sútil JC, Betes M, Muñoz-Navas M. Gallbladder drainage guided by endoscopic ultrasound. *World J Gastrointest Endosc* 2010; **2**: 203-209 [PMID: 21160934 DOI: 10.4253/wjge.v2.i6.203]
- 20 Widmer J, Singhal S, Gaidhane M, Kahaleh M. Endoscopic ultrasound-guided endoluminal drainage of the gallbladder. *Dig Endosc* 2014; **26**: 525-531 [PMID: 24422762 DOI: 10.1111/den.12221]
- 21 Choi JH, Lee SS. Endoscopic ultrasonography-guided gallbladder drainage for acute cholecystitis: from evidence to practice. *Dig Endosc* 2015; **27**: 1-7 [PMID: 25284030 DOI: 10.1111/den.12386]
- 22 Peñas-Herrero I, de la Serna-Higuera C, Perez-Miranda M. Endoscopic ultrasound-guided gallbladder drainage for the management of acute cholecystitis (with video). *J Hepatobiliary Pancreat Sci* 2015; **22**: 35-43 [PMID: 25392972 DOI: 10.1002/jhbp.182]
- 23 Testoni PA. Endoscopic pancreatic duct stent placement for inflammatory pancreatic diseases. *World J Gastroenterol* 2007; **13**: 5971-5978 [PMID: 18023085]
- 24 Irisawa A, Hikichi T, Shibukawa G, Takagi T, Wakatsuki T, Takahashi Y, Imamura H, Sato A, Sato M, Ikeda T, Suzuki R, Obara K, Ohira H. Pancreatobiliary drainage using the EUS-FNA technique: EUS-BD and EUS-PD. *J Hepatobiliary Pancreat Surg* 2009; **16**: 598-604 [PMID: 19649561 DOI: 10.1007/s00534-009-0131-5]
- 25 Shami VM, Kahaleh M. Endoscopic ultrasound-guided cholangiopancreatography and rendezvous techniques. *Dig Liver Dis* 2010; **42**: 419-424 [PMID: 19897427 DOI: 10.1016/j.dld.2009.09.009]
- 26 Perez-Miranda M, de la Serna C, Diez-Redondo P, Vila JJ. Endosonography-guided cholangiopancreatography as a salvage drainage procedure for obstructed biliary and pancreatic ducts. *World J Gastrointest Endosc* 2010; **2**: 212-222 [PMID: 21160936 DOI: 10.4253/wjge.v2.i6.212]
- 27 Itoi T, Kasuya K, Sofuni A, Itokawa F, Kurihara T, Yasuda I, Nakai Y, Isayama H, Moriyasu F. Endoscopic ultrasonography-guided pancreatic duct access: techniques and literature review of pancreatography, transmural drainage and rendezvous techniques. *Dig Endosc* 2013; **25**: 241-252 [PMID: 23490022 DOI: 10.1111/den.12048]
- 28 Fujii-Lau LL, Levy MJ. Endoscopic ultrasound-guided pancreatic duct drainage. *J Hepatobiliary Pancreat Sci* 2015; **22**: 51-57 [PMID: 25385528 DOI: 10.1002/jhbp.187]
- 29 Babich JP, Friedel DM. Endoscopic approach to pancreatic pseudocysts: An American perspective. *World J Gastrointest Endosc* 2010; **2**: 77-80 [PMID: 21160706 DOI: 10.4253/wjge.v2.i3.77]
- 30 Samuelson AL, Shah RJ. Endoscopic management of pancreatic pseudocysts. *Gastroenterol Clin North Am* 2012; **41**: 47-62 [PMID: 22341249 DOI: 10.1016/j.gtc.2011.12.007]
- 31 Seewald S, Ang TL, Teng KY, Groth S, Zhong Y, Richter H, Imazu H, Omar S, Polese L, Seitz U, Bertschinger P, Altörfer J, Soehendra N. Endoscopic ultrasound-guided drainage of abdominal abscesses and infected necrosis. *Endoscopy* 2009; **41**: 166-174 [PMID: 19214899 DOI: 10.1055/s-0028-1119501]
- 32 Giovannini M. Endoscopic ultrasonography-guided pancreatic drainage. *Gastrointest Endosc Clin N Am* 2012; **22**: 221-230, viii [PMID: 22632945 DOI: 10.1016/j.giec.2012.04.004]
- 33 Fabbri C, Luigiano C, Maimone A, Polifemo AM, Tarantino I, Cennamo V. Endoscopic ultrasound-guided drainage of pancreatic fluid collections. *World J Gastrointest Endosc* 2012; **4**: 479-488 [PMID: 23189219 DOI: 10.4253/wjge.v4.i11.479]
- 34 Singhal S, Rotman SR, Gaidhane M, Kahaleh M. Pancreatic fluid collection drainage by endoscopic ultrasound: an update. *Clin Endosc* 2013; **46**: 506-514 [PMID: 24143313 DOI: 10.5946/

ce.2013.46.5.506]

- 35 **Braden B**, Dietrich CF. Endoscopic ultrasonography-guided endoscopic treatment of pancreatic pseudocysts and walled-off

necrosis: new technical developments. *World J Gastroenterol* 2014; **20**: 16191-16196 [PMID: 25473173 DOI: 10.3748/wjg.v20.i43.16191]

P- Reviewer: Kawaguchi T, Robles-Medrand C
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Lu YJ



Review of current and evolving clinical indications for endoscopic ultrasound

Anjuli K Luthra, John A Evans

Anjuli K Luthra, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27103, United States

John A Evans, Department of Gastroenterology, Wake Forest University School of Medicine, Winston-Salem, NC 27103, United States

Author contributions: Luthra AK performed research; analyzed articles; wrote the paper; Evans JA analyzed information obtained from researched literature; edited manuscript.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Anjuli K Luthra, MD, Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27103, United States. jluthra@wakehealth.edu
Telephone: +1-336-7168203
Fax: +1-336-7167359

Received: June 27, 2015
Peer-review started: June 30, 2015
First decision: September 17, 2015
Revised: October 20, 2015
Accepted: December 1, 2015
Article in press: December 2, 2015
Published online: February 10, 2016

Abstract

For the first several years after its development,

endoscopic ultrasound (EUS) was primarily limited to identification of pancreatic malignancies. Since this time, the field of EUS has advanced at a tremendous speed in terms of additional clinical diagnostic and therapeutic uses. The combination of ultrasound with endoscopy provides a unique interventional modality that is a minimally invasive alternative to various surgical interventions. Given the expanding recommended indications for EUS, this article will serve to review the most common uses with supporting evidence, while also exploring innovative endeavors that may soon become common clinical practice.

Key words: Endoscopic ultrasound; Pancreatic carcinoma; Celiac plexus neurolysis; Mediastinal lymphadenopathy; Pancreatic fluid collection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopy has presented the opportunity to improve outcomes and lessen complications in a multitude of diseases and disorders. Endoscopic ultrasound (EUS) in particular has been at the forefront in the development of novel treatment and diagnostic methods. While there have been prior articles reviewing common indications for the clinical use of EUS, the sheer volume of recent studies centered on this modality denotes an opportunity to provide an update on that information. Additionally, recent reports of using EUS with innovative techniques, such as anal dyssynergia refractory to standard therapy, warrant discussion in this forum.

Luthra AK, Evans JA. Review of current and evolving clinical indications for endoscopic ultrasound. *World J Gastrointest Endosc* 2016; 8(3): 157-164 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/157.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.157>

INTRODUCTION

Advancement in the clinical application and use of endoscopic ultrasound (EUS) in recent years has transformed the field of gastroenterology, with the ability to identify and manage a wide variety of disorders, even extending beyond the gastrointestinal tract (GIT). EUS combines endoscopy with intraluminal ultrasonography using a high frequency transducer to produce high-resolution ultrasound (US) images. Prior to its development in the early 1980s, external US imaging was the primary means of diagnosing clinical problems related to the biliary system. However, trans-abdominal US was limited in providing a diagnosis in 30% of cases secondary to the presence of intestinal gas obstructing views^[1].

SRI international (Menlo Park, California) produced a high-resolution ultrasonic probe used in conjunction with a side-viewing endoscope with which to evaluate the ability to identify important vasculature and organs within the upper abdomen. This prototype EUS was used in a canine as the 80-mm rigid end prevented safe use in humans; it demonstrated real-time images of the aorta, spleen, gallbladder, left kidney and gastric rugae, as well as the hepatic and portal venous systems^[1].

The original EUS prototype to be used in humans was developed by Olympus Opt. Company (Tokyo, Japan) using a conventional gastroscope^[2]. This instrument consisted of attaching an ultrasonic probe to the rigid end of a fiberscope which transmitted at a frequency of 5 MHz to a depth of 3 cm. Strohm *et al*^[2] conducted a study in which this endoscope model was used to identify organs proximal to the stomach in 18 patients. Using the aorta and vena cava as landmarks, the pancreas was identified and measured in 9 of 18 patients. The gallbladder and distal bile duct were also found on imaging in some patients, but the scope's limited mobility prevented passage through the pylorus and, thus, visualization of the duodenum. They compared the quality of these images to those obtained with conventional US, and discovered that those obtained *via* EUS appeared equivocal. This new EUS, however, provided sharper visualization of the distal common bile duct (CBD) than transabdominal US^[2].

Both studies demonstrated a new means of acquiring high-resolution views of various organs and vessels that with further development could prove to be superior to transcutaneous US^[1,2]. With improvement in the echoendoscope, various groups began applying this technology to advance clinical diagnoses of upper abdominal pathology. Current guidelines for the diagnostic indication of EUS produced by the American Cancer Society and American Society for Gastrointestinal Endoscopy (ASGE) include evaluation of upper gastrointestinal malignancies, mediastinal adenopathy, pancreatic lesions and cancers, and submucosal tumors^[3,4]. The use of EUS has expanded beyond purely investigative uses to also become a minimally invasive means of

therapeutic intervention. This article will review the primary clinical uses for EUS along with fundamental supporting study data.

Diagnostic indications

Pancreatic cancer: EUS was first evaluated for its efficacy in confirming suspected pancreatic carcinoma in the mid-1980s. These early studies revealed EUS was superior to trans-abdominal US, including differentiating pancreatitis from a pancreatic tumor and identifying ampullary and papillary tumors^[4]. After multiple studies throughout the 1990s, EUS sensitivity approached beyond 90% in detecting malignant pancreatic tumors^[5]. One such study from Akahoshi *et al*^[6] sought to analyze the precision of EUS in earlier diagnosis of pancreatic cancer with accurate tumor staging. In this era, pancreatic cancers were identified primarily by abnormal laboratory results or abdominal US and computed tomography (CT), and thus found at very advanced stages. In the study's evaluation of 96 patients suspected of having pancreatic carcinoma based on abnormal labs or imaging and their clinical presentation, diagnosis was confirmed by post-operative histology, autopsy, or surgical exploration in non-resectable cases. They found EUS had a sensitivity of 83% in diagnosing malignant pancreatic masses less than 3 cm in size, and a sensitivity of 92% for those beyond 3 cm, with an overall specificity of 97%^[6]. This high sensitivity rate was not significantly decreased by location within the pancreas; although, masses in the pancreatic body or tail were identified with a sensitivity of 100% relative to 85% for the body of the pancreas. EUS in this study revealed 64% accuracy in pancreatic tumor staging T1-T3. The main etiology for incorrect staging was those patients with masses larger than 3 cm, which limited the tissue depth penetration of the 7.5 MHz transducer^[6]. These were, and remain, profound findings, as earlier diagnosis and more accurate local staging could improve patient survival. Current studies have demonstrated diagnostic sensitivity of EUS approaches 99% for malignant pancreatic tumors of 2-3 cm size which is far superior to other imaging modalities, including CT, transabdominal US, and magnetic resonance imaging (MRI)^[7-9]. This is likely due to the ability to have close proximity of the endoscope transducer to the lesion of interest. Of course, EUS is not without limitations in the accuracy of diagnosing pancreatic cancer. The presence of pancreatitis, which can result in significant heterogeneous appearance of pancreatic tissue, may result in highly trained endosonographers missing an underlying pancreatic neoplasm^[4,10]. As MRI techniques and equipment become more high-tech, magnetic resonance cholangiopancreatography (MRCP) has been used with increasing frequency in patients suspected of having a pancreatic malignancy. MRI has superior soft-tissue contrast compared to CT imaging, resulting in the ability to differentiate pancreatic masses^[4,11]. However, as EUS affords superb visualization of the

pancreas and remains one of the most accurate means for identifying pancreatic lesions, it is considered a first-line modality for diagnosing and staging of pancreatic adenocarcinoma.

EUS is not only accurate in detecting pancreatic malignancies, but is the primary tool to rule out pancreatic cancer^[8]. A large single study completed at UC Irvine by Klapman *et al*^[8] determined the negative predictive value (NPV) of EUS for patients with possible cancer of the pancreas. A total 693 patients were referred for EUS due to the potential of pancreatic cancer; focus was placed on the 155 with normal pancreatic imaging on EUS. Most of this group had been referred for EUS based on abnormal CT imaging. These patients were monitored for 24 mo, at the end of which none developed malignancy of the pancreas, resulting in a 100% NPV (95%CI: 98.2-100.0)^[8].

Today, EUS imaging is combined with fine-needle aspiration (FNA) to improve diagnostic accuracy of pancreatic masses. Cytological or histological confirmation of the lesion is required to determine the appropriate treatment, especially if the mass is unresectable. Retrospective reviews of EUS database information shows EUS-FNA diagnostic precision of 89% for solid pancreatic masses^[9,11,12,13]. The ability to obtain samples of pancreatic lesions concerning for malignancy during real-time imaging has a direct impact on the medical management of these patients. As only a minority of patients are candidates for curative surgery at time of presentation with pancreatic carcinoma, obtaining cytological or histological diagnostic confirmation is necessary to proceed with chemotherapy^[9,12,13]. Touchefu *et al*^[12] examined the influence of EUS-FNA on patient management in 100 patients; intention-to-diagnose analysis revealed the FNA results directly guided treatment plans in 62 patients.

It is additionally highly recommended, and in many healthcare settings standard of care, that a cytopathologist or cytology technician be onsite to guide FNA sampling. Various studies have demonstrated the likelihood of diagnosis obtained is much improved. A large prospective multicenter study conducted in the mid-1990s evaluated 474 EUS-guided FNA diagnoses of various sites and lesions. NPV was 72% without an on-site pathologist vs 100% in those centers with direct pathologist assistance^[4,14]. Furthermore, a retrospective study evaluating academic centers with cytopathologists on site ruled in or out a malignant diagnosis twice as often and were less likely to have unacceptable samples^[14-17].

Additional supportive data for on-site cytopathology with EUS-FNA of suspicious lesions was revealed in a recent large meta-analysis by Hébert-Magee *et al*^[16] reviewing 34 studies with approximately 3600 patients with solid pancreatic masses. Of those patients, a total of 2285 were found to have pancreatic adenocarcinomas. Sensitivity of FNA ranged from 0.50-1.00, with sensitivity rates notably lower in those studies without on-

site cytopathology, even when correcting for sources of heterogeneity of study size and diagnostic reference standard used^[16,17]. Thus, given the continued dismal survival rates for pancreatic cancer (approximately 24% survival at 1 year and 5% at 2 years) and increased chance of unresectability with late presentation, EUS-FNA biopsy can provide an earlier diagnosis and potential alternative diagnosis to decrease patient mortality. It remains superior in accurately identifying and ruling out pancreatic malignancies compared to imaging *via* CT, conventional US, and MR^[8].

Mediastinal adenopathy and non small-cell lung cancer:

Patients with suspected lung cancer often undergo further imaging to help with staging, as up to 26% of newly diagnosed lung cancers present with mediastinal lymph node involvement^[18,19]. Imaging modalities may vary between CT, MRI, or US. A 2003 CHEST systematic database review evaluated the accuracy of mediastinal staging in CT compared to positron emission tomography (PET), MR, and EUS^[19]. The analysis of EUS assessment consisted of five studies for a total of 163 patients and exhibited a pooled sensitivity of 78% (95%CI: 0.61-0.89) and specificity of 71% (95%CI: 0.56-0.82). However, PET scan demonstrated the highest accuracy in detecting malignant metastases to mediastinal nodes with sensitivity and specificity of 84% (95%CI: 0.78-0.89) and 89% (95%CI: 0.83-0.93), respectively. As EUS is often limited in its inability to image all node stations, this may partially explain its inferiority to PET imaging of the mediastinum^[19]. Specifically, EUS is unable to visualize anterior upper mediastinal nodes as a result of air within the trachea obstructing US imaging^[18,20].

While CT and PET detect mediastinal lymphadenopathy and suspicious masses on imaging, a lack of tissue sampling results in a presumptive diagnosis only. Thus, obtaining tissue samples is necessary to definitively confirm and stage a possible pulmonary malignancy. The American Society of Thoracic Surgery currently recognizes mediastinoscopy as the favored modality for biopsy^[18]. However, the 2011 ASGE Standards of Practice state that linear echoendoscopy can perform EUS-guided FNA of the posterior and inferior mediastinum with success in obtaining specimens from nodes 5 mm in size or larger. Additionally, nodal stations 8 and 9 and posterior nodes at station 7 are accessible by EUS with a sensitivity of 90% in confirming diagnosis. This accuracy drops to 66% for station 5 nodes based on one retrospective series by Eloubeidi *et al*^[21] due to logistical difficulties when inserting the biopsy needle in attempts to reach this sub-aortic locations^[18]. One prospective cohort study of 104 patients with malignant posterior mediastinal lymph nodes assessed the yield and precision of EUS-FNA using pathologic confirmation *via* thoracotomy^[21]. The accuracy of EUS-FNA was 97%, which was significantly increased from PET imaging alone. More invasive surgical intervention was

avoided in 57% of the patients to determine malignant spread to lymph nodes. No patients experienced major complications peri-procedurally or at 30-d follow up^[21]. EUS-FNA has been recommended by Maluf-Filho *et al*^[4] to detect metastasis to the posterior mediastinum in non-small-cell lung cancer (Grade A, evidence level 1). EUS-FNA of mediastinal lymphadenopathy averages a complication rate of 0.2%, compared to 1.3%-3.0% with mediastinoscopy. The American Society of Thoracic Surgery does recognize EUS-FNA as an efficient, minimally invasive alternative method to confirm and stage lung cancer involving mediastinal lymph nodes.

Choledocholithiasis, suspected: CBD stones remain a common complication related to the presence of gallstones, occurring in nearly 20% of patients with known cholelithiasis. Identifying CBD stones remains a challenge, as laboratory findings and clinical presentation is often nonspecific^[22]. EUS has been studied over several years in its ability to accurately detect choledocholithiasis. Endoscopic retrograde cholangiopancreatography (ERCP) remains standard of care, as rates for successful identification of bile duct stones approaches 100%, compared with abdominal CT and US where diagnostic accuracy approximates to 50%^[22,23]. ERCP is also not purely diagnostic, as it allows for CBD stone removal at time of detection; however, complication rates occur in up to 11% of patients^[23,24]. Various studies performed in the 2000s evaluated EUS ability to diagnose suspected choledocholithiasis, as this could negate ERCP and its associated risks in certain patient cases. However, the data was widely variable in rates of sensitivity and sensitivity^[22,23].

In order to more precisely estimate diagnostic accuracy of EUS for choledocholithiasis, Tse *et al*^[22] identified 27 prospective cohort studies consisting of EUS results compared with ERCP, intraoperative cholangiogram (IOC), or surgical exploration. Included studies also had a minimum of three months follow up if initially negative EUS results with suspicion of CBD stones based on history, exam, laboratory findings, or trans-abdominal US imaging. Studies were excluded if they lacked a comparison group, demonstrated possible bias, or insufficient data. Pooled diagnostic accuracy was 98% (area under the curve). EUS decisively ruled in and ruled out CBD stones with a positive likelihood ratio (LR) of 22.41 (95%CI: 12.53-40.08) and negative LR of 0.09 (95%CI: 0.06-0.12)^[22]. This impressive diagnostic ability of EUS is likely related to its high resolution down to 0.1 mm compared to ERCP or MRCP^[22].

IOC is often performed during laparoscopic cholecystectomy to evaluate biliary patency. CBD stones are present in up to 15% of these patients, but the false positive rate of IOC approaches 60% in some studies^[23]. Given the combination of IOC's high false positive detection of choledocholithiasis and the complication rates of ERCP, it would be ideal to have an alternative, less invasive modality of confirming CBD stones

with decreased risk in patients with low suspicion for requiring stone extraction. EUS may have a potential role in a diagnostic algorithm to stratify patients proceeding to ERCP vs EUS initially. EUS is felt to be as sensitive and more specific than ERCP or MRCP for the diagnosis of CBD stones, especially those of smaller size (Grade A, Evidence Level 1)^[4].

The use of EUS as the primary diagnostic tool, however, may be limited. While it is less invasive than ERCP resulting in lower rates of post-procedure pancreatitis, patients still require sedation. As with ERCP, EUS requires an experienced endoscopist to obtain acceptable images. Unfortunately if CBD stones are discovered on EUS imaging and require removal, these patients would require ERCP, an additional procedure.

Therapeutic indications

Pancreatic fluid collection drainage: Potential indications for intervention in pancreatic pseudocysts include abdominal pain, gastric outlet obstruction, early satiety, weight loss, jaundice, infection, or progressive enlargement^[3]. Surgery has historically been accepted as the standard of care for draining pancreatic pseudocysts and walled-off pancreatic necrosis. In recent years, multiple studies examining the success of EUS-guided drainage has resulted in this becoming an established technique with comparable outcomes and significantly lower medical costs^[17]. This procedure was first described in a 1992 case report by Grimm *et al*^[25] with management of a pancreatic tail pseudocyst^[17]. A randomized controlled trial conducted in 2009 directly compared surgical vs EUS-guided endoscopic pancreatic fluid collection (PFC) drainage in 40 patients^[26]. A pseudocyst was defined as "a fluid collection in... pancreatic...area (with) a well-defined wall and...no solid debris or recognizable parenchymal necrosis"^[26]. One-half of the patients were randomized to surgical cystogastrostomy under a single pancreatic surgeon while the other half underwent EUS with fluoroscopy. Endoscopic cystogastrostomy was achieved *via* EUS-guided 19-gauge-needle access of the fluid collection with subsequent deployment of two plastic stents to allow PFC contents to drain into stomach. ERCP was performed in the experimental arm following EUS in order to identify and treat pancreatic duct leaks, if present. Traditional surgical drainage resulted in a 100% successful treatment. However, several of these patients experience postoperative complications, including recurrent pseudocyst, surgical wound infection, inability to tolerate oral intake, and pancreatic tail stricture. EUS-guided pseudocyst drainage was efficacious in 95% of patients with pseudocyst resolution by 8 wk in all 20 patients. Most importantly, these patients did not experience peri- or post-procedural complications^[26]. Additional studies have since demonstrated clinical success rates of PFC drainage *via* EUS imaging approach 90% with complication rate of less than 5%^[17,24,26,27]. PFC drainage under EUS guidance is a minimally

invasive procedure, resulting in a shorter hospital length of stay, lower overall healthcare costs, and feasibility in vast majority (more than 90%) of patients^[24,26].

Prior to the establishment of EUS-guided PFC drainage, transmural drainage *via* esophagogastroduodenoscopy (EGD) had been accepted as a reputable technique to manage PFCs. This was attributable to data from two prospective nonrandomized trials in the early 2000s that revealed no statistical difference in treatment success or complication rates when compared with surgery^[26,27]. EGD identified the location of a PFC by evaluating for a site of stomach or duodenal lumen compression. The site was punctured by a needle to allow aspiration of pseudocyst fluid and placement of double pigtail stents to allow intraluminal drainage of PFC contents^[27]. Varadarajulu *et al.*^[27] conducted the first randomized control trial directly pitting EUS against EGD for transmural drainage of pancreatic pseudocysts in 42 patients. All patients initially underwent contrast-enhanced CT imaging to exclude those without a pseudocyst, then ERCP to assess and manage CBD stones or pancreatic duct stricture, if present. Patients were subsequently randomized to the EGD or EUS arms with treatment failures crossing over to the opposite arm. Ultimately, complete resolution of pseudocysts was achieved in 91% of the EGD arm vs 97% in the EUS group (10 of which crossed-over from EGD arm). Although no statistical significance was noted in improved safety with EUS, it did reveal a significantly higher technical success rate^[26,27]. This is likely due to the ability of directly imaging extramural lesions.

EUS provides additional benefits over EGD beyond definitive drainage of PFCs. EUS imaging can more clearly differentiate pseudocysts from cystic neoplasms and visualize pseudocysts that spontaneously resolved, thus negating a need for PFC drainage^[27]. Bleeding is one of the most common complications of endoscopic PFC drainage, occurring in up to 10% of patients. This often occurs due to the presence of gastric varices or collaterals not visible with EGD. As EUS allows real-time visualization of vasculature near a pseudocyst, one can identify a safe window for transmural puncture to achieve drainage^[26,27].

Celiac plexus neurolysis: Chronic pain is a common, and at times, debilitating complication of intra-abdominal malignancies and chronic pancreatitis. It is often difficult to control with opioid analgesics, and these medications have various adverse effects. Wiersema *et al.*^[28] first described a technique of treating intractable pain with EUS-guided celiac plexus neurolysis (CPN) in a prospective study of 30 patients with pancreatic carcinoma or intra-abdominal metastases in 1996^[17,24]. This procedure consisted of identifying the celiac trunk, as the celiac plexus is located anterolateral to this site, and injecting a local anesthetic such as bupivacaine followed by dehydrated ethanol^[24,28]. Data was notable for a 79%-88% improvement in the patients' pain

scores at a mean 10 wk post-procedure. Furthermore, 91% of these patients did not require increased dosages of their opioid analgesics, with nearly half using less pain medication by the last study follow up. The only complication was self-resolving diarrhea in four patients^[28].

While CPN was found to provide pain relief in patients with pancreatic and intra-abdominal malignancies, Levy *et al.*^[29] considered whether directly injecting the celiac ganglia with a local anesthetic might result in enhanced efficacy^[24]. Seventeen patients with unresectable pancreatic carcinoma and moderate to severe narcotic-dependent pain underwent EUS-guided direct celiac ganglia injections with bupivacaine and dehydrated alcohol. Immediate partial pain relief was experienced by 94% of patients. Opioid medication use decreased for 3 patients, while remaining equivalent in 13 patients. There were no major complications, suggesting this new technique for pain relief in certain patients is a safe alternative and potentially more efficacious than CPN^[29].

The most recent data demonstrates substantial pain relief coupled with a reduction in narcotic dosage for patients with intra-abdominal malignancies undergoing EUS-guided CPN or celiac ganglia neurolysis (CGN). A large meta-analysis from Puli *et al.*^[30] in 2014 pooled data from 8 studies (approximately 300 patients) comparing EUS-CPN to analgesics in unresectable pancreatic carcinoma^[24,30]. Review of data revealed EUS-guided CPN achieved pain relief in 80% of patients with bilateral celiac plexus injection. A majority of the studies again resulted in a reduction of opioid analgesic use and no major complications, thus reiterating this is a safe and effective treatment for pancreatic cancer-related pain^[24,30]. Another review of 6 studies consisting of 358 patients revealed statistically significant reduction in pain at four and eight weeks and superiority in pain reduction compared to narcotic medications^[24].

A multicenter randomized controlled trial by Doi *et al.*^[31] was the first to directly compare efficacy of EUS-guided CPN to EUS-guided CGN in reducing pain from upper abdominal malignancies. Four of the 34 patients randomized to the CGN arm crossed over to CPN due to inability to visualize the celiac ganglia. The EUS-CGN group had improved response (73.5% with decreased pain) relative to the EUS-CPN arm (45.5%), and EUS-CGN attained complete pain relief in 50% of patients compared to only 18.2% who underwent EUS-CPN^[24,31].

EUS-guided CPN and CGN both inhibit the transmission of pain signals from the pancreas and abdominal viscera to the central nervous system. The celiac plexus location permits successful direct EUS visualization, and allows a method of palliation for those with unresectable pancreatic carcinoma^[24,28-30]. Patients may thus require less opioid medications, which translates into fewer medication side effects of anorexia, constipation, nausea, and vomiting.

The celiac plexus is also accessible percutane-

ously when combined with CT or fluoroscopy imaging. Prior to the 1990s, this was the primary manner of performing CPN in settings of chronic abdominal pain secondary to intra-abdominal malignancies and chronic pancreatitis^[24,32]. Given EUS capability to visualize vascular structures in real-time and ability to perform FNA, EUS-guided CPN using ethanol was first developed in the late 1990s^[24]. To further assess this new technique, Gress *et al.*^[32] performed a randomized-controlled trial involving 22 patients receiving either CT-guided or EUS-guided CPN for persistent, uncontrolled abdominal pain due to chronic pancreatitis. Patients in the EUS arm had statistically significant ($P = 0.02$) reduced pain score. Neither group experience serious complications. Diarrhea was noted in three subjects (one from the EUS group, two from the CT arm) and attributed as a direct side effect of CPN^[32]. Nine patients in the experimental group had a prior CT-guided CPN; the majority preferred the EUS technique citing less post-procedure back pain and "more completed sedation"^[32]. Furthermore, the use of EUS in guiding CPN resulted in lower cost per patient relative to CT-guided CPN^[24,32].

FUTURE ENDEAVORS

Anti-tumor injection therapy

Several malignancies metastasize to the liver, which often complicates treatment with intent to cure. Patients with diffuse hepatic metastases have therapy options limited to systemic chemotherapy. In the recent years, drug-eluting microbeads have been introduced as a means of delivering treatment, primarily chemotherapy, into a target tissue^[24]. A relatively new study conducted by Faigel *et al.*^[33] evaluated the use of EUS-guided Portal Injection of Chemotherapy (EPIC) with irinotecan-containing microbeads in porcine subjects in comparison to the conventional systemic administration of irinotecan. EPIC achieved double the concentration of chemotherapy within the liver, and halved its concentration in plasma, bone marrow, and skeletal muscle, relative to what is seen with systemic irinotecan^[33,34]. This new method of delivery chemotherapy to target malignant lesions of the liver has the potential of increasing the efficacy of treatment while decreased adverse effects. It may be possible to extrapolate this technique in developing alternative management strategies for primary liver malignancies, such as hepatocellular carcinoma.

Anal sphincter dyssynergia

A hypertensive anal sphincter may result in severe constipation due to defecatory dyssynergia and subsequent rectal outlet obstruction. Biofeedback therapy to correct patient contraction of the pelvic floor muscles and external anal sphincter often results in clinical improvement superior to that of laxatives alone^[35]. Byrne *et al.*^[36] used EUS to guide injection of Botulinum toxin (Botox) into the internal anal sphincter of nine

patients who had failed biofeedback therapy for anal dyssynergia. Patients underwent anal manometry prior to the procedure and again at two weeks post-injection. Within the 8-wk follow-up, 89% of these patients had improvement in their constipation. Objective findings at this time included decreased anal sphincter pressure in all patients as well as improved defecatory index with balloon expulsion. A single patient developed fecal incontinence, which was the only associated complication from this procedure. While a larger study is needed, this novel technique may prove to be a formidable therapy option for those with constipation due to a hypertensive anal sphincter with alternative treatment failure^[34].

Novel peri-procedure analgesia

Traditional Chinese Medicine has included the use of electro-acupuncture for treatment of pain. Electro-acupuncture needles are placed in particular sites on the body to correlate with the specific source of pain. While endoscopic procedures such as EUS are minimally invasive, they are often uncomfortable for patients and necessitate the use of pain control and sedation with intravenous opioid analgesics and benzodiazepines, respectively. Teoh *et al.*^[37] hypothesized that electro-acupuncture could be used during EUS in order to decrease associated pain and the use of additional analgesics. This randomized, double-blind, sham-controlled trial applied electro-acupuncture to three acupoints related to upper abdominal pain and anxiety in 64 patients undergoing EUS. This study ended early as all patients in the electro-acupuncture group required lower doses of propofol, decreased use of patient-controlled analgesia pumps, and lower pain scores. These data points were all statistically significant^[34]. As administration of sedative analgesics is not without potentially dangerous adverse events, this novel technique could lead to fewer associated complications in patients undergoing endoscopic evaluation.

CONCLUSION

EUS has continued to evolve since its conception several decades ago. It is persistently at the forefront of gastroenterological procedures in expanding its diagnostic and therapeutic use for a variety of diseases and clinical presentations. EUS often provides a marginally invasive alternative to many treatments previously requiring surgical intervention, which ultimately may result in lower healthcare costs and fewer complications in patients.

REFERENCES

- 1 DiMagno EP, Buxton JL, Regan PT, Hattery RR, Wilson DA, Suarez JR, Green PS. Ultrasonic endoscopy. *Lancet* 1980; 1: 629-631 [PMID: 6102631 DOI: 10.1016/S0140-6736(80)91122-8]
- 2 Strohm WD, Phillip J, Hagenmüller F, Classen M. Ultrasonic tomography by means of an ultrasonic fiberendoscope. *Endoscopy*

- 1980; **12**: 241-244 [PMID: 7428729 DOI: 10.1055/s-2007-1021752]
- 3 **Nguyen VX**, Le Nguyen VT, Nguyen CC. Appropriate use of endoscopy in the diagnosis and treatment of gastrointestinal diseases: up-to-date indications for primary care providers. *Int J Gen Med* 2010; **3**: 345-357 [PMID: 21116340 DOI: 10.2147/IJGM.S14555]
- 4 **Maluf-Filho F**, Dotti CM, Halwan B, Queiros AF, Kupski C, Chaves DM, Nakao FS, Kumar A. An evidence-based consensus statement on the role and application of endosonography in clinical practice. *Endoscopy* 2009; **41**: 979-987 [PMID: 19866396 DOI: 10.1055/s-0029-1215192]
- 5 **Strohm WD**, Kurtz W, Hagenmüller F, Classen M. Diagnostic efficacy of endoscopic ultrasound tomography in pancreatic cancer and cholestasis. *Scand J Gastroenterol Suppl* 1984; **102**: 18-23 [PMID: 6591373]
- 6 **Akahoshi K**, Chijiwa Y, Nakano I, Nawata H, Ogawa Y, Tanaka M, Nagai E, Tsuneyoshi M. Diagnosis and staging of pancreatic cancer by endoscopic ultrasound. *Br J Radiol* 1998; **71**: 492-496 [PMID: 9691893 DOI: 10.1259/bjr.71.845.9691893]
- 7 **Gonzalo-Marin J**, Vila JJ, Perez-Miranda M. Role of endoscopic ultrasound in the diagnosis of pancreatic cancer. *World J Gastrointest Oncol* 2014; **6**: 360-368 [PMID: 25232461 DOI: 10.4251/wjgo.v6.i9.360]
- 8 **Klapman JB**, Chang KJ, Lee JG, Nguyen P. Negative predictive value of endoscopic ultrasound in a large series of patients with a clinical suspicion of pancreatic cancer. *Am J Gastroenterol* 2005; **100**: 2658-2661 [PMID: 16393216 DOI: 10.1111/j.1572-0241.2005.00315.x]
- 9 **Müller MF**, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. *Radiology* 1994; **190**: 745-751 [PMID: 8115622 DOI: 10.1148/radiology.190.3.8115622]
- 10 **Bhutani MS**, Gress FG, Giovannini M, Erickson RA, Catalano MF, Chak A, Deprez PH, Faigel DO, Nguyen CC. The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography. *Endoscopy* 2004; **36**: 385-389 [PMID: 15100944 DOI: 10.1055/s-2004-814320]
- 11 **Lee ES**, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. *World J Gastroenterol* 2014; **20**: 7864-7877 [PMID: 24976723 DOI: 10.3748/wjg.v20.i247864]
- 12 **Toucheffu Y**, Le Rhun M, Coron E, Alamdari A, Heymann MF, Mosnier JF, Matysiak T, Galmiche JP. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of solid pancreatic masses: the impact on patient-management strategy. *Aliment Pharmacol Ther* 2009; **30**: 1070-1077 [PMID: 19735232 DOI: 10.1111/j.1365-2036.2009.04138.x]
- 13 **Wilson JL**, Kalade A, Prasad S, Cade R, Thomson B, Banting S, Mackay S, Desmond PV, Chen RY. Diagnosis of solid pancreatic masses by endoscopic ultrasound-guided fine-needle aspiration. *Intern Med J* 2009; **39**: 32-37 [PMID: 18422561 DOI: 10.1111/j.1445-5995.2008.01633.x]
- 14 **Wiersema MJ**, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997; **112**: 1087-1095 [PMID: 9097990 DOI: 10.1016/S0016-5085(97)70164-1]
- 15 **Klapman JB**, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol* 2003; **98**: 1289-1294 [PMID: 12818271 DOI: 10.1111/j.1572-0241.2003.07472.x]
- 16 **Hébert-Magee S**, Bae S, Varadarajulu S, Ramesh J, Frost AR, Eloubeidi MA, Eltoum IA. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. *Cytopathology* 2013; **24**: 159-171 [PMID: 23711182 DOI: 10.1111/cyt.12071]
- 17 **Yamao K**, Bhatia V, Mizuno N, Sawaki A, Shimizu Y, Irisawa A. Interventional endoscopic ultrasonography. *J Gastroenterol Hepatol* 2009; **24**: 509-519 [PMID: 19220671 DOI: 10.1111/j.1440-1746.2009.05783.x]
- 18 **Jue TL**, Sharaf RN, Appalaneni V, Anderson MA, Ben-Menachem T, Decker GA, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan KM, Krinsky ML, Malpas PM, Maple JT, Fisher D, Hwang JH, Early D, Evans JA, Dominitz JA. Role of EUS for the evaluation of mediastinal adenopathy. *Gastrointest Endosc* 2011; **74**: 239-245 [PMID: 21802583 DOI: 10.1016/j.gie.2011.03.1255]
- 19 **Tolosa EM**, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 2003; **123**: 137S-146S [PMID: 12527573 DOI: 10.1378/chest.123.1_suppl.137S]
- 20 **von Bartheld MB**, Rabe KF, Annema JT. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. *Gastrointest Endosc* 2009; **69**: 345-349 [PMID: 19100979 DOI: 10.1016/j.gie.2008.6.021]
- 21 **Eloubeidi MA**, Cerfolio RJ, Chen VK, Desmond R, Syed S, Ojha B. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg* 2005; **79**: 263-268 [PMID: 15620955 DOI: 10.1016/j.athoracsur.2004.06.089]
- 22 **Tse F**, Liu L, Barkun AN, Armstrong D, Moayyedi P. EUS: a meta-analysis of test performance in suspected choledocholithiasis. *Gastrointest Endosc* 2008; **67**: 235-244 [PMID: 18226685 DOI: 10.1016/j.gie.2007.09.047]
- 23 **Vadlamudi R**, Conway J, Mishra G, Baillie J, Gilliam J, Fernandez A, Evans J. Identifying patients most likely to have a common bile duct stone after a positive intraoperative cholangiogram. *Gastroenterol Hepatol (N Y)* 2014; **10**: 240-244 [PMID: 24976807]
- 24 **Fabbri C**, Luigiano C, Lisotti A, Cennamo V, Virgilio C, Caletti G, Fusaroli P. Endoscopic ultrasound-guided treatments: are we getting evidence based--a systematic review. *World J Gastroenterol* 2014; **20**: 8424-8448 [PMID: 25024600 DOI: 10.3748/wjg.v20.i26.8424]
- 25 **Grimm H**, Binmoller KF, Soehendra N. Endosonography guided drainage of a pancreatic pseudocyst. *Gastrointest Endosc* 1992; **38**: 170-173 [PMID: 6102631]
- 26 **Varadarajulu S**, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583-90.e1 [PMID: 23732774 DOI: 10.1053/j.gastro.2013.05.046]
- 27 **Varadarajulu S**, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111 [PMID: 18640677 DOI: 10.1016/j.gie.2008.04.028]
- 28 **Wiersema MJ**, Wiersema LM. Endosonography-guided celiac plexus neurolysis. *Gastrointest Endosc* 1996; **44**: 656-662 [PMID: 8979053 DOI: 10.1016/S0016-5107(96)70047-0]
- 29 **Levy MJ**, Topazian MD, Wiersema MJ, Clain JE, Rajan E, Wang KK, de la Mora JG, Gleeson FC, Pearson RK, Pelaez MC, Petersen BT, Vege SS, Chari ST. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. *Am J Gastroenterol* 2008; **103**: 98-103 [PMID: 17970834 DOI: 10.1111/j.1572-0241.2007.01607.x]
- 30 **Puli SR**, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci* 2009; **54**: 2330-2337 [PMID: 19137428 DOI: 10.1007/s10620-008-0651-x]
- 31 **Doi S**, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, Mukai T, Katanuma A, Kubota K, Ohnishi T, Ryozaawa S, Hara K, Itoi T, Hanada K, Yamao K. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. *Endoscopy* 2013; **45**: 362-369 [PMID: 23616126 DOI: 10.1055/s-0032-1326225]
- 32 **Gress F**, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. *Am J Gastroenterol* 1999; **94**: 900-905 [PMID: 10201454 DOI: 10.1111/j.1572-0241.1999.01042.x]

- 33 **Faigel DO**, Lake D, Landreth TL, Kelman CC, Marler RJ. EUS-guided portal injection chemotherapy for treatment of hepatic metastases: feasibility in the acute porcine model. *Gastrointest Endosc* 2016; **83**: 444-446 [PMID: 26358330 DOI:10.1016/j.gie.2015.08.064]
- 34 **Bhutani MS**. Endoscopic ultrasound comes of age: Mature, established, creative and here to stay! *Endosc Ultrasound* 2014; **3**: 143-151 [PMID: 25184120 DOI: 10.4103/2303-9027.138782]
- 35 **Chiarioni G**, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. *Gastroenterology* 2006; **130**: 657-664 [PMID: 16530506 DOI: 10.1053/j.gastro.2005.11.014]
- 36 **Byrne KR**, Glapa S, Khan AH, Young OH, Hogan WJ, Dua KS. Manometric Evaluation of Endoscopic Ultrasound Guided Botulinum Toxin Injection into the internal anal sphincter in patients with anal sphincter dyssynergia. *Gastrointest Endosc* 2014; **79** (Suppl): AB404 [in-press]
- 37 **Teoh AY**, Leung WW, Chong C, et al. Electroacupuncture analgesia for endoscopic ultrasound: A prospective, randomized, double-blinded, sham-controlled study. *Gastroenterology* 2014; **146** (Suppl 1): S902 [DOI: 10.1016/S0016-5085(14)63282-0]

P- Reviewer: Amornyotin S, Goral V **S- Editor:** Song XX
L- Editor: A **E- Editor:** Wu HL



Treatment of gastric outlet obstruction that results from unresectable gastric cancer: Current evidence

Yasuhiro Miyazaki, Shuji Takiguchi, Tsuyoshi Takahashi, Yukinori Kurokawa, Tomoki Makino, Makoto Yamasaki, Kiyokazu Nakajima, Masaki Mori, Yuichiro Doki

Yasuhiro Miyazaki, Shuji Takiguchi, Tsuyoshi Takahashi, Yukinori Kurokawa, Tomoki Makino, Makoto Yamasaki, Kiyokazu Nakajima, Masaki Mori, Yuichiro Doki, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita-shi, Osaka 565-0871, Japan

Author contributions: Miyazaki Y, Takiguchi S, Nakajima K, Mori M and Doki Y designed the research; Miyazaki Y, Takiguchi S and Takahashi T performed the research; Kurokawa Y, Makino T and Yamasaki M contributed analytic tools; Kurokawa Y analyzed the data; Miyazaki Y wrote the paper.

Conflict-of-interest statement: The authors declare there is no conflict of interest for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Shuji Takiguchi, MD, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2-E2, Yamadaoka, Suita, Osaka 565-0871, Japan. stakiguchi@gesurg.med.osaka-u.ac.jp
Telephone: +81-6-68793259
Fax: +81-6-68793259

Received: May 25, 2015
Peer-review started: May 27, 2015
First decision: August 31, 2015
Revised: October 2, 2015
Accepted: December 13, 2015
Article in press: December 14, 2015
Published online: February 10, 2016

Abstract

Malignant gastric outlet obstruction (GOO) is a com-

mon condition that results from locally advanced malignancies in the upper gastrointestinal tract, such as pancreatic, gastric, and other carcinomas. Two types of procedures for malignant GOO, namely, gastrojejunostomy (GJ) with laparotomy or a laparoscopic approach and endoscopic stenting (ES), are currently available. Although numerous previous reports have clarified the benefits and drawbacks of each procedure, whether GJ or ES should be used in patients with GOO that results from gastric cancer who may have a longer life expectancy than patients with other malignancies has not been determined. In this review, which focuses on gastric cancer-induced GOO, we analyzed the two systematic reviews and a meta-analysis that compared GJ and ES and outlined the current status of GOO treatment. We also provide an updated review that includes laparoscopic GJ. Various data from 13 studies in one review and 6 studies in another review were analyzed. Although the main results of the present review indicated that both GJ and ES were efficacious treatments in patients with GOO that resulted from gastric cancer, current evidence suggests that GJ may be the preferable procedure given its good performance status and improved prognosis in gastric cancer patients.

Key words: Gastric outlet obstruction; Gastrojejunostomy; Endoscopic stenting; Gastric cancer; Review

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Both gastrojejunostomy (GJ) and endoscopic stenting (ES) are effective treatments in patients with gastric outlet obstruction that results from gastric cancer. The advantages of GJ include fewer late complications and a long patency, whereas the advantages of ES include better short-term outcomes, including the length of the hospital stay. Although no large-scale randomized clinical trials have compared the safety and efficacy of the two procedures, this present literature review

indicates the superiority of GJ compared with ES given its good performance status and improved prognosis in gastric cancer patients as well as the widespread use of the less invasive laparoscopic GJ procedure.

Miyazaki Y, Takiguchi S, Takahashi T, Kurokawa Y, Makino T, Yamasaki M, Nakajima K, Mori M, Doki Y. Treatment of gastric outlet obstruction that results from unresectable gastric cancer: Current evidence. *World J Gastrointest Endosc* 2016; 8(3): 165-172 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/165.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.165>

INTRODUCTION

Malignant gastric outlet obstruction (GOO) is a clinical symptom of advanced malignancies in the upper gastrointestinal tract, most commonly pancreatic and gastric malignancies. Other causes include lymphomas, ampullary carcinomas, biliary tract cancers, and metastases^[1-3]. Associated symptoms, including nausea, vomiting, reflux, malnutrition, dehydration, and abdominal distention, reduce patient quality of life (QOL), and patients with malignant GOO often present with a poor condition and performance status (PS)^[4]. Furthermore, palliative treatment is important and required for patients with unresectable primary malignancies or metastatic lesions.

Treatments for malignant GOO include gastrojejunostomy (GJ), which is traditionally adopted, and palliative endoscopic stenting (ES), which is considered less invasive with a faster improvement of oral intake compared with GJ^[5]. Recently, the use of palliative ES has increased^[6]. In addition, various types of stents are now available, and the procedure has been established and advocated^[7-11]. However, the disadvantages of ES include a high rate of stent re-obstruction and migration as late complications, and pleural treatment is required with some frequency^[2].

Many comparative trials of GJ and ES in patients with malignant GOO have been performed to evaluate the safety, feasibility, costs, and patient QOL. However, to date, the available data regarding "gastric cancer" patients with GOO who could theoretically have a longer life expectancy than patients with other malignancies are not sufficient to definitively conclude the comparative benefits and limitations of GJ and ES. In this review, we outline the current status of GJ and ES treatment for malignant GOO, especially in gastric cancer, and provide a future perspective.

STUDY STRATEGY

Data source and search strategy

An increasing number of studies regarding ES, including novel devices, has been reported during the past decade, especially in the most recent five years; thus,

the outcome of GJ should be compared with recent ES. Literature searches of the electronic PubMed and Embase databases were performed. The searches were limited to articles published from January 2010 to December 2014 in English as well as human- and clinical trial-related articles to identify objective articles from January 2010 to December 2014. The following terms were utilized: "Gastric outlet obstruction", "GOO", "gastric cancer", and "gastric carcinoma". The abstracts were reviewed, and articles not related to the specific content were excluded. Duplicate references and repeated articles were also excluded. All articles considered eligible were selected, and the final selection was based on the full research papers.

Study selection

We included review articles, studies that reported randomized and controlled trials or experimental studies, and case studies. Articles were first screened and selected based on the titles. The full text was obtained for 45 articles.

MALIGNANT GOO THAT RESULTS FROM OF GASTRIC CANCER

Despite a decrease in the incidence of gastric cancer over previous decades, gastric cancer remains the fourth most common malignant disease and the second main cause of cancer-related death worldwide^[12]. To date, the curative resection ratio for newly diagnosed gastric cancer is approximately 50%, and 20% to 30% of patients with gastric cancer present with stage IV disease^[13,14].

Malignant GOO is a common condition among locally advanced gastric cancer patients and can lead to significant morbidity, including nausea, vomiting, abdominal pain, dehydration, malnutrition, and weight loss. Not surprisingly, these clinical symptoms have a negative impact on QOL^[15]. To avoid the disastrous consequences of malignant GOO, appropriate treatment is indispensable, which enables not only an amelioration of the patient's QOL but also the commencement of chemotherapy, including essential oral agents, such as S1 or capecitabine^[16]. These treatments are included in the first-line regimen for unresectable gastric cancer recommended in the Japanese gastric cancer treatment guidelines^[17].

GJ is traditionally the palliative treatment of choice for patients with malignant unresectable GOO, whereas the palliative endoscopic treatment of GOO with endoluminal self-expanding metallic stents has only recently become available. Both treatments have benefits and limitations associated with prognosis; thus, it is important to determine the optimal treatment approach. Although GOO may occur with other malignancies, such as pancreatic periampullary carcinoma, lymphoma, and metastases to the duodenum of jejunum^[1-3], GOO in gastric cancer should be considered separately. First,

gastric cancer has a longer life expectancy than other biological malignancies, and more chemotherapy agents have been developed for this malignancy compared with other diseases^[18-20]. Second, GOO that results from gastric cancer has a reduced possibility of co-occurring with an obstruction of the bile duct compared with biliopancreatic malignancies. Several studies have reported a median overall survival of 13 mo for unresectable or recurrent gastric carcinoma^[21], which is longer than pancreatic cancer (6.7-8.5 mo)^[22].

Therefore, the decision regarding whether to select GJ or ES should depend on the condition and PS of patients. Furthermore, prior to any procedure, information regarding the benefits and drawbacks of GJ and ES is necessary for well-informed consent.

TREATMENTS FOR GASTRIC OUTLET OBSTRUCTION

GJ

Traditionally, GOO caused by malignancy is treated with a palliative "open" GJ (OGJ), which is surgically performed^[23]. Although this modality has a favorable outcome and relieves many symptoms derived from GOO, it results in some morbidity and mortality given the poor condition of these patients^[1,24]. Several recent studies have reported the effectiveness of "laparoscopic" GJ (LGJ) with regard to safety, feasibility, and invasiveness; however, its role has not been clarified^[25,26]. Jeurnink *et al.*^[5] reported that LGJ appears to be more favorable regarding tolerable oral administration, the duration of the hospital stay, and the complication ratio compared with OGJ. However, no significant differences were identified between the two approaches^[27]. Navarra *et al.*^[28] also published a randomized controlled trial (RCT) that compared LGJ and OGJ ($n = 12$ patients each). LGJ resulted in significantly less intra-operative blood loss, a shorter time to tolerating solid food intake, and a reduced rate of complications; however, no significant difference was identified in the postoperative hospital stay^[28]. In contrast, older retrospective studies have reported benefits with regard to intra-operative blood loss and hospital stay as well as a high conversion rate to OGJ^[29,30]. Different outcomes of LGJ have been reported, and this variation can be explained by the small sample sizes and low power. However, no clinical trials with sufficient power have demonstrated the effectiveness of LGJ compared with OGJ, and LGJ is now the preferred standard for malignant GOO treatment^[31].

ES

Endoscopic treatment of GOO with endoluminal self-expanding metallic stents was first described by Topazian *et al.*^[6] in the early 1990s. Over the previous decade, experiences and reports of the use of ES have increased. In addition, various types of upper gastrointestinal stents have become available, and well-established ES procedures have been advocated

and performed^[32]. Recently, several articles have reported that patients who present with GOO with a long life expectancy should undergo ES given its safety, minimal invasiveness, and cost-effectiveness^[33]. Self-expandable metallic stents (SEMSs) are the standard devices for recanalization of an obstructed digestive lumen. However, some SEMSs exhibit re-occlusion because of tumor in growth through openings between the stent wire filaments or stent migration as late major complications^[34]. Covered SEMSs prevent ingrowth through the mesh wall, and they are advantageous compared with uncovered SEMSs in esophageal cancer^[35]. However, in malignant colorectal obstruction, covered stents do not exhibit an advantage compared with uncovered stents due to high migration rates^[36]. Several studies have also suggested that covered stents are associated with more frequent re-intervention despite approximately similar outcomes and complications in malignant GOO. Therefore, with regard to ES for GOO, the effectiveness and complications of covered and uncovered SEMSs in patients with GOO have recently been highlighted. Kim *et al.*^[37] reported a prospective RCT of covered vs uncovered stents for the palliation of GOO in gastric cancer patients and concluded that the overall stent patency did not differ between the two groups; moreover, frequent migration of the covered SEMSs offsets its advantages in the prevention of re-stenosis. Maetani *et al.*^[38] also reported similar results in a multicenter randomized trial in Japan, *i.e.*, no significant difference in the stent patency between triple-layered covered and uncovered metallic stents for the palliation of malignant GOO; however, the use of a triple-layered covered SEMS was associated with less frequent stent dysfunction more than 4 wk after the initial stent. Regardless of the stent configuration, covered or uncovered, the ES procedure for GOO caused by malignancy is considered safe and efficacious.

RECENT SYSTEMATIC REVIEW AND COMPARATIVE RESEARCH OF TREATMENTS FOR GOO THAT RESULTS FROM GASTRIC CANCER

Two systematic reviews

Two systematic reviews and a meta-analysis that compared GJ and ES have been published since 2010. In review 1 in 2010, Ly *et al.*^[27] performed a comprehensive search of the literature for the period from 1990 to 2008 using Medline, EMBASE, Google Scholar, ISI Proceedings, the Cochrane Library, and online registers of CCTs but not PubMed. This review included only clinical studies that directly compared GJ and ES for the palliative treatment of GOO, which included randomized clinical trials (RCTs) and prospective and retrospective cohort comparison studies. Thirteen studies were analyzed, including 10 retrospective cohort comparison studies^[1,26,39-46], 1 prospective study^[41], and 2 RCTs^[25,47]. In review 2 in

Table 1 Characteristics and main results of two reviews

Review	Year	Study type			Primary tumor			Procedure		Favorable group regarding several variables			
		Retro	Pro	RCT	Stomach	Pancreas	Others	GJ	ES	Toleration of oral intake ¹	Time to oral intake ² (d)	Hospital stay ³ (d)	Complication
1	2010	10	1	2	94 (18.3%)	240 (46.7%)	180 (35.0%)	255 (LGJ 37)	244	ES	ES (2.0 d)	ES (9.4 d)	GJ is approximately equal to ES
2	2012	0	3	3	55 (28.6%)	86 (44.8%)	51 (26.6%)	92 (LGJ 0)	74	GJ (not-RCT)	ES (2.1-5.0 d)	ES (2.5-7.0 d)	Major: GJ is approximately equal to ES Minor: ES

¹Patients were more likely to tolerate oral intake following ES than GJ in Review 1; however, Review 2 reported the opposite results. The difference was only significant in the non-RCT group; ²The mean time from the procedure to initiate oral intake was 7 d (Review 1) and 3.6 d (Review 2) less for ES compared with GJ; ³The mean length of hospital stay was reduced by 12 d (Review 1) and 7.5 d (Review 2) for ES compared with GJ. Retro: Retrospective; Pro: Prospective; RCT: Randomized controlled trial; GJ: Gastrojejunostomy; ES: Endoscopic stenting; LGJ: Laparoscopic GJ.

2012, Zheng *et al.*^[48] searched the PubMed, Embase, Chinese Biomedical Database, and Cochrane Library for all studies between 1996 and 2010. The inclusion criteria were as follows: controlled clinical trials (CCTs) and RCTs; analyses of “both” GJ (OGJ and LGJ) and ES; any sample size; full paper; and not a duplicate report. Six studies remained in the final analysis, including three RCTs^[25,47,49] and three CCTs^[41,50,51]. Both reviews included the same two studies. One study was a RCT reported by Mehta *et al.*^[25] in 2006, and the other study was a CCT reported by Johnsson *et al.*^[41] in 2004.

Table 1 provides the characteristics of the comparative data and main results for GJ and ES in the two reviews with regard to the study type, primary tumor site, number of procedures, and favorable procedure group with better results regarding: (1) the number of patients who tolerated oral intake; (2) time to oral intake (days); (3) length of hospital stay (days); and (4) complications. Ninety-four (18.2%) of 514 patients and 55 (28.6%) of 192 patients with GOO that resulted from “gastric cancer” were included. Technical success was only documented in Review 2, and GJ exhibited greater technical success than ES [odds ratio (OR) = 0.10, 95%CI: 0.02-0.47, $I^2 = 0\%$, $P = 0.0039$] according to a meta-analysis. However, the significant difference remained only in the non-RCT group. Nevertheless, both GJ and ES demonstrated satisfactory results regarding technical success (success rates of 99% to 100% and 8% to 100%, respectively). The ability to tolerate oral intake after palliative treatments for GOO is one of the most important endpoints and was documented as a “clinical success” in Review 2. With regard to the ability to tolerate oral intake, 11 studies included in Review 1 reported more favorable results following ES compared with GJ. Although no significant difference was identified in the two studies included in Review 2, one study reported that ES was associated with greater clinical success than GJ ($P = 0.007$). Regarding the time to oral intake after the palliative procedure, all reported

data in both reviews indicated that ES had clear merits compared with GJ. The average time from the procedure to the initiation of oral intake was approximately 3 d less for ES compared with GJ. Several studies have evaluated the length of hospital stay and medical costs. All studies reported a significantly reduced hospital stay for patients who underwent ES compared with GJ (mean difference of 12 d). One RCT and one CCT demonstrated reduced total medical costs and hospital stay costs with ES compared with GJ. In summary, approximately all studies indicated that ES has advantages compared with GJ. However, cost should not be the main factor in decisions regarding procedures for malignant GOO patients because the costs per day for patients who consumed at least a soft diet were quite similar between both procedures. Better long-term clinical outcomes after GJ compared with ES were noted in the major prospective randomized SUSTENT study, which was included in Review 2^[52].

Both reviews indicated that there are no significant differences in the major complication rates between GJ and ES (OR = 1.04, 95%CI: 0.47-2.29, $P = 0.93$ according to meta-analysis data in Review 1; OR = 3.76, 95%CI: 0.57-24.72, $P = 0.17$ in Review 2). The detailed major medical complications that result from GJ were reported as respiratory tract infections, myocardial infarction, and acute renal failure, whereas the complications of ES were procedure-related, including stent failure migration and obstruction. Although minor complications were described only in Review 2, they were less likely the result of ES compared with GJ (OR = 0.28, 95%CI: 0.10-0.83, $P = 0.02$). Regarding morality, both reviews indicated similar conclusions indicating no differences between the two treatments (OR = 0.58, 95%CI: 0.18-1.86, $P = 0.36$).

The length of survival was estimated in both reviews. Despite the inclusion of both randomized and non-RCT, no significant difference was identified between GJ and ES (mean difference 26 d; 95%CI: 69.03-16.40 d, $P = 0.23$ in Review 1).

Table 2 Patient demographics and main results in two reviews

Ref.	Study type	Procedure		Performance status		Comparison between GJ and ES regarding several variables				
		GJ	ES	GJ	ES	Tolerance of oral intake	GOO recurrence	Time to oral intake	Hospital stay	Complication
Fiori <i>et al</i> ^[53]	Prospective	9 (LGJ 0)	9	NR	NR	GJ is approximately equal to ES	GJ (0%) < ES (33%) ^a	GJ (6.3 d) ES (3.1 d)	GJ (10 d) ES (4.8 d)	GJ: SSI, bleeding, ventral hernia ES: Stent dislocation, re-obstruction
No <i>et al</i> ^[54]	Retrospective	41 (LGJ 9)	72	0-1 ¹ : 68.3% 2 ¹ : 31.7%	0-1 ¹ : 59.7% 2 ¹ : 40.3%	GJ (95.1%) is approximately equal to ES (87.5%)	GJ (12.2%) < ES (44.4%) ^a	GJ (16 d) > ES (10 d) ^a	GJ (18 d) > ES (16 d) ³	GJ is approximately equal to ES
Keränen <i>et al</i> ^[55]	Retrospective	21 (LGJ 0)	50	I-II ² : 90.5% III-IV ² : 9.5%	I-II ² : 58% III-IV ² : 42%	GJ (81%) is approximately equal to ES (88%)	GJ (9.5%) ES (24%)	GJ (4 d) > ES (1 d) ^a	GJ (8 d) > ES (3 d) ^a	GJ (10%) ES (26%)

¹ECOG performance status; ²WHO score; ³Not significant; ^a $P < 0.05$. GJ: Gastrojejunostomy; ES: Endoscopic stenting; LGJ: Laparoscopic GJ; NR: Not reported; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization.

DISCUSSION

Comparative studies between GJ and ES for malignant GOO that results from gastric cancer

One non-randomized prospective study^[53] and two retrospective studies^[54,55] are available regarding malignant GOO caused by limited unresectable or metastatic gastric cancer. Table 2 provides patient demographics and the main results of three studies with regard to study type, number of procedures, PS, and the favorable procedure group with better results regarding: (1) the number of patients who tolerated oral intake; (2) time to oral intake (d); (3) length of hospital stay (d); and (4) complications.

In a prospective study of 18 patients (9 OGJ and 9 ES treatment)^[53], ES had more favorable results regarding the mean time to resume oral feeding (3.1 d) and mean length of hospital stay (4.8 d) compared with GJ (6.3 d and 10 d, respectively). Regarding the late results, such as the recurrence of GOO, late complications due to the procedure, overall survival, and patient satisfaction, no significant differences were identified between OGJ and ES. Recurrent symptoms of GOO were evident only in ES ($n = 3$ patients, 33%) due to stent migration and obstruction of the stent by food. Both procedures resulted in sufficient patient satisfaction.

In their retrospective study, No *et al*^[54] concluded that GJ is preferable to ES for the palliation of GOO that results from gastric cancer in patients with a good PS, especially Eastern Cooperative Oncology Group (ECOG) 0 to 1. In this study, 72 ES and 41 GJ (32 OGJ and 9 LGJ) patients were compared regarding patient demographics, early outcomes and adverse events, late adverse events, patency duration, and survival. The two groups did not differ in most characteristics with the exception of sex (more men in the GJ group). The technical success rates in both groups were excellent (ES: 95.8% vs GJ: 97.6%); however, three technical

failures were noted in the ES group. However, the time to oral intake was significantly less in the ES group compared with the GJ group (liquid diet: ES 2 d vs GJ 5 d, solid diet: ES 10 d vs GJ 16 d). Regarding adverse events, a higher rate of late adverse events was identified in the ES group compared with the GJ group (44.4% vs 12.2%, $P < 0.01$), whereas early adverse events were not significantly different between the two groups. The adverse events in the ES group were not significantly different according to the stent type ($P = 0.158$). Similarly, the number of re-interventions was significantly greater in the ES group compared with the GJ group (31 (43%) vs 4 (5.5%)), respectively, $P < 0.001$. Regarding the patency duration, the median duration of both the first stent patency and total stent patency, including the patency achieved by an additional stent, was 210 d shorter in the ES group compared with the GJ group ($P = 0.001$, $P = 0.044$, respectively). The interesting finding in this previous study was the analysis according to PS (ECOG status). Patients in the GJ group exhibited significantly longer overall survival compared with the ES group, but only for ECOG 0 to 1.

Keränen *et al*^[55] compared three palliative methods, including 50 ES, 26 palliative resections of the stomach (PR), and 21 GJ. All palliative surgeries were performed with laparotomy. Patients with ES presented with the poorest general condition among all groups in terms of the pre-procedure albumin level, PS, and amount of oral intake; thus, the ES group exhibited the worst survival. The main results regarding the palliation of GOO symptoms demonstrated that ES resulted in a faster improvement of oral intake, relief of GOO symptoms, and reduced hospital stay compared with GJ. The authors advocated considering how the clinical condition before treatment affects survival in malignant GOO that results from gastric cancer when determining the type of palliative procedures. Furthermore, the authors indicated that the study had several limitations. The study was non-randomized, retrospective, and

had a certain degree of defective follow-up data, which led to selection bias between the treatment groups. However, this retrospective study reported the time between ES treatment and re-obstruction; however, this information was described only in context, not in tables or figures. The median time to re-obstruction after ES was 95 d; thus, most patients had died before re-obstruction occurred. Therefore, re-obstruction of the stent is not a major problem for patients with a poor prognosis (< 3 mo), even in patients with gastric cancer and particularly in patients with pancreatic cancer or other malignancies with a worse prognosis.

In summary, the main findings of comparative studies between GJ and ES that focused on gastric cancer patients were similar to the findings of other RCTs, CCTs, and retrospective studies of patients with GOO that resulted from malignancies other than gastric carcinoma. In addition, no articles have referred to precise cost performance or compared LGJ and ES. Compared with GJ, ES is preferred for the rapid improvement of oral intake, relief of GOO symptoms, and reduced hospital stay, whereas the occurrence of late complications, such as stent obstruction or migration, is higher. The differences compared with other malignant GOOs are patient survival after GJ or ES and patient PS. The median survival durations in these three articles were 283, 189 to 293, and 50 to 241 d. Thus, the potential survival of GOO patients with gastric cancer may be increased by approximately 2 or 3 mo. Because several studies have reported that GJ is preferable for patients with a longer life expectancy^[49], GJ should be selected more frequently in clinical practice for good PS patients with GOO that results from gastric cancer.

CONCLUSION

Both GJ and ES are effective treatments in patients with GOO that results from gastric cancer. GJ exhibits better long-term outcomes with regard to fewer late complications and long patency, whereas ES exhibits better short-term outcomes, including the length of the hospital stay. Although no large-scale studies or RCTs have compared the safety and efficacy of the two procedures, literature reviews suggest that GJ may be the preferable procedure because of the good PS and long prognosis of gastric cancer patients.

However, the bypass procedure is currently performed laparoscopically (LGJ), and various novel devices in the ES field can minimize stent obstruction or migration. Therefore, to determine the more preferable procedure in patients with GOO that results from gastric cancer, a prospective RCT of LGJ and ES with current devices specialized for gastric cancer patients is warranted.

REFERENCES

- 1 Del Piano M, Ballarè M, Montino F, Todesco A, Orsello M, Magnani C, Garelo E. Endoscopy or surgery for malignant GI outlet obstruction? *Gastrointest Endosc* 2005; **61**: 421-426 [PMID: 15758914 DOI: 10.1016/S0016-5107(04)02757-9]
- 2 Pinto Pabón IT, Díaz LP, Ruiz De Adana JC, López Herrero J. Gastric and duodenal stents: follow-up and complications. *Cardiovasc Intervent Radiol* 2001; **24**: 147-153 [PMID: 11443401 DOI: 10.1007/s002700001742]
- 3 Park KB, Do YS, Kang WK, Choo SW, Han YH, Suh SW, Lee SJ, Park KS, Choo IW. Malignant obstruction of gastric outlet and duodenum: palliation with flexible covered metallic stents. *Radiology* 2001; **219**: 679-683 [PMID: 11376254 DOI: 10.1148/radiology.219.3.r01jn21679]
- 4 Lopera JE, Brazzini A, Gonzales A, Castaneda-Zuniga WR. Gastroduodenal stent placement: current status. *Radiographics* 2004; **24**: 1561-1573 [PMID: 15537965 DOI: 10.1148/rg.246045033]
- 5 Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol* 2007; **7**: 18 [PMID: 17559659 DOI: 10.1186/1471-230X-7-18]
- 6 Topazian M, Ring E, Grendell J. Palliation of obstructing gastric cancer with steel mesh, self-expanding endoprostheses. *Gastrointest Endosc* 1992; **38**: 58-60 [PMID: 1377147 DOI: 10.1016/S0016-5107(92)70334-4]
- 7 Binkert CA, Jost R, Steiner A, Zollikofer CL. Benign and malignant stenoses of the stomach and duodenum: treatment with self-expanding metallic endoprostheses. *Radiology* 1996; **199**: 335-338 [PMID: 8668774 DOI: 10.1148/radiology.199.2.8668774]
- 8 Feretis C, Benakis P, Dimopoulos C, Manouras A, Tsimbloulis B, Apostolidis N. Duodenal obstruction caused by pancreatic head carcinoma: palliation with self-expandable endoprostheses. *Gastrointest Endosc* 1997; **46**: 161-165 [PMID: 9283868 DOI: 10.1016/S0016-5107(97)70066-X]
- 9 Dumas R, Demarquay JF, Caroli-Bosc FX, Paolini O, Guenenna D, Peten EP, Delmont JP, Rampal P. [Palliative endoscopic treatment of malignant duodenal stenosis by metal prosthesis]. *Gastroenterol Clin Biol* 2000; **24**: 714-718 [PMID: 11011246]
- 10 Espinel J, Vivas S, Muñoz F, Jorquera F, Olcoz JL. Palliative treatment of malignant obstruction of gastric outlet using an endoscopically placed enteral Wallstent. *Dig Dis Sci* 2001; **46**: 2322-2324 [PMID: 11713929]
- 11 Siddiqui A, Spechler SJ, Huerta S. Surgical bypass versus endoscopic stenting for malignant gastroduodenal obstruction: a decision analysis. *Dig Dis Sci* 2007; **52**: 276-281 [PMID: 17160470 DOI: 10.1007/s10620-006-9536-z]
- 12 Carcas LP. Gastric cancer review. *J Carcinog* 2014; **13**: 14 [PMID: 25589897 DOI: 10.4103/1477-3163.146506]
- 13 Kokkola A, Sipponen P, Arkkila P, Danielson H, Puolakkainen P. Does the eradication of *Helicobacter pylori* delay the diagnosis of gastric cancer? *Scand J Gastroenterol* 2008; **43**: 1456-1460 [PMID: 18663664 DOI: 10.1080/00365520802273041]
- 14 Lagman RL, Davis MP, LeGrand SB, Walsh D. Common symptoms in advanced cancer. *Surg Clin North Am* 2005; **85**: 237-255 [PMID: 15833469 DOI: 10.1016/j.suc.2004.11.004]
- 15 Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. *Am J Gastroenterol* 2002; **97**: 72-78 [PMID: 11808972 DOI: 10.1111/j.1572-0241.2002.05423.x]
- 16 Pasini F, Fraccon AP, DE Manzoni G. The role of chemotherapy in metastatic gastric cancer. *Anticancer Res* 2011; **31**: 3543-3554 [PMID: 21965776]
- 17 Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123 [PMID: 21573742 DOI: 10.1007/s10120-011-0042-4]
- 18 Emoto S, Sunami E, Yamaguchi H, Ishihara S, Kitayama J, Watanabe T. Drug development for intraperitoneal chemotherapy against peritoneal carcinomatosis from gastrointestinal cancer. *Surg Today* 2014; **44**: 2209-2220 [PMID: 24482110 DOI: 10.1007/s00595-014-0848-x]
- 19 Imano M, Okuno K. Treatment strategies for gastric cancer patients with peritoneal metastasis. *Surg Today* 2014; **44**: 399-404 [PMID: 23677598 DOI: 10.1007/s00595-013-0603-8]

- 20 **Yoshikawa T**, Rino Y, Yukawa N, Oshima T, Tsuburaya A, Masuda M. Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy. *Surg Today* 2014; **44**: 11-21 [PMID: 23508452 DOI: 10.1007/s00595-013-0529-1]
- 21 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/S1470-2045(08)70035-4]
- 22 **Bergmann L**, Maute L, Heil G, Rüssel J, Weidmann E, Köberle D, Fuxius S, Weigang-Köhler K, Aulitzky WE, Wörmann B, Hartung G, Moritz B, Edler L, Burkholder I, Scheulen ME, Richly H. A prospective randomised phase-II trial with gemcitabine versus gemcitabine plus sunitinib in advanced pancreatic cancer: a study of the CESAR Central European Society for Anticancer Drug Research-EWIV. *Eur J Cancer* 2015; **51**: 27-36 [PMID: 25459392 DOI: 10.1016/j.ejca.2014.10.010]
- 23 **Takeno A**, Takiguchi S, Fujita J, Tamura S, Imamura H, Fujitani K, Matsuyama J, Mori M, Doki Y. Clinical outcome and indications for palliative gastrojejunostomy in unresectable advanced gastric cancer: multi-institutional retrospective analysis. *Ann Surg Oncol* 2013; **20**: 3527-3533 [PMID: 23715966 DOI: 10.1245/s10434-013-3033-3]
- 24 **Bozzetti F**, Bonfanti G, Audisio RA, Doci R, Dossena G, Gennari L, Andreola S. Prognosis of patients after palliative surgical procedures for carcinoma of the stomach. *Surg Gynecol Obstet* 1987; **164**: 151-154 [PMID: 2433778]
- 25 **Mehta S**, Hindmarsh A, Cheong E, Cockburn J, Saada J, Tighe R, Lewis MP, Rhodes M. Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. *Surg Endosc* 2006; **20**: 239-242 [PMID: 16362479 DOI: 10.1007/s00464-005-0130-9]
- 26 **Mittal A**, Windsor J, Woodfield J, Casey P, Lane M. Matched study of three methods for palliation of malignant pyloroduodenal obstruction. *Br J Surg* 2004; **91**: 205-209 [PMID: 14760669 DOI: 10.1002/bjs.4396]
- 27 **Ly J**, O'Grady G, Mittal A, Plank L, Windsor JA. A systematic review of methods to palliate malignant gastric outlet obstruction. *Surg Endosc* 2010; **24**: 290-297 [PMID: 19551436 DOI: 10.1007/s00464-009-0577-1]
- 28 **Navarra G**, Musolino C, Venneri A, De Marco ML, Bartolotta M. Palliative antecolic isoperistaltic gastrojejunostomy: a randomized controlled trial comparing open and laparoscopic approaches. *Surg Endosc* 2006; **20**: 1831-1834 [PMID: 17063298 DOI: 10.1007/s00464-005-0454-5]
- 29 **Bergamaschi R**, Mårvik R, Thoresen JE, Ystgaard B, Johnsen G, Myrvold HE. Open versus laparoscopic gastrojejunostomy for palliation in advanced pancreatic cancer. *Surg Laparosc Endosc* 1998; **8**: 92-96 [PMID: 9566559 DOI: 10.1097/00019509-199804000-00002]
- 30 **Nagy A**, Brosseuk D, Hemming A, Scudamore C, Mamazza J. Laparoscopic gastroenterostomy for duodenal obstruction. *Am J Surg* 1995; **169**: 539-542 [PMID: 7538268 DOI: 10.1016/S0002-9610(99)80213-X]
- 31 **Al-Rashedy M**, Dadibhai M, Shareif A, Khandelwal MI, Ballester P, Abid G, McCloy RF, Ammori BJ. Laparoscopic gastric bypass for gastric outlet obstruction is associated with smoother, faster recovery and shorter hospital stay compared with open surgery. *J Hepatobiliary Pancreat Surg* 2005; **12**: 474-478 [PMID: 16365822 DOI: 10.1007/s00534-005-1013-0]
- 32 **Adler DG**. Enteral stents for malignant gastric outlet obstruction: testing our mettle. *Gastrointest Endosc* 2007; **66**: 361-363 [PMID: 17643713 DOI: 10.1016/j.gie.2006.12.053]
- 33 **Tringali A**, Didden P, Repici A, Spaander M, Bourke MJ, Williams SJ, Spicak J, Drastich P, Mutignani M, Perri V, Roy A, Johnston K, Costamagna G. Endoscopic treatment of malignant gastric and duodenal strictures: a prospective, multicenter study. *Gastrointest Endosc* 2014; **79**: 66-75 [PMID: 23932009 DOI: 10.1016/j.gie.2013.06.032]
- 34 **Dormann A**, Meisner S, Verin N, Wenk Lang A. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. *Endoscopy* 2004; **36**: 543-550 [PMID: 15202052 DOI: 10.1055/s-2004-814434]
- 35 **Vakil N**, Morris AI, Marcon N, Segalin A, Peracchia A, Bethge N, Zuccaro G, Bosco JJ, Jones WF. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. *Am J Gastroenterol* 2001; **96**: 1791-1796 [PMID: 11419831 DOI: 10.1111/j.1572-0241.2001.03923.x]
- 36 **Lee KM**, Shin SJ, Hwang JC, Cheong JY, Yoo BM, Lee KJ, Hahm KB, Kim JH, Cho SW. Comparison of uncovered stent with covered stent for treatment of malignant colorectal obstruction. *Gastrointest Endosc* 2007; **66**: 931-936 [PMID: 17767930 DOI: 10.1016/j.gie.2007.02.064]
- 37 **Kim CG**, Choi IJ, Lee JY, Cho SJ, Park SR, Lee JH, Ryu KW, Kim YW, Park YI. Covered versus uncovered self-expandable metallic stents for palliation of malignant pyloric obstruction in gastric cancer patients: a randomized, prospective study. *Gastrointest Endosc* 2010; **72**: 25-32 [PMID: 20381802 DOI: 10.1016/j.gie.2010.01.039]
- 38 **Maetani I**, Mizumoto Y, Shigoka H, Omuta S, Saito M, Tokuhisa J, Morizane T. Placement of a triple-layered covered versus uncovered metallic stent for palliation of malignant gastric outlet obstruction: a multicenter randomized trial. *Dig Endosc* 2014; **26**: 192-199 [PMID: 23621572 DOI: 10.1111/den.12117]
- 39 **Wong YT**, Brans DM, Munson L, Sanders L, Heiss F, Chase M, Birkett DH. Gastric outlet obstruction secondary to pancreatic cancer: surgical vs endoscopic palliation. *Surg Endosc* 2002; **16**: 310-312 [PMID: 11967685 DOI: 10.1007/s00464-001-9061-2]
- 40 **Yim HB**, Jacobson BC, Saltzman JR, Johannes RS, Bounds BC, Lee JH, Shields SJ, Ruymann FW, Van Dam J, Carr-Locke DL. Clinical outcome of the use of enteral stents for palliation of patients with malignant upper GI obstruction. *Gastrointest Endosc* 2001; **53**: 329-332 [PMID: 11231392 DOI: 10.1016/S0016-5107(01)70407-5]
- 41 **Johnsson E**, Thune A, Liedman B. Palliation of malignant gastroduodenal obstruction with open surgical bypass or endoscopic stenting: clinical outcome and health economic evaluation. *World J Surg* 2004; **28**: 812-817 [PMID: 15457364 DOI: 10.1007/s00268-004-7329-0]
- 42 **Maetani I**, Akatsuka S, Ikeda M, Tada T, Ukita T, Nakamura Y, Nagao J, Sakai Y. Self-expandable metallic stent placement for palliation in gastric outlet obstructions caused by gastric cancer: a comparison with surgical gastrojejunostomy. *J Gastroenterol* 2005; **40**: 932-937 [PMID: 16261429 DOI: 10.1007/s00535-005-1651-7]
- 43 **Mejia A**, Ospina J, Munoz A, Albis R, Oliveros R. Palliation of a malignant gastroduodenal obstruction. *Rev Col Gastroenterol* 2006; **21**: 17-21
- 44 **Espinell J**, Sanz O, Vivas S, Jorquera F, Muñoz F, Olcoz JL, Pinedo E. Malignant gastrointestinal obstruction: endoscopic stenting versus surgical palliation. *Surg Endosc* 2006; **20**: 1083-1087 [PMID: 16703436 DOI: 10.1007/s00464-005-0354-8]
- 45 **Maetani I**, Tada T, Ukita T, Inoue H, Sakai Y, Nagao J. Comparison of duodenal stent placement with surgical gastrojejunostomy for palliation in patients with duodenal obstructions caused by pancreaticobiliary malignancies. *Endoscopy* 2004; **36**: 73-78 [PMID: 14722859 DOI: 10.1055/s-2004-814123]
- 46 **El-Shabrawi A**, Cerwenka H, Bacher H, Kornprat P, Schweiger J, Mischinger HJ. Treatment of malignant gastric outlet obstruction: endoscopic implantation of self-expanding metal stents versus gastric bypass surgery. *Eur Surg* 2006; **38**: 451-455 [DOI: 10.1007/s10353-006-0295-z]
- 47 **Fiori E**, Lamazza A, Volpino P, Burza A, Paparelli C, Cavallaro G, Schillaci A, Cangemi V. Palliative management of malignant antropyloric strictures. Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. *Anticancer Res* 2004; **24**: 269-271 [PMID: 15015607]
- 48 **Zheng B**, Wang X, Ma B, Tian J, Jiang L, Yang K. Endoscopic stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction. *Dig Endosc* 2012; **24**: 71-78 [PMID: 22348830 DOI: 10.1111/j.1443-1661.2011.01186.x]

- 49 **Jeurnink SM**, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, Kuipers EJ, Siersema PD. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc* 2010; **71**: 490-499 [PMID: 20003966 DOI: 10.1016/j.gie.2009.09.042]
- 50 **Guo JJ**, Liang WX, Zhang T. A prospective comparative study of three treatment options in patients with malignant gastric outlet obstruction. *Zhonghua Weichang Waike Zazhi* 2010; **13**: 598-600 [PMID: 20737313]
- 51 **Schmidt C**, Gerdes H, Hawkins W, Zucker E, Zhou Q, Riedel E, Jaques D, Markowitz A, Coit D, Schattner M. A prospective observational study examining quality of life in patients with malignant gastric outlet obstruction. *Am J Surg* 2009; **198**: 92-99 [PMID: 19482259 DOI: 10.1016/j.amjsurg.2008.09.030]
- 52 **Jeurnink SM**, Polinder S, Steyerberg EW, Kuipers EJ, Siersema PD. Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. *J Gastroenterol* 2010; **45**: 537-543 [PMID: 20033227 DOI: 10.1007/s00535-009-0181-0]
- 53 **Fiori E**, Lamazza A, Demasi E, Decesare A, Schillaci A, Sterpetti AV. Endoscopic stenting for gastric outlet obstruction in patients with unresectable antro pyloric cancer. Systematic review of the literature and final results of a prospective study. The point of view of a surgical group. *Am J Surg* 2013; **206**: 210-217 [PMID: 23735668 DOI: 10.1016/j.amjsurg.2012.08.018]
- 54 **No JH**, Kim SW, Lim CH, Kim JS, Cho YK, Park JM, Lee IS, Choi MG, Choi KY. Long-term outcome of palliative therapy for gastric outlet obstruction caused by unresectable gastric cancer in patients with good performance status: endoscopic stenting versus surgery. *Gastrointest Endosc* 2013; **78**: 55-62 [PMID: 23522025 DOI: 10.1016/j.gie.2013.01.041]
- 55 **Keränen I**, Kylänpää L, Udd M, Louhimo J, Lepistö A, Halttunen J, Kokkola A. Gastric outlet obstruction in gastric cancer: a comparison of three palliative methods. *J Surg Oncol* 2013; **108**: 537-541 [PMID: 24590674 DOI: 10.1002/jso.23442]

P- Reviewer: Gurkan A, Huang CM, Kim JJ **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Wu HL



Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection

Su-Jin Kim, Cheol-Woong Choi, Dae-Hwan Kang, Hyung-Wook Kim, Su-Bum Park

Su-Jin Kim, Cheol-Woong Choi, Dae-Hwan Kang, Hyung-Wook Kim, Su-Bum Park, Department of Internal Medicine, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan 626-770, South Korea

Author contributions: Kim SJ wrote the manuscript; Choi CW organized the manuscript; Kang DH, Kim HW and Park SB contributed to the design, organization, and draft of the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Cheol-Woong Choi, MD, Department of Internal Medicine, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Beomeo-ri, Mulgeum-eup, Yangsan-si, Yangsan 626-770, South Korea. luckyace@hanmail.net
Telephone: +82-55-3601535
Fax: +82-55-3601536

Received: April 20, 2015
Peer-review started: April 21, 2015
First decision: September 8, 2015
Revised: October 1, 2015
Accepted: December 4, 2015
Article in press: December 8, 2015
Published online: February 10, 2016

Abstract

Endoscopic submucosal dissection (ESD) is a widely

used procedure as curative treatment for superficial gastric neoplasms, including early gastric cancer without lymph node metastasis. However, ESD requires advanced endoscopic skill and there is a major concern regarding complications from bleeding. So far, extensive efforts have been made to develop strategies to reduce post-ESD bleeding. Use of proton pump inhibitors and coagulating exposed vessels on the ulcer floor after ESD are strategies known to reduce the risk of delayed bleeding. Second-look endoscopy (SLE) is also carried out to reduce delayed bleeding following ESD in many institutions. However, the incidence of bleeding still remains around 5%, and further measures are needed to reduce delayed bleeding after gastric ESD. Recently, three randomized studies indicated that routine SLE was unnecessary. Although routine SLE may not be recommended for all patients after gastric ESD, SLE might be an important tool for the prevention of the delayed bleeding in selected high-risk patients. Thus, the identification of the risk factors, such as large size of resected specimen and treatment with multiple antiplatelet medications, may help to further guide clinicians in deciding whether to perform SLE. Studies carried out on larger cohorts are necessary to clarify the efficacy of SLE after ESD in the prevention of post-ESD bleeding in potentially high-risk patients.

Key words: Endoscopic submucosal dissection; Second-look endoscopy; Early gastric cancer

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Second-look endoscopy (SLE) for selected patients might be an important tool for the prevention of delayed bleeding following endoscopic submucosal dissection (ESD). Risk factors for bleeding after ESD include large size of resected specimen and use of multiple antiplatelet agents. In addition, submucosal fibrosis and nausea might be risk factors associated with high-risk ulcer stigmata. Such risk factors require further evaluation as to whether SLE is indicated.

Kim SJ, Choi CW, Kang DH, Kim HW, Park SB. Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016; 8(3): 173-179 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/173.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.173>

INTRODUCTION

In recent years, endoscopic submucosal dissection (ESD) for superficial gastric epithelial neoplasms including early gastric cancer has been commonly used in clinical practice in Asian countries. While a snare is used in conventional endoscopic mucosal resection (EMR), various types of endoscopic surgical knives are used in ESD for the purpose of mucosal incision and submucosal dissection. Therefore, this technique enables higher en bloc resection and histologic complete resection rates in patients with larger or ulcerated tumors^[1,2]. However, with ESD, concerns still exist regarding technical difficulties and a higher risk of complications, especially bleeding and perforation^[1,2]. Immediate intraoperative bleeding is easily recognized at the time of the procedure and can be treated endoscopically in most cases. However, delayed bleeding, manifesting as hematemesis or melena, may occur days after the procedure, occasionally even after discharge from hospital. The reported incidence of delayed bleeding after gastric ESD varies from 5.4% to 22%^[3-9]. As any delay in the recognition of such an event may result in serious cardiovascular complications, such as hypovolemic shock, prevention of delayed bleeding is an important clinical problem following ESD to address.

ESD causes large artificial ulcers, but there is no consensus regarding second-look endoscopy (SLE), and when or whether the procedure should be used. Although recent randomized studies demonstrated no benefit for the use of SLE in the prevention of post-ESD bleeding, a multicenter survey of patient management following gastric ESD demonstrated that SLE was utilized by most institutions^[9]. In the present review article, the optimal perioperative management to reduce bleeding following ESD, including SLE, and the high-risk patients SLE will benefit most will be discussed.

SLE after endoscopic submucosal dissection

Delayed bleeding still occurs in approximately 5% of patients who have undergone gastric ESD, despite proton pump inhibitor (PPI) neutralization of intragastric acidity and endoscopic hemostasis through prophylactic coagulation of visible vessels at the ulcer base^[3,5,10-12]. SLE is generally defined as repeat endoscopy within 24 h after the initial endoscopy and hemostatic therapy. For the management of peptic ulcer bleeding, routine SLE is not recommended following successful endoscopic hemostasis. Repeat endoscopy should be performed

on patients with clinical evidence of recurrent bleeding. Hemostatic therapy should furthermore be applied to patients with higher risk stigmata of hemorrhage^[13]. For the perioperative management of post-ESD bleeding, the benefit of SLE remains controversial. However, routine SLE continues to be performed in many medical centers which have inpatients-based ESD treatment setting, probably because the delayed bleeding rate overall remains at approximately 5%^[9]. If high-risk ulcer stigmata after ESD are treated only using PPI without endoscopic therapy, the bleeding risk might be higher, and more serious complication may develop following discharge. Recently, the efficacy of SLE for ESD induced ulcers was evaluated in several retrospective studies and three prospective randomized trials^[8,14-17] (Table 1). The results indicated that the incidence of post-ESD bleeding was not significantly affected by SLE. However, three prospective studies had several limitations that should be taken into account. Ryu *et al*^[17] reported that 12 patients (16.2%) in the SLE group and 9 (11.1%) in the no SLE group experienced bleeding after ESD ($P = 0.66$). The delayed bleeding was defined as the presence of any symptoms or signs of bleeding such as melena or hematemesis from 2 to 28 d. This definition can include the past bleeding episode and other site bleeding, therefore, it may be the reason of higher incidence of bleeding than other studies. The number of enrolled patients was smaller than the calculated sample size, it might be under powered to assess their statistics between two groups. Kim *et al*^[15] demonstrated that delayed bleeding occurred in 8 lesions (3.6%) receiving a SLE and 6 (2.8%) not receiving a SLE ($P = 0.79$). Delayed bleeding was defined as bleeding at 3 to 56 d requiring emergency hemostasis for bleeding on artificial ulcer sites because of hematemesis, melena, hematochezia. The sample sized was not calculated statistically in this study. Mochizuki *et al*^[8] reported that post-ESD bleeding occurred in 7 patients (5.4%) with SLE and five patients with (3.8%) non-SLE (95%CI: -6.7-3.5); meeting the non-inferiority criterion (7%). Delayed bleeding was defined as hemorrhage confirmed by emergency endoscopy from the time of the completion of ESD to 28 d and showed clinical symptoms including hematemesis, melena or a decrease in hemoglobin of > 2 g/dL. The sample sized was adequately calculated for the assessment of non-inferiority of the non-SLE compared with the SLE. The limitation of three randomized controlled trial (RCT) was different definitions of delayed bleeding used. In addition, the patients taking antiplatelet or anticoagulant drug during the perioperative period were excluded in all three RCT. Is it possible to conclude that the SLE is no longer necessary following gastric ESD? Unfortunately the results remain inconclusive, as the studies so far have been performed only on relatively small cohorts.

Most delayed bleeding events have been shown to occur within the first 24 to 48 h, but remained a possibility for up to 2 wk following ESD. In many institutions, SLE was routinely carried out within 1-2 d

Table 1 Influence of second-look endoscopy on the incidence of bleeding following endoscopic submucosal dissection

Ref.	Year	n	Study design	Bleeding: SLE vs no SLE (%)	Risk factors for delayed bleeding	SLE benefit
Ryu <i>et al</i> ^[17]	2013	182	Prospective, single center	16.2% vs 11.1%	No risk factors	No
Mochizuki <i>et al</i> ^[8]	2014	262	Prospective, Multicenter center	5.4% vs 3.8%	Resected specimen size > 40 mm	No
Kim <i>et al</i> ^[16]	2014	437	Prospective, single center	3.6% vs 2.8%	Large tumor size (> 20 mm)	No
Park <i>et al</i> ^[14]	2015	445	Retrospective	3.0% vs 2.0%	Tumor in the upper-third of the stomach, resected specimen size > 40 mm	No
Kim <i>et al</i> ^[15]	2015	502	Retrospective	1.0% vs 2.5%	Large tumor size (> 15 mm)	No

SLE: Second-look endoscopy.

following ESD as a precaution against the more serious clinical outcomes for delayed bleeding^[9]. The potential advantage of routine SLE is that the procedure can be used to evaluate the status of healing ulcers and to perform additional hemostasis if necessary. However, there are arguments concerning the cost/benefit of SLE for ESD ulcers as well as peptic ulcers. If a subgroup of patients at high risk for recurrent bleeding following ESD could be identified, this group potentially could derive benefit from SLE. Risk factors leading to postoperative bleeding remain controversial however because the perioperative management of gastric ESD has not been standardized. Although several factors are reported to be associated with an increased risk of delayed bleeding after ESD, none have been identified that reliably detect a high-risk population. It is therefore possible that risk factors for bleeding following ESD originate from technical parameters which are more difficult to assess objectively.

Role of proton-pump inhibitors in the prevention of bleeding events

Intraoperative bleeding is an unavoidable consequence during mucosal incision or submucosal dissections. Thus, most endoscopist never consider intraoperative bleeding as a complication except in cases requiring emergency surgery or blood transfusion, or in cases where ESD is discontinued because of bleeding^[18].

One strategy to control bleeding is to regulate intra-gastric acidity, as intragastric pH above 5.4 facilitates blood coagulation and platelet aggregation^[19]. In order to achieve this pH level, PPI is more effective than of H2RA. Previous meta-analysis result compared with PPI vs H2RA for the management of iatrogenic gastric ulcer after EMR or ESD showed that PPIs are more effective than H2RA^[20]. Therefore, PPI infusion therapy is routinely used to prevent bleeding and promote ulcer healing following ESD in most institutions. But, recent randomized controlled studies showed conflicting results that H2RA was comparable healing rate and delayed bleeding rate^[21-25].

Pre-endoscopic intravenous PPI therapy in peptic ulcer bleeding, which inhibits production of gastric

acid, significantly reduces the incidence of bleeding at higher risk stigmata of hemorrhage, such as active bleeding, non-bleeding visible vessels, and adherent clots^[26]. However, the effectiveness of preoperative administration of PPI in the management of artificial ulcers following ESD remains unclear. As raising intra-gastric pH preoperatively may lead to easy and complete endoscopic hemostasis during ESD and increases blood coagulation of iatrogenic ulcers, a randomized study has been conducted to determine the effectiveness of preoperative administration of a PPI for the prevention of bleeding. A trial of 24-h pre-administration of omeprazole increased intra-gastric pH at the time of ESD^[27]. However, results demonstrated no additional benefit of a higher intra-gastric pH in the prevention of bleeding, including intraoperative and post-operative delayed bleeding following the procedure.

Because intraoperative bleeding is generally characterized as spurting or oozing, a high intra-gastric pH might not be an effective preventive measure against intraoperative bleeding. In our opinion, the occurrence of intraoperative bleeding may be related not only to measurable risk factors, such as size of resected specimen and location, but also to unquantifiable technical factors, such as electrosurgical unit settings, the type of electrosurgical knife, injection solutions, and experience of the operator^[18,28]. Furthermore, this study was complicated by the fact that all patients in the study groups had been administered a regular dose of PPI for 4 wk. Thus, short course pre-operative administration of PPI might not be sufficient to produce a difference in the incidence of delayed bleeding events.

Prophylactic coagulation of visible vessel at the ulcer base following ESD

Recent guidelines for the management of peptic ulcer bleeding suggest that endoscopic therapy should be provided to patients with a non-bleeding visible vessel^[13,29]. In addition, endoscopic therapy may be considered for patients with an adherent clot resistant to vigorous irrigation. Furthermore, the benefit of endoscopy may be greater for patients with clinical features associated with a higher risk of rebleeding,

Table 2 Incidence of delayed bleeding and associated risk factors after gastric endoscopic submucosal dissection

Ref.	Year	n	Study design	Bleeding (%)	Risk factors	Remarks
Takizawa <i>et al</i> ^[5]	2008	968	Retrospective	5.8% (7.1% vs 3.1% with PEC)	Tumor location in middle and lower regions of the stomach, PEC	PEC of visible vessels in the resected area following ESD may lead to a decreased bleeding rate
Chung <i>et al</i> ^[30]	2009	952	Retrospective	15.60%	Upper region, size of the tumor (> 40 mm), recurrent lesion, flat morphology	A significant bleeding incidence was at 0.6%
Okada <i>et al</i> ^[10]	2011	582	Retrospective	4.81%	Resected specimen width (≥ 40 mm)	Mechanism of delayed bleeding may differ depending on the time elapsed between ESD and bleeding episodes
Toyokawa <i>et al</i> ^[11]	2012	1123	Retrospective	5.00%	Age ≥ 80 yr, extended duration of procedure	-
Goto <i>et al</i> ^[9]	2012	1814	Retrospective	5.50%	No statistical parameters	Multicenter survey clarified that post-ESD management (duration of PPI use, resumption of food intake, and performance of SLE) varied among the medical centers
Koh <i>et al</i> ^[12]	2013	1032	Retrospective	5.30%	Size of resected specimen	The incidence of delayed bleeding in patients with two risk factors was 11.6%
Choi <i>et al</i> ^[3]	2014	614	Prospective observation	Early (3.7%) Late (1.9%)	(> 40 mm), use of antithrombotic drugs (only for delay bleeding) Surface erosion, high risk of stigmata during SLE, location in the middle of the stomach	Nausea and submucosal fibrosis increase the incidence of high risk of stigmata in SLE

PEC: Post-endoscopic submucosal dissection coagulation; ESD: Endoscopic submucosal dissection; PPI: Proton pump inhibitor; SLE: Second-look endoscopy.

such as older age, concurrent illness, and inpatient status at occurrence^[13]. For the management of artificial ulcers generated during ESD, prophylactic coagulation of exposed visible vessels at the base of a mucosal defect following ESD was shown to lead to a reduction in the incidence of bleeding (7.1% vs 3.1%; $P < 0.01$)^[5]. Routine coagulation of all non-bleeding visible vessels at the ulcer base is thus performed as standard practice. However, both prophylactic coagulation of all visible vessels at the ulcer bed and administration of PPIs do not completely eliminate the possibility of delayed bleeding (Table 2).

Patient-related risk factors associated with delayed bleeding

Most studies reported large resected specimen size to be an independent risk factor for delayed bleeding^[10,12,30] (Table 2). Theoretically, a large lesion has a more expansive vascular network than a small lesion, which enhances the possibility of bleeding during and following ESD.

Still, risks of lesion location were variable. Intraoperative bleeding risk was reported to be higher in the upper region than in the middle and lower regions of the stomach. Arteries in the submucosal layer of the upper stomach are significantly thicker or more stubby than in other gastric sites, and the diameter of

submucosal arteries is larger in the upper area than in the middle or lower stomach^[5]. Therefore, the risk of intraoperative bleeding is greater in the upper stomach, and intraoperative hemostasis is more frequently necessary during removal of a lesion in this region. In contrast, a delayed bleeding risk was reported to be greater in the lower region of the stomach^[5]. In other words, while intraoperative hemostasis is less frequently necessary in the middle and lower gastric regions, bleeding may still occur here later if vessels in these areas are not coagulated at the time of procedure. The occurrence of delayed bleeding might not have been due to insufficient hemostasis, but rather to insufficient coagulation during resection, because the sites where delayed bleeding occurred were different than those where immediate bleeding has been controlled endoscopically^[31]. Antral peristaltic activity and bile juice reflux might also contribute to some degree.

The Forrest classification provides prognostic information regarding the risk of rebleeding, and the need for therapeutic intervention in ulcer disease. Endoscopic therapy is indicated for patients with high-risk ulcer stigmata (Forrest type I and IIa). For this reason, additional hemostasis for high-risk ulcer stigmata may decrease the chance of further bleeding and/or emergency intervention. In a prospective observation study, submucosal fibrosis [odds ratios (OR) = 3.91;

Table 3 Antiplatelet medication and the risk of delayed bleeding

Ref.	Year	<i>n</i>	Design	Method	Comparison of bleeding incidence	Comments
Lim <i>et al</i> ^[32]	2012	1591	Retrospective	ESD	No antiplatelet medication: 5.2% Antiplatelet withdrawal: 5.9% Antiplatelet continuation: 11.6%	Continuous administration of antiplatelet medication was not found to have an independent significant association with bleeding
Cho <i>et al</i> ^[33]	2012	514	Retrospective	ESD	No aspirin medication: 3.4% Aspirin withdrawal: 3.6% Aspirin continuation: 21.1%	Continuous aspirin use increases the risk of bleeding after gastric ESD
Sanomura <i>et al</i> ^[35]	2014	94	Retrospective	ESD	Aspirin interruption: 7.1% Aspirin continuation: 4.8%	Continued use of aspirin does not increase the risk of bleeding during or after ESD
Tounou <i>et al</i> ^[34]	2015	377	Retrospective	ESD	No aspirin medication: 6.1% Aspirin continuation: 14.4% Single antiplatelet: 15.5% Dual antiplatelet: 35.5%	Aspirin was not a significant risk factor for post-ESD bleeding
Ono <i>et al</i> ^[36]	2015	28	Prospective, observational	ESD/EMR	The study was terminated in accordance with predetermined safety criteria because 7 of 28 consecutive patients experienced major bleeding complications (25.0%)	Subanalysis of gastric ESD (23 lesions in 19 patients) confirmed that the administration of thienopyridine derivatives ($P = 0.01$) and multiple agents ($P = 0.02$) were the significant factors Continuation of aspirin alone during these endoscopic procedures may be acceptable

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

95%CI: 1.92-7.94] and nausea after ESD (OR = 4.76; 95%CI: 2.39-9.43) were risk factors significantly associated with high-risk ulcers^[3]. To resect submucosal fibrosis, deeper submucosal dissection is generally necessary, but superficial proper muscle damage might occur. Such manipulation of the tissue might lead to the development of ulcers with a high-risk of bleeding. Furthermore, the lesions with more submucosal vessels may require more frequent coagulation during ESD. This treatment may result in coagulation-induced gastric edema and a more intense inflammatory response, which will cause nausea. A significant amount of blood from an artificial ulcer can also induce nausea. In fact, despite additive coagulation in patients with high-risk ulcer stigmata, the rebleeding incidence on SLE was 8.6% relative to patients with low-risk stigmata. A potential explanation is that ulcers at high risk for bleeding tend to also be rich in vascularity.

Drug-related risk factors for delayed bleeding

An increasing number of patients are taking multiple antiplatelet medications or antithrombotic drugs as the incidence of cardiovascular disease rises. Antiplatelet or antithrombotic medications to prevent cardiovascular events in patients present an additional concern, as ESD is a procedure with high risk of bleeding. Most endoscopists prefer to interrupt the use of antiplatelet or antithrombotic drugs for as long as possible. In one retrospective observational study, continuous administration of antiplatelet medication was not found to be a significantly associated with bleeding^[32] (OR = 1.596; 95%CI: 0.877-2.903; $P = 0.126$), whereas in another retrospective study, the use of aspirin by itself was associated with post-ESD bleeding^[33] (OR = 4.49; 95%CI: 1.09-18.38). In the latter, the resumption

specifically of clopidogrel combined with aspirin use (OR = 26.71; 95%CI: 7.09-100.53) was significantly associated with post-ESD bleeding. In recent two retrospective studies to evaluate the hemorrhagic risk of ESD in patients on antiplatelet drug, Tounou *et al*^[34] demonstrated that dual antiplatelet therapy markedly increased the risk for bleeding (HR = 16.3; 95%CI: 3.4-78.2), but continuous low dose aspirin does not. Sanomura *et al*^[35] also reported that continued use of low dose aspirin does not increased the risk of bleeding during or after ESD. In a recent prospective study, subanalysis of gastric ESD showed that administration of thienopyridine derivatives ($P = 0.01$) and multiple antiplatelet agents ($P = 0.02$) were significant contributing factors to bleeding^[36] (Table 3), but the continuation of aspirin alone appeared to be acceptable.

In general, post-ESD bleeding in patients taking aspirin can be managed effectively without increasing long-term morbidity or mortality. However, cerebral infarction upon discontinuation of aspirin intake is a critical complication. Therefore, ASGE and ESGE and JGES guideline recommend low dose aspirin should be continued for endoscopic treatment with high bleeding risk when the risk of thromboembolism is high^[37-39]. Taken together, the results indicate that if a patient has a low risk for a thromboembolic event, aspirin use should be ceased. However, if a patient has a high risk for thromboembolism, aspirin may be continued as a thromboembolic event could otherwise result in more serious consequences affecting quality of life.

CONCLUSION

Bleeding is a major potential complication both during and post-ESD. Decreased incidence of delayed bleeding

is associated with the use of anti-secretory agents, especially PPI, and prophylactic coagulation of visible vessels at the ulcer base following ESD. However, despite these therapeutic interventions, delayed bleeding still occurs in approximately 5% of patients who undergo gastric ESD. To date, SLE after ESD has been a common therapeutic strategy in order to avoid a bleeding event. The results of recent randomized studies however were unfavorable for routine SLE after gastric ESD. Although routine SLE for all patients after gastric ESD might be unnecessary, SLE may be an important tool in the treatment of a subgroup of patients at risk for bleeding or high-risk ulcer stigmata. Well-known potential risk factors of delayed bleeding are large size of resected specimen and treatment with multiple antiplatelet agents. Submucosal fibrosis and nausea after ESD might be associated with high-risk ulcer stigmata. Thus, these factors can be considered as indications for the use of SLE following ESD. To establish the optimal perioperative strategies for safe ESD, well-designed prospective studies should be conducted in the future to more clearly identify at risk patients.

REFERENCES

- 1 Min BH, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH, Rhee PL, Kim KM, Park CK, Rhee JC. Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). *Dig Liver Dis* 2009; **41**: 201-209 [PMID: 18571998 DOI: 10.1016/j.dld.2008.05.006]
- 2 Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
- 3 Choi CW, Kim HW, Kang DH, Hong YM, Kim SJ, Park SB, Cho M, Kim DJ, Hong JB. Clinical outcomes of second-look endoscopy after gastric endoscopic submucosal dissection: predictive factors with high risks of bleeding. *Surg Endosc* 2014; **28**: 2213-2220 [PMID: 24570014 DOI: 10.1007/s00464-014-3457-2]
- 4 Nakamura M, Nishikawa J, Hamabe K, Nishimura J, Satake M, Goto A, Kiyotoki S, Saito M, Fukagawa Y, Shirai Y, Okamoto T, Sakaida I. Risk factors for delayed bleeding from endoscopic submucosal dissection of gastric neoplasms. *Scand J Gastroenterol* 2012; **47**: 1108-1114 [PMID: 22783937 DOI: 10.3109/00365521.2012.699550]
- 5 Takizawa K, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy* 2008; **40**: 179-183 [PMID: 18322872 DOI: 10.1055/s-2007-995530]
- 6 Goto O, Fujishiro M, Kodashima S, Ono S, Niimi K, Hirano K, Yamamichi N, Koike K. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest Endosc* 2010; **71**: 241-248 [PMID: 19922919 DOI: 10.1016/j.gie.2009.08.030]
- 7 Ohkuwa M, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221-226 [PMID: 11293753 DOI: 10.1055/s-2001-12805]
- 8 Mochizuki S, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut* 2015; **64**: 397-405 [PMID: 25301853 DOI: 10.1136/gutjnl-2014-307552]
- 9 Goto O, Fujishiro M, Oda I, Kakushima N, Yamamoto Y, Tsuji Y, Ohata K, Fujiwara T, Fujiwara J, Ishii N, Yokoi C, Miyamoto S, Itoh T, Morishita S, Gotoda T, Koike K. A multicenter survey of the management after gastric endoscopic submucosal dissection related to postoperative bleeding. *Dig Dis Sci* 2012; **57**: 435-439 [PMID: 21901257 DOI: 10.1007/s10620-011-1886-5]
- 10 Okada K, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]
- 11 Toyokawa T, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]
- 12 Koh R, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]
- 13 Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012; **107**: 345-360; quiz 361 [PMID: 22310222 DOI: 10.1038/ajg.2011.480]
- 14 Park CH, Park JC, Lee H, Shin SK, Lee SK, Lee YC. Second-look endoscopy after gastric endoscopic submucosal dissection for reducing delayed postoperative bleeding. *Gut Liver* 2015; **9**: 43-51 [PMID: 25170062 DOI: 10.5009/gnl13252]
- 15 Kim ER, Kim JH, Kang KJ, Min BH, Lee JH, Rhee PL, Rhee JC, Kim JJ. Is a second-look endoscopy necessary after endoscopic submucosal dissection for gastric neoplasm? *Gut Liver* 2015; **9**: 52-58 [PMID: 25071070 DOI: 10.5009/gnl13422]
- 16 Kim JS, Chung MW, Chung CY, Park HC, Ryang DY, Myung DS, Cho SB, Lee WS, Joo YE. The need for second-look endoscopy to prevent delayed bleeding after endoscopic submucosal dissection for gastric neoplasms: a prospective randomized trial. *Gut Liver* 2014; **8**: 480-486 [PMID: 25228971 DOI: 10.5009/gnl13226]
- 17 Ryu HY, Kim JW, Kim HS, Park HJ, Jeon HK, Park SY, Kim BR, Lang CC, Won SH. Second-look endoscopy is not associated with better clinical outcomes after gastric endoscopic submucosal dissection: a prospective, randomized, clinical trial analyzed on an as-treated basis. *Gastrointest Endosc* 2013; **78**: 285-294 [PMID: 23531425 DOI: 10.1016/j.gie.2013.02.008]
- 18 Fujishiro M, Chiu PW, Wang HP. Role of antisecretory agents for gastric endoscopic submucosal dissection. *Dig Endosc* 2013; **25** Suppl 1: 86-93 [PMID: 23368844 DOI: 10.1111/j.1443-1661.2012.01370.x]
- 19 Green FW, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology* 1978; **74**: 38-43 [PMID: 21830]
- 20 Yang Z, Wu Q, Liu Z, Wu K, Fan D. Proton pump inhibitors versus histamine-2-receptor antagonists for the management of iatrogenic gastric ulcer after endoscopic mucosal resection or endoscopic submucosal dissection: a meta-analysis of randomized trials. *Digestion* 2011; **84**: 315-320 [PMID: 22075541 DOI: 10.1159/000331138]
- 21 Imaeda H, Hosoe N, Suzuki H, Saito Y, Ida Y, Nakamura R, Iwao Y, Ogata H, Hibi T. Effect of lansoprazole versus roxatidine on prevention of bleeding and promotion of ulcer healing after endoscopic submucosal dissection for superficial gastric neoplasia. *J Gastroenterol* 2011; **46**: 1267-1272 [PMID: 21805066 DOI: 10.1007/s00535-011-0447-1]
- 22 Jeong HK, Park CH, Jun CH, Lee GH, Kim HI, Kim HS, Choi

- SK, Rew JS. A prospective randomized trial of either famotidine or pantoprazole for the prevention of bleeding after endoscopic submucosal dissection. *J Korean Med Sci* 2007; **22**: 1055-1059 [PMID: 18162722 DOI: 10.3346/jkms.2007.22.6.1055]
- 23 **Ohya TR**, Endo H, Kawagoe K, Yanagawa T, Hanawa K, Ohata K, Asayama M, Hisatomi K, Teratani T, Gunji T, Sato H, Matsushita N. A prospective randomized trial of famotidine vs ranitidine on post-ESD gastric ulcers. *World J Gastrointest Endosc* 2010; **2**: 36-40 [PMID: 21160677 DOI: 10.4253/wjge.v2.i1.36]
 - 24 **Tomita T**, Kim Y, Yamasaki T, Okugawa T, Kondo T, Toyoshima F, Sakurai J, Tanaka J, Morita T, Oshima T, Fukui H, Hori K, Watari J, Matsumoto T, Miwa H. Prospective randomized controlled trial to compare the effects of omeprazole and famotidine in preventing delayed bleeding and promoting ulcer healing after endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2012; **27**: 1441-1446 [PMID: 22497427 DOI: 10.1111/j.1440-1746.2012.07144.x]
 - 25 **Uedo N**, Takeuchi Y, Yamada T, Ishihara R, Ogiyama H, Yamamoto S, Kato M, Tatsumi K, Masuda E, Tamai C, Yamamoto S, Higashino K, Iishi H, Tatsuta M. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol* 2007; **102**: 1610-1616 [PMID: 17403076 DOI: 10.1111/j.1572-0241.2007.01197.x]
 - 26 **Lau JY**, Leung WK, Wu JC, Chan FK, Wong VW, Chiu PW, Lee VW, Lee KK, Cheung FK, Siu P, Ng EK, Sung JJ. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007; **356**: 1631-1640 [PMID: 17442905 DOI: 10.1056/NEJMoa065703]
 - 27 **Ono S**, Kato M, Ono Y, Nakagawa M, Nakagawa S, Shimizu Y, Asaka M. Effects of preoperative administration of omeprazole on bleeding after endoscopic submucosal dissection: a prospective randomized controlled trial. *Endoscopy* 2009; **41**: 299-303 [PMID: 19340731 DOI: 10.1055/s-0029-1214530]
 - 28 **Jeon SW**, Jung MK, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH. Predictors of immediate bleeding during endoscopic submucosal dissection in gastric lesions. *Surg Endosc* 2009; **23**: 1974-1979 [PMID: 18553202 DOI: 10.1007/s00464-008-9988-7]
 - 29 **Hwang JH**, Fisher DA, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, Early DS, Evans JA, Fanelli RD, Foley K, Fukami N, Jain R, Jue TL, Khan KM, Lightdale J, Malpas PM, Maple JT, Pasha S, Saltzman J, Sharaf R, Shergill AK, Dominitz JA, Cash BD. The role of endoscopy in the management of acute non-variceal upper GI bleeding. *Gastrointest Endosc* 2012; **75**: 1132-1138 [PMID: 22624808 DOI: 10.1016/j.gie.2012.02.033]
 - 30 **Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]
 - 31 **Okano A**, Hajiro K, Takakuwa H, Nishio A, Matsushita M. Predictors of bleeding after endoscopic mucosal resection of gastric tumors. *Gastrointest Endosc* 2003; **57**: 687-690 [PMID: 12709698 DOI: 10.1067/mge.2003.192]
 - 32 **Lim JH**, Kim SG, Kim JW, Choi YJ, Kwon J, Kim JY, Lee YB, Choi J, Im JP, Kim JS, Jung HC, Song IS. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; **75**: 719-727 [PMID: 22317881 DOI: 10.1016/j.gie.2011.11.034]
 - 33 **Cho SJ**, Choi IJ, Kim CG, Lee JY, Nam BH, Kwak MH, Kim HJ, Ryu KW, Lee JH, Kim YW. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; **44**: 114-121 [PMID: 22271021 DOI: 10.1055/s-0031-1291459]
 - 34 **Tounou S**, Morita Y, Hosono T. Continuous aspirin use does not increase post-endoscopic dissection bleeding risk for gastric neoplasms in patients on antiplatelet therapy. *Endosc Int Open* 2015; **3**: E31-E38 [PMID: 26134769 DOI: 10.1055/s-0034-1390764]
 - 35 **Sanomura Y**, Oka S, Tanaka S, Numata N, Higashiyama M, Kanao H, Yoshida S, Ueno Y, Chayama K. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2014; **17**: 489-496 [PMID: 24142107 DOI: 10.1007/s10120-013-0305-3]
 - 36 **Ono S**, Fujishiro M, Yoshida N, Doyama H, Kamoshida T, Hirai S, Kishihara T, Yamamoto Y, Sakae H, Imagawa A, Hirano M, Koike K. Thienopyridine derivatives as risk factors for bleeding following high risk endoscopic treatments: Safe Treatment on Antiplatelets (STRAP) study. *Endoscopy* 2015; **47**: 632-637 [PMID: 25590184 DOI: 10.1055/s-0034-1391354]
 - 37 **Anderson MA**, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Lichtenstein DR, Maple JT, Shen B, Strohmeyer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; **70**: 1060-1070 [PMID: 19889407 DOI: 10.1016/j.gie.2009.09.040]
 - 38 **Boustière C**, Veitch A, Vanbiervliet G, Bulois P, Deprez P, Laquiere A, Laugier R, Lesur G, Mosler P, Nalet B, Napoleon B, Rembacken B, Ajzenberg N, Collet JP, Baron T, Dumonceau JM. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2011; **43**: 445-461 [PMID: 21547880 DOI: 10.1055/s-0030-1256317]
 - 39 **Fujimoto K**, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, Mine T, Yoshino J, Kinoshita Y, Ichinose M, Matsui T. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; **26**: 1-14 [PMID: 24215155 DOI: 10.1111/den.12183]

P- Reviewer: Abe S, Kiriya S S- Editor: Kong JX

L- Editor: A E- Editor: Wu HL



Retrospective Cohort Study

Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis

Tomoyasu Ito, Jin Kan Sai, Hironao Okubo, Hiroaki Saito, Shigeto Ishii, Ryo Kanazawa, Ko Tomishima, Sumio Watanabe, Shuichiro Shiina

Tomoyasu Ito, Jin Kan Sai, Hiroaki Saito, Shigeto Ishii, Ryo Kanazawa, Ko Tomishima, Sumio Watanabe, Shuichiro Shiina, Department of Gastroenterology, Juntendo University School of Medicine, Tokyo 113-8421, Japan

Hironao Okubo, Department of Gastroenterology, Juntendo University Nerima Hospital, Tokyo 177-8521, Japan

Author contributions: Ito T and Sai JK contributed equally to this work; Ito T collected and analyzed the data, and drafted the manuscript; Sai JK provided analytical oversight and designed and supervised the study; Watanabe S and Shiina S revised the manuscript for the important intellectual content; Okubo H, Saito H, Ishii S, Kanazawa R and Tomishima K participated in collecting the data; all authors have read and approved the final version to be published.

Institutional review board statement: This study was approved by the Institutional Review Board of Juntendo University.

Informed consent statement: Written informed consent for the procedures and treatment was obtained from patients or their next of kin in accordance with normal clinical practice.

Conflict-of-interest statement: No conflict of interests.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (jinkans@juntendo.ac.jp). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Jin Kan Sai, MD, Associate Professor,

Department of Gastroenterology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. jinkans@juntendo.ac.jp
Telephone: +81-3-58021061
Fax: +81-3-56845960

Received: July 23, 2015

Peer-review started: July 30, 2015

First decision: September 14, 2015

Revised: September 28, 2015

Accepted: October 20, 2015

Article in press: October 27, 2015

Published online: February 10, 2016

Abstract

AIM: To examine the safety of immediate endoscopic sphincterotomy (EST) in patients with acute suppurative cholangitis (ASC) caused by choledocholithiasis, as compared with elective EST.

METHODS: Patients with ASC due to choledocholithiasis were allocated to two groups: Those who underwent EST immediately and those who underwent EBD followed by EST 1 wk later because they were under anticoagulant therapy, had a coagulopathy (international normalized ratio > 1.3, partial thromboplastin time greater than twice that of control), or had a platelet count < 50000 × 10³/μL. One of four trainees [200-400 cases of endoscopic retrograde cholangiopancreatography (ERCP)] supervised by a specialist (> 10000 cases of ERCP) performed the procedures. The success and complication rates associated with EST in each group were examined.

RESULTS: Of the 87 patients with ASC, 59 were in the immediate EST group and 28 in the elective EST group. EST was successful in all patients in both groups. There were no complications associated with EST in either group of patients, although white blood cell count, C-reactive

protein, total bilirubin, and serum concentrations of liver enzymes just before EST were significantly higher in the immediate EST group than in the elective EST group.

CONCLUSION: Immediate EST can be as safe as elective EST for patients with ASC associated with choledocholithiasis provided they are not under anticoagulant therapy, or do not have a coagulopathy or a platelet count $< 50000 \times 10^3/\mu\text{L}$. Moreover, the procedure was safely performed by a trainee under the supervision of an experienced specialist.

Key words: Acute cholangitis; Complications; Endoscopic sphincterotomy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Immediate endoscopic sphincterotomy (EST) can be as safe as elective EST for patients with acute suppurative cholangitis associated with choledocholithiasis, because there were no complications associated with EST in either group of patients, although white blood cell count, C-reactive protein, total bilirubin, and serum concentrations of liver enzymes just before EST were significantly higher in the immediate EST group ($n = 59$) than in the elective EST group ($n = 28$). Moreover, the procedure was safely performed by a trainee under the supervision of an experienced specialist.

Ito T, Sai JK, Okubo H, Saito H, Ishii S, Kanazawa R, Tomishima K, Watanabe S, Shiina S. Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis. *World J Gastrointest Endosc* 2016; 8(3): 180-185 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/180.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.180>

INTRODUCTION

Acute suppurative cholangitis (ASC) is a life-threatening condition that requires prompt treatment^[1,2]. At present, endoscopic biliary drainage (EBD), including endoscopic nasobiliary drainage (ENBD) and endoscopic retrograde biliary drainage (ERBD), followed by elective endoscopic sphincterotomy (EST) is the established mode of treatment for ASC, with a high success rate and low morbidity and mortality^[3-7]. However, the validity of immediate EST with stone extraction is uncertain.

In the present study, we examined the success and complication rates of immediate EST for patients with ASC associated with bile duct stones and compared them with those of elective EST.

MATERIALS AND METHODS

Patient characteristics

Between January 2009 and February 2013, patients with acute cholangitis, suspected of having ASC due

to choledocholithiasis were enrolled for the present study. The diagnosis of acute cholangitis was based on clinical evidence of both infection (fever, chills, leukocytosis, or abdominal pain) and biliary obstruction (clinical jaundice or hyperbilirubinemia), and patients with any of the following at admission were suspected of having ASC requiring emergency endoscopic retrograde cholangiopancreatography (ERCP): (1) fever (temperature $> 39^\circ\text{C}$); (2) septicemic shock (systolic blood pressure < 90 mmHg); (3) increasing abdominal pain with clinical evidence of peritoneal inflammation (right upper quadrant pain with guarding on palpation); or (4) an impaired level of consciousness on admission. In the present study, ASC was defined based on the evidence of purulent bile. Therefore, patients were included in the current study after bile duct access was gained, the cholangiogram confirmed the presence of bile duct stones, and bile aspiration through the catheter showed the presence of purulent bile on ERCP. Exclusion criteria were prior sphincterotomy, concomitant pancreatic or biliary malignancies, and coexisting intrahepatic stones. Patients who died within 6 h after admission were also excluded.

Patients were allocated to two groups: Immediate EST with stone extraction, and EBD followed by elective EST 1 wk later because they were under anticoagulant therapy, had a coagulopathy (international normalized ratio > 1.3 , partial thromboplastin time greater than twice that of control), or had a platelet count $< 50000 \times 10^3/\mu\text{L}$.

Complete blood count, serum electrolytes, clotting profile, and biochemical tests of liver function were monitored daily. Blood pressure, pulse rate, and body temperature were monitored every 4 h. All patients were administered antibiotics intravenously and underwent abdominal CT before ERCP.

Written informed consent for the procedures and treatment was obtained from patients or their next of kin in accordance with normal clinical practice. This study was approved by the Institutional Review Board of Juntendo University.

Endoscopic procedure

ERCP was performed using a side-viewing duodenoscope (JF-240, JF-260V, TJF-260; Olympus, Tokyo, Japan). Electrocautery was administered using a 120-watt endocut current (ERBE International, Erlangen, Germany). One of four trainees (200-400 cases of ERCP) supervised by a specialist (> 10000 cases of ERCP) performed the procedures. If the trainee could not cannulate the bile duct within 3 min, the specialist did it, and then the trainee was in charge again after deep bile duct cannulation was attained in both groups. All the subjects in the present study started to receive drip infusion of protease inhibitors prior to EST to prevent the occurrence of pancreatitis. Following preparation with pharyngeal anesthesia and intravenous injection of midazolam (0.06 mg/kg), ERCP was performed. After deep cannulation into the bile duct, bile was aspirated to

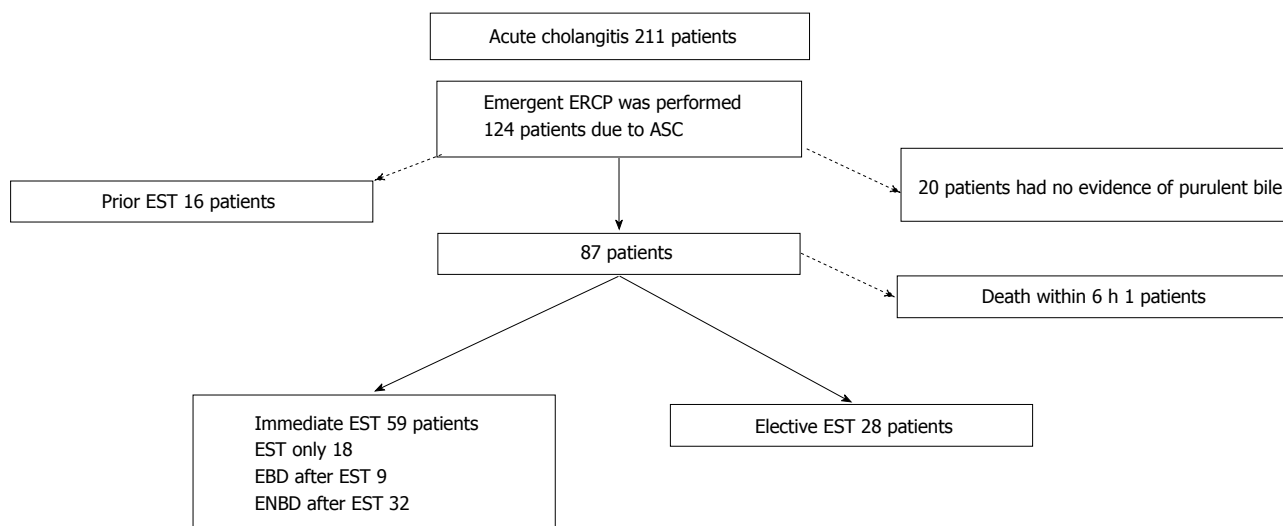


Figure 1 Patient inclusion flow chart. EBD: Endoscopic biliary drainage; ENBD: Endoscopic nasobiliary drainage; EST: Endoscopic sphincterotomy; ASC: Acute suppurative cholangitis; ERCP: Endoscopic retrograde cholangiopancreatography.

reduce intrabiliary pressure, and low-osmolar nonionic contrast medium was carefully injected to confirm the etiology of cholangitis. After the cholangiogram confirmed the presence of bile duct stones and bile aspiration through the catheter showed the presence of purulent bile, EST or EBD including ENBD and ERBD was performed.

EST was performed with a 30 mm pull-type sphincterotome (Clever Cut 3; KD-V41M, Olympus) under the guidewire. For ENBD, a 6F nasobiliary tube (Gadellus, Tokyo) was inserted in the bile duct. For ERBD, a 7F double pig type plastic endoprosthesis (Wilson-Cook Medical Inc., Winston-Salem, NC) was placed across the papilla. For patients in the immediate EST group, stone removal by retrieval balloon catheter was tried at first ERCP, and EBD (ERBD or ENBD) was performed if the patient had or was suspected of having remnant stones. In the elective EST group, EST was performed 1 wk after EBD for stone removal. After ERCP, all the patients were kept under strict observation.

Procedure-related pancreatitis was defined as abdominal pain, with at least a 3-fold elevation of serum amylase more than 24 h after the procedure. Continuation of preexisting acute pancreatitis was not included as a complication. Hemorrhage was considered clinically significant only if there was clinical evidence of bleeding, such as melena or hematemesis, with an associated decrease of at least 2 g per deciliter of the hemoglobin concentration, or the need for a blood transfusion. Bleeding that was controlled during the procedure without hemodynamic instability or transfusion was not considered a complication^[8].

The clinical characteristics of both groups of patients were compared. The primary endpoints of the study were the success and complication rates of immediate EST compared with elective EST. Secondary endpoints were the period for normalization of body temperature, leukocytosis, and C-reactive protein (CRP) leading to

discharge from hospital in both groups of patients.

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 for Windows. Data are presented as the mean \pm SD and were compared using paired *t*-test. Mann-Whitney *U* test was used for comparing continuous data with skewed distribution in the two groups. A χ^2 test with Yate's correction was used to analyze gender. Statistical significance was defined as a *P*-value < 0.05 (two tailed). The statistical methods of this study were reviewed by Jin Kan Sai from Juntendo University.

RESULTS

A total of 211 patients were hospitalized for acute cholangitis during the study period, and 124 of them underwent emergency ERCP within 24 h after admission. Sixteen patients were excluded because of prior sphincterotomy.

Thus, 88 had bile duct stones associated with the evidence of purulent bile and were diagnosed as having ASC. Among them, 27 had anticoagulant therapy, and 2 had a coagulopathy with a platelet count $< 50000 \times 10^3/\mu\text{L}$; one of these two patients died within 6 h after successful EBD because of uncontrolled sepsis and multi-organ failure and was excluded from the study. Therefore, there were 59 in the immediate EST group and 28 in the elective EST group (Figure 1). Patient characteristics and demographic data of the patients on admission are shown in Table 1. Patients were significantly older and PT (%) was significantly lower in the elective EST group. Peritonism and pre-existing pancreatitis were more frequent in the immediate EST group. All procedures of EBD were successful, but one patient in the elective EST group had pancreatitis associated with EBD. Demographic data of the two groups just before immediate and elective EST (1 wk after EBD) are shown in Table 2. Compared

Table 1 Characteristics of patients undergoing emergency endoscopic retrograde cholangiopancreatography

	Immediate EST group (n = 59)	Elective EST group (n = 28)	P value
Sex (M:F)	31:28	13:15	0.59
Age (mean ± SD, range)	68.76 ± 14.58	78.82 ± 9.07	0.0001
Clinical presentation, n (%)			
Peritonism	51 (86)	19 (68)	0.04
Fever	28 (47)	15 (54)	0.59
Hypotension	1 (1.6)	1 (3.5)	0.54
Altered sensorium	1 (1.6)	0 (0)	0.67
Pre-existing pancreatitis (%)	15 (25)	1 (3.5)	0.01
WBC	10959 ± 5857	10025 ± 4110	0.39
Plt	20.4 ± 8.0	18.5 ± 6.3	0.26
PT (%)	86.7 ± 15.8	72.7 ± 22.2	0.009
CRP	5.32 ± 5.59	7.84 ± 6.76	0.069
T-Bil	4.09 ± 2.8	3.9 ± 2.5	0.76
AST	253.3 ± 215.2	262.3 ± 370.3	0.90
ALT	243.5 ± 182	262.3 ± 278.7	0.83
γGTP	458.6 ± 326.7	453.4 ± 233.6	0.82
ALP	760.1 ± 404.9	826.3 ± 608.4	0.60

CRP: C-reactive protein; EST: Endoscopic sphincterotomy; WBC: White blood cells; Plt: Blood platelet; T-Bil: Serum total bilirubin; AST: Aspartate aminotransferase; ALT: Glutamic-pyruvic transaminase; ALP: Alkalinephosphatase; γGTP: Serum gamma gamma glutamyl transpeptidase.

Table 2 Demographic data of patients before endoscopic sphincterotomy

	Immediate EST group	Elective EST group	P value
WBC	10959 ± 5857	6521 ± 2274	0.0002
Plt	20.4 ± 8.0	32.6 ± 42.2	0.03
PT (%)	86.7 ± 15.8	82.9 ± 14.1	0.23
CRP	5.32 ± 5.59	1.82 ± 1.65	0.0017
T-Bil	4.09 ± 2.8	1.4 ± 1.0	< 0.0001
AST	253.3 ± 215.2	50.6 ± 53.5	< 0.0001
ALT	243.5 ± 182	66.9 ± 55.3	< 0.0001
γGTP	458.6 ± 326.7	254.3 ± 230.3	< 0.0001
ALP	760.1 ± 404.9	494.5 ± 241.7	< 0.0001

CRP: C-reactive protein; EST: Endoscopic sphincterotomy; WBC: White blood cells; Plt: Blood platelet; T-Bil: Serum total bilirubin; AST: Aspartate aminotransferase; ALT: Glutamic-pyruvic transaminase; ALP: Alkalinephosphatase; γGTP: Serum gamma gamma glutamyl transpeptidase.

with the elective EST group, white blood cell count, CRP, total bilirubin, and serum concentrations of liver enzymes before EST were significantly higher in the immediate EST group, while the platelet count was significantly lower.

All EST procedures were successful, and there were no complications such as pancreatitis, bleeding (hemorrhage), or perforation in the two groups, although trainees achieved deep cannulation of the bile duct in 31 (35.6%) of them. Deterioration of pre-existing pancreatitis and cholangitis as a direct result of ERCP is difficult to assess; however, all indicators, including daily serum levels of amylase, liver enzymes, white blood cell count, and CRP, improved after the procedure (data not shown). In the immediate EST group complete stone extraction was achieved at once in 30.5% (18/59) of the patients while 69.5% (41/59) were suspected of having remnant stones and required EBD. Time for normalization of CRP and discharge was significantly

shorter in patients who underwent immediate EST and the stones were extracted at once, although the period for normalization of body temperature and leukocytosis was not significantly different between the two groups (Table 3).

DISCUSSION

ASC requires early drainage of the biliary system to reduce the incidence of septic complications^[1,2]. The endoscopic techniques used for biliary drainage include EST with stone extraction, and EBD, either ENBD or ERBD. EBD is an established mode of treatment for ASC, with a high success rate and low morbidity and mortality^[3-7]. Lin *et al*^[9] reported a 100% success rate and no mortality with ENBD in 40 patients with acute cholangitis. Leung *et al*^[1] treated 105 patients with acute cholangitis by ERBD, with a success rate of 97% and mortality of 4.7%. EBD can be performed easily, quickly, and safely at the endoscopy, avoiding the risk of bleeding in patients with coagulopathy.

On the other hand, EST with stone extraction is another mode of biliary drainage in ASC with an associated mortality rate of 4.7%-7.6%, although EST related complications, such as bleeding, retroduodenal perforation, and acute pancreatitis, may occur in 6%-12% of cases^[1,10-12]. The complications associated with EST are most undesirable in acutely ill patients. Moreover, EST cannot be performed in patients with coagulopathy. Therefore, most endoscopists currently prefer EBD to EST as the first treatment for ASC.

In the present study, immediate and elective EST was performed by one of four trainees supervised by one experienced specialist, and there were no complications associated with EST in either group. Therefore we think

Table 3 Outcome of patients subjected to endoscopic retrograde cholangiopancreatography

	Elective EST group (n = 28)		P value
Immediate EST group (n = 59)			
Normalization of body temperature	1.37 ± 1.86	1.68 ± 2.83	0.6
Normalization of WBC	2.19 ± 2.87	1.39 ± 1.13	0.06
Normalization of CRP	9.12 ± 7.73	13.75 ± 9.32	0.017
Time to discharge	16.79 ± 11.89	21.75 ± 14.1	0.09
Immediate EST with stone extraction group (n = 18)			
Normalization of body temperature	1.61 ± 0.98	1.68 ± 2.83	0.92
Normalization of WBC	1.78 ± 0.9	1.39 ± 1.13	0.53
Normalization of CRP	7.0 ± 5.7	13.75 ± 9.32	0.008
Time to discharge	13.2 ± 7.5	21.75 ± 14.1	0.02

CRP: C-reactive protein; EST: Endoscopic sphincterotomy; WBC: White blood cells.

that EST can be safely performed in patients with ASC by trainees supported by an experienced specialist, although it is undoubtedly that the frequency of post-EST complications is closely related to endoscopic techniques, case volume, skill, and training^[13]. Furthermore, despite EBD was conducted as the initial treatment in order to perform EST safely in the elective EST group, in the present study, immediate EST did not increase the risk of post-EST complications provided the patient was not under anticoagulant therapy, or do not have a coagulopathy or a platelet count $< 50000 \times 10^3/\mu\text{L}$, despite patients in the immediate EST group were in worse general conditions than those in the elective EST group at the time of EST. The immediate EST group patients were significantly younger and the occurrence of post-EST complication was not significantly higher than that in older patients of the elective EST group, although Ueki *et al*^[7] reported that younger patients with moderate acute cholangitis due to choledocholithiasis were likely to experience post-EST pancreatitis and hemorrhage. However, we do not have a clear explanation as to why no complication associated with EST was encountered in these groups of patients, although we suspect that with a larger sample size, complications would occur.

In this study complete stone extraction was achieved in 30.5% (18/59) of patients in the immediate EST group, and 69.5% (41/59) of them suspected of having remnant stones required EBD. Hui *et al*^[4] reported that when endoscopic sphincterotomy is performed with biliary stent insertion in patients with severe acute cholangitis, the procedure is prolonged and the patient is exposed to the risks associated with endoscopic sphincterotomy. However, immediate EST followed by EBD was not associated with an increased frequency of complications in the present study.

Hospitalization of immediate EST patients with stone extraction at once was significantly shorter than that of elective EST patients, and the validity of immediate EST followed by stone extraction was definitive in this aspect for patients with ASC caused by choledocholithiasis. Our results were in line with those of Jang *et al*^[14] who reported that hospitalization of patients with moderate cholangitis subjected to EBD plus EST as the initial

treatment (emergency EST) was significantly shorter than that of those who palliatively underwent EST after EBD.

The present study has several limitations. First, patients with anticoagulant therapy, coagulopathy, or platelet count $< 50000 \times 10^3/\mu\text{L}$ were included in the EBD group because they were at high risk for post-EST bleeding. This may have resulted in selection bias. Second, time for the procedure, the volume of contrast, and number of injections made into the bile duct were not monitored. Third, in a review by Freeman *et al*^[15], suspected sphincter Oddi dysfunction (SOD), history of post-ERCP pancreatitis (PEP), and absence of chronic pancreatitis on the pancreatogram were identified as independent patient-related risk factors for PEP. Moreover, significant procedure-related risk factors were the number of pancreatic duct injections, and difficult or failed cannulation. And we did not examine those factors in the present study, although it is noteworthy that pancreatography was not intended to be performed in the present study. Fourth, this study was done by very experienced endoscopists, limiting to generalize the trial findings. Finally, the present study was not a randomized study, although such trials would be of great interest.

In conclusion, the present study indicated that immediate EST may be equally safe and effective compared with elective EST, and can be definitive for patients with ASC caused by choledocholithiasis provided they are not under anticoagulant therapy, or do not have a coagulopathy or a platelet count $< 50000 \times 10^3/\mu\text{L}$. Furthermore, EST can be safely performed by a trainee supervised by an experienced specialist even in patients with ASC.

COMMENTS

Background

Acute suppurative cholangitis (ASC) is a life-threatening condition that requires prompt treatment. At present, endoscopic biliary drainage (EBD), including endoscopic nasobiliary drainage and endoscopic retrograde biliary drainage, followed by elective endoscopic sphincterotomy (EST) is the established mode of treatment for ASC, with a high success rate and low morbidity and mortality.

However, the validity of immediate EST with stone extraction is uncertain.

Research frontiers

To examine the safety of immediate EST in patients with ASC caused by choledocholithiasis, as compared with elective EST.

Innovations and breakthroughs

Patients with ASC due to choledocholithiasis were allocated to two groups: Those who underwent EST immediately and those who underwent EBD electively followed by EST 1 wk later. There were no complications associated with EST in either group of patients, although white blood cell count, C-reactive protein, total bilirubin, and serum concentrations of liver enzymes just before EST were significantly higher in the immediate EST group than in the elective EST group.

Applications

The paper may interest readers in particular because immediate EST can be as safe as elective EST for patients with acute suppurative cholangitis associated with choledocholithiasis.

Peer-review

This manuscript "Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis" is very interesting.

REFERENCES

- 1 **Leung JW**, Chung SC, Sung JJ, Banez VP, Li AK. Urgent endoscopic drainage for acute suppurative cholangitis. *Lancet* 1989; **1**: 1307-1309 [PMID: 2566834 DOI: 10.1016/S0140-6736(89)92696-2]
- 2 **Lai EC**, Mok FP, Tan ES, Lo CM, Fan ST, You KT, Wong J. Endoscopic biliary drainage for severe acute cholangitis. *N Engl J Med* 1992; **326**: 1582-1586 [PMID: 1584258 DOI: 10.1056/NEJM199206113262401]
- 3 **Lee DW**, Chan AC, Lam YH, Ng EK, Lau JY, Law BK, Lai CW, Sung JJ, Chung SC. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. *Gastrointest Endosc* 2002; **56**: 361-365 [PMID: 12196773 DOI: 10.1016/S0016-5107(02)70039-4]
- 4 **Hui CK**, Lai KC, Yuen MF, Ng M, Chan CK, Hu W, Wong WM, Lai CL, Wong BC. Does the addition of endoscopic sphincterotomy to stent insertion improve drainage of the bile duct in acute suppurative cholangitis? *Gastrointest Endosc* 2003; **58**: 500-504 [PMID: 14520280 DOI: 10.1067/S0016-5107(03)01871-6]
- 5 **Park SY**, Park CH, Cho SB, Yoon KW, Lee WS, Kim HS, Choi SK, Rew JS. The safety and effectiveness of endoscopic biliary decompression by plastic stent placement in acute suppurative cholangitis compared with nasobiliary drainage. *Gastrointest Endosc* 2008; **68**: 1076-1080 [PMID: 18635173 DOI: 10.1016/j.gie.2008.04.025]
- 6 **Sharma BC**, Kumar R, Agarwal N, Sarin SK. Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. *Endoscopy* 2005; **37**: 439-443 [PMID: 15844022 DOI: 10.1055/s-2005-861054]
- 7 **Ueki T**, Otani K, Fujimura N, Shimizu A, Otsuka Y, Kawamoto K, Matsui T. Comparison between emergency and elective endoscopic sphincterotomy in patients with acute cholangitis due to choledocholithiasis: is emergency endoscopic sphincterotomy safe? *J Gastroenterol* 2009; **44**: 1080-1088 [PMID: 19597758 DOI: 10.1007/s00535-009-0100-4]
- 8 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]
- 9 **Lin XZ**, Chang KK, Shin JS, Lin CY, Lin PW, Yu CY, Chou TC. Emergency endoscopic nasobiliary drainage for acute calculous suppurative cholangitis and its potential use in chemical dissolution. *J Gastroenterol Hepatol* 1993; **8**: 35-38 [PMID: 8439660 DOI: 10.1111/j.1440-1746.1993.tb01172.x]
- 10 **Leese T**, Neoptolemos JP, Baker AR, Carr-Locke DL. Management of acute cholangitis and the impact of endoscopic sphincterotomy. *Br J Surg* 1986; **73**: 988-992 [PMID: 3790964 DOI: 10.1002/bjs.1800731214]
- 11 **Lam SK**. A study of endoscopic sphincterotomy in recurrent pyogenic cholangitis. *Br J Surg* 1984; **71**: 262-266 [PMID: 6704674 DOI: 10.1002/bjs.1800710404]
- 12 **Gogel HK**, Runyon BA, Volpicelli NA, Palmer RC. Acute suppurative obstructive cholangitis due to stones: treatment by urgent endoscopic sphincterotomy. *Gastrointest Endosc* 1987; **33**: 210-213 [PMID: 3596186 DOI: 10.1016/S0016-5107(87)71560-0]
- 13 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]
- 14 **Jang SE**, Park SW, Lee BS, Shin CM, Lee SH, Kim JW, Jeong SH, Kim N, Lee DH, Park JK, Hwang JH. Management for CBD stone-related mild to moderate acute cholangitis: urgent versus elective ERCP. *Dig Dis Sci* 2013; **58**: 2082-2087 [PMID: 23456495 DOI: 10.1007/s10620-013-2595-z]
- 15 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864 [PMID: 15173799 DOI: 10.1016/S0016-5107(04)00353-0]

P- Reviewer: Shih SC S- Editor: Qi Y L- Editor: Wang TQ
E- Editor: Lu YJ



Retrospective Study

Percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy: First clinical series

Hiroyuki Imaeda, Kiyokazu Nakajima, Naoki Hosoe, Masanori Nakahara, Shinichiro Zushi, Motohiko Kato, Kazuhiro Kashiwagi, Yasushi Matsumoto, Kayoko Kimura, Rieko Nakamura, Norihito Wada, Masahiko Tsujii, Naohisa Yahagi, Toshifumi Hibi, Takanori Kanai, Tetsuo Takehara, Haruhiko Ogata

Hiroyuki Imaeda, Department of General Internal Medicine, Saitama Medical University, Saitama 350-0495, Japan

Kiyokazu Nakajima, Division of Next Generation Endoscopic Intervention, Osaka University, Osaka 565-0871, Japan

Naoki Hosoe, Kazuhiro Kashiwagi, Kayoko Kimura, Rieko Nakamura, Haruhiko Ogata, Center for Diagnostic and Therapeutic Endoscopy, School of Medicine, Keio University, Tokyo 160-8582, Japan

Masanori Nakahara, Shinichiro Zushi, Yasushi Matsumoto, Department of Gastroenterology, Ikeda City Hospital, Osaka 563-8510, Japan

Motohiko Kato, Masahiko Tsujii, Tetsuo Takehara, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan

Norihito Wada, Department of Surgery, School of Medicine, Keio University, Tokyo 160-8582, Japan

Naohisa Yahagi, Division of Research and Development for Minimally Invasive Treatment, Cancer Center, School of Medicine, Keio University, Tokyo 160-8582, Japan

Toshifumi Hibi, Takanori Kanai, Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo 160-8582, Japan

Author contributions: Imaeda H and Nakajima K planed the study design; Hosoe N and Kashiwagi K advised the study design, data analyst and enrollment of patients; Nakahara M, Zushi S, Kato M and Matsumoto Y enrolled the patients; Kimura K and Nakamura R were the endoscopist; Wada N, Tsujii M, Yahagi N, Hibi T, Kanai T, Takehara T and Ogata H supervised the study.

Institutional review board statement: The study protocol was approved by the institutional review board at our institutions.

Informed consent statement: Written informed consent was

obtained from all the patients.

Conflict-of-interest statement: The authors disclosed no financial relationships relevant to this study.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Hiroyuki Imaeda, MD, Department of General Internal Medicine, Saitama Medical University, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan. imaedahi@yahoo.co.jp
Telephone: +81-49-2761667
Fax: +81-49-2761667

Received: September 11, 2015

Peer-review started: September 16, 2015

First decision: October 21, 2015

Revised: November 8, 2015

Accepted: December 8, 2015

Article in press: December 11, 2015

Published online: February 10, 2016

Abstract

AIM: To elucidate the safety of percutaneous endoscopic gastrostomy (PEG) under steady pressure automatically controlled endoscopy (SPACE) using carbon dioxide (CO₂).

METHODS: Nine patients underwent PEG with a modified introducer method under conscious sedation. A T-tube was attached to the channel of an endoscope connected to an automatic surgical insufflator. The stomach was inflated under the SPACE system. The intragastric pressure was kept between 4–8 mmHg with a flow of CO₂ at 35 L/min. Median procedure time, intragastric pressure, median systolic blood pressure, partial pressure of CO₂, abdominal girth before and immediately after PEG, and free gas and small intestinal gas on abdominal X-ray before and after PEG were recorded.

RESULTS: PEG was completed under stable pneumostomach in all patients, with a median procedural time of 22 min. Median intragastric pressure was 6.9 mmHg and median arterial CO₂ pressure before and after PEG was 42.1 and 45.5 Torr (NS). The median abdominal girth before and after PEG was 68.1 and 69.6 cm (NS). A mild free gas image after PEG was observed in two patients, and faint abdominal gas in the downstream bowel was documented in two patients.

CONCLUSION: SPACE might enable standardized pneumostomach and modified introducer procedure of PEG.

Key words: Percutaneous endoscopic gastrostomy; Steady pressure automatically controlled endoscopy; Carbon dioxide

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We report the safety of percutaneous endoscopic gastrostomy (PEG) under steady pressure automatically controlled endoscopy (SPACE) using carbon dioxide (CO₂). Nine patients underwent PEG with a modified introducer method under conscious sedation. The stomach was inflated under the SPACE system. PEG was completed under stable pneumostomach in all patients. Median arterial CO₂ pressure before and after PEG was 42.1 and 45.5 Torr (NS). The median abdominal girth before and after PEG was 68.1 and 69.6 cm (NS). A mild free gas image after PEG was observed in two patients. SPACE might enabled standardized pneumostomach which leads to easier and safer PEG procedures.

Imaeda H, Nakajima K, Hosoe N, Nakahara M, Zushi S, Kato M, Kashiwagi K, Matsumoto Y, Kimura K, Nakamura R, Wada N, Tsujii M, Yahagi N, Hibi T, Kanai T, Takehara T, Ogata H. Percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy: First clinical series. *World J Gastrointest Endosc* 2016; 8(3): 186–191 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/186.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.186>

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) has been

widely accepted for external feeding since Gauderer *et al*^[1] first reported it in 1980. A conventional on-demand insufflation using atmospheric air through the endoscope has been a gold standard in performing PEG, not only for optimal visualization but also for maintaining pneumostomach to keep puncture sites on the gastric/abdominal walls stabilized. Abdominal distension and pneumoperitoneum often occur after PEG^[2–7]. Carbon dioxide (CO₂) insufflation has been initially reported for colonoscopic electrosurgical polypectomy in the field of gastrointestinal (GI) endoscopy^[8]. CO₂ is now increasingly being used instead of atmospheric air in GI endoscopic procedures since CO₂ is rapidly absorbed *via* the gut lining. Total colonoscopy^[9–13], endoscopic retrograde cholangiopancreatography^[14–17], peroral cholangioscopy^[18], double-balloon enteroscopy^[19], PEG^[20], gastric and colonic endoscopic submucosal dissection (ESD)^[21–25], and upper GI intragastric endoscopy during laparoscopic surgery under CO₂ insufflation^[26] have been reported to be safe and more comfortable compared with air insufflation.

GI endoscopy has been performed under on-demand insufflation by endoscopists through the endoscope itself in a manual manner without pressure monitoring. This practice has been justified because the gastrointestinal tract allows migration of excessive gas into the upstream/downstream bowel. Excessive air supply may result in gaseous regurgitation, vomiting, and abdominal bloating. Steady pressure automatically controlled endoscopy (SPACE) using CO₂, developed by Nakajima *et al*^[27,28], Kato *et al*^[29] and Yamada *et al*^[30] is expected to improve and standardize endoscopic visualization and working space in the GI lumen. Although SPACE has been reported to shorten procedural time and improve the safety of endoscopic intervention^[28–30], CO₂ narcosis is of concern during PEG under sedation, since patients usually suffer from respiratory disease and/or consciousness disturbance. The SPACE system consists of a standard commercially available endoscope overtube (Top Co., Ltd., Tokyo, Japan) and a newly developed detachable leak-proof device with an anti-reflux valve and a Luer lock connection (Leak Cutter; Top)^[28,29]. A commercially available automatic surgical insufflator is then connected to the system. Esophageal ESD under SPACE has been reported to be feasible and safe^[28,29]. Recently, gastric ESD under SPACE has been also reported to be feasible and safe in an preclinical study^[30].

The aim of this study is to elucidate the safety of PEG under the SPACE system. To our knowledge, this is the first clinical study regarding application of SPACE technology in PEG.

MATERIALS AND METHODS

Ten patients undergoing treatment at our institutions were enrolled in the study. Patients who had CO₂ retention due to chronic obstructive pulmonary dysfunction were excluded. One of the ten enrolled patients was excluded because he withdrew his consent after informed consent

Table 1 Clinical characteristic of patients

Clinical characteristics	Data
Male/female	6/3
Mean age	78 (61-89)
Comorbid disease	
Parkinson's disease	4
Cerebrovascular disease	1
Amyotrophic lateral sclerosis	1
Necrotizing fasciitis	1
Disuse syndrome	1
Laryngeal cancer	1

was obtained. Therefore, a total of nine patients, six males and three females, underwent PEG under SPACE. The mean age of patients was 78 years (ranging from 61 to 89). Four patients had Parkinson's disease, one had cerebrovascular disease, one had amyotrophic lateral sclerosis, one had necrotizing fasciitis, one had disuse syndrome, and one had laryngeal cancer (Table 1).

PEG was performed under conscious sedation using intravenous injection of 35 mg pethidine chloride and 0.1-0.2 mg of flunitrazepam or 1-2 mg of midazolam and oxygen inhalation. A T-tube with two junctions (MD-807, Olympus Medical Systems Co. Ltd., Tokyo, Japan) was connected directly to the channel of the flexible gastroscope (GIF-H260, Olympus Medical Systems Co. Ltd., Tokyo, Japan) (Figure 1). One of the junctions was connected to a commercially available automatic surgical insufflator (UHI-3, Olympus Medical Systems Co. Ltd., Tokyo, Japan) that feeds 35 L of CO₂ per minute into the stomach through the channel (Figure 2). The intragastric pressure was kept between 4-8 mmHg. PEG was performed using a modified introducer procedure and a dedicated kit (Direct Ideal PEG kit, Olympus Medical Systems Co. Ltd., Tokyo, Japan). The gastroscope was inserted from the mouth to the esophagus under conventional manual air insufflation. After insertion into the stomach, conventional manual air insufflation was switched to the SPACE system. First, percutaneous gastropexy was conducted at two sites while the stomach was inflated under the SPACE system through the endoscope channel. Second, after puncture using an indwelling needle was performed between the two gastropexy sites, a guide-wire was replaced with the needle. Third, the PEG site was dilated by the dilator through the guide-wire. When the dilator was withdrawn, the CO₂ supply was temporarily stopped, the PEG tube was inserted through the guide-wire, and the CO₂ supply was restarted and checked to ensure it had been located correctly.

Data such as mean procedure time, intragastric pressure, mean systolic blood pressure, partial pressure of CO₂ (PaCO₂), abdominal circumference before and soon after PEG, and change of free gas and small intestinal gas on abdominal X-ray before and immediately after PEG were obtained and prospectively recorded in the database.

**Figure 1** T-tube attached to the endoscopic channel.**Figure 2** Automatic surgical insufflator connected to the T-tube.

The study protocol was in accordance with the tenets of the revised Declaration of Helsinki (1989) and was approved by the institutional review board at our institutions. Written informed consent was obtained from all the patients.

Statistical analysis

Statistical analysis was performed by Fischer's test using SPSS software, version 17 (SPSS Inc., Chicago, IL). For therapeutic performance, sensitivity, specificity, and accuracy are presented as percentages with 95% CIs. All probability values calculated in this analysis were sided, and $P < 0.05$ was considered significant.

RESULTS

The median procedural time was 22 min (14-38 min) (Table 2). It was possible to maintain a good endoscopic visualization and a sufficient pneumostomach to keep puncture sites stabilized during PEG, which was completed easily in all 9 patients. Visualization after intentional suction was regained more quickly than with conventional endoscopy (Video 1). PEG was established exactly in the scheduled puncture sites. Median intragastric pressure was kept at 6.9 mmHg as preset (5-8 mmHg). Median O₂ inhalation was 1.7 L/min (0-3). Median systolic blood pressure before and immediately after PEG was 129.3 mmHg (101-158 mmHg) and 120.6 mmHg (90-145

Table 2 Results of percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy

Clinical outcomes		P value
Median procedural time (min)	22 (14-38)	
Median intragastric pressure (mmHg)	6.9 (5-8)	
Median systolic pressure		
Before PEG (mmHg)	129.3 (101-158)	0.33
Soon after PEG (mmHg)	120.6 (90-145)	
Median PaCO ₂		
Before PEG (Torr)	42.1 (35.2-45.7)	0.10
Soon after PEG (Torr)	45.5 (41.0-54.6)	
Median abdominal girth		
Before PEG (cm)	68.1 (58-85)	0.38
Soon after PEG (cm)	69.6 (60-86)	
Mild free gas after PEG (n)	2	
Mild increase of small intestinal gas after PEG (n)	2	

PEG: Percutaneous endoscopic gastrostomy.

mmHg). There was no significant difference in these data ($P = 0.33$). Median PaCO₂ before and after PEG was 42.1 Torr (35.2-45.7 Torr) and 45.5 Torr (41.0-54.6 Torr). There was a tendency to an elevated median PaCO₂ after PEG compared with prior values ($P = 0.10$); however no CO₂ narcosis was encountered in the series.

The median abdominal girth before and immediately after PEG was 68.1 cm (58-85 cm) and 69.6 cm (60-86 cm), and there was no significant difference ($P = 0.38$). Mild free gas was observed postoperatively in two patients, and small intestinal gas was slightly increased in two patients (Figure 3). All these were subclinical, and no other serious adverse events were encountered in any patients.

DISCUSSION

Several endoscopic procedures under CO₂ insufflation have been reported to be safe and more comfortable compared with air insufflation because CO₂ is absorbed rapidly *via* the gut lining. CO₂ insufflation during PEG reduces risk of pneumoperitoneum and bloating^[8-25]. Technically, it is a key point to maintain pneumostomach stabilized during PEG so that PEG can be fashioned in the scheduled puncture sites.

In our study, although PaCO₂ was subclinically elevated during and after the procedure, there were no adverse events associated with CO₂ insufflation. The insufflation is mandatory in PEG for maintaining a pneumostomach to keep puncture sites stabilized. Nishiwaki *et al*^[20] reported that PEG under CO₂ insufflation compared with air insufflation was safer and more comfortable because of the lower incidence of pneumoperitoneum, less distension of the small bowel, and no adverse events. Our present data first showed that PEG is safely fashioned under SPACE.

Nakajima *et al*^[27] reported that a steady-pressure pneumostomach was successfully created and maintained for 100 min on average without clamping the



Figure 3 Free air (indicated by arrows) in abdominal X-ray after percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy.

downstream bowel in laparoscopic intragastric surgery (LIGS). The stomach was insufflated with a UHI-3 surgical insufflation unit connected to a transgastric port at an intragastric pressure of 6-8 mmHg. No adverse events were noted during LIGS, and no postoperative abdominal distention was observed. Nakajima *et al*^[28] have also reported esophageal ESD under SPACE using a standard endoscopic overtube and a detachable leak-proof valve with a luer-lock connection in an animal model. Moreover, Kato *et al*^[29] reported on the feasibility and safety of esophageal ESD under SPACE in a clinical study, and Yamada *et al*^[30] reported on the feasibility and safety of gastric ESD under SPACE in an animal model. In SPACE, endoscopic visualization is automatically obtained once the insufflation pressure and flow rate are set. Visualization after suction is automatically regained more quickly than with conventional endoscopy. The flow capacity of current surgical insufflators is higher than that of manual endoscopic insufflators and is considered responsible for the rapid regaining. UHI-3 can supply 35 L of CO₂ per minute and these flow rates are significantly higher than those of actual endoscopic flow with manual CO₂ insufflation (1.4 L/min). The insufflation process is automatic in SPACE. Air/water button manipulation is no longer necessary, leaving the endoscopist free to focus on the intervention itself. SPACE can prevent excessive CO₂ supply, which may result in gaseous regurgitation, vomiting, and abdominal bloating^[30].

In this study, CO₂ was successfully supplied through the endoscopic channel using a T-tube without an overtube. The intragastric pressure was kept from 5 to 8 mmHg throughout the procedure. PEG under SPACE had no negative effects such as vomiting or abdominal bloating and no impact on vital signs. Mild postprocedural free gas was observed in two patients and abdominal gas was slightly increased in another two patients. There were, however, no adverse events in any patients. Even if CO₂ is leaked into the abdominal cavity through the PEG site, CO₂ can be absorbed quickly *via* the peritoneal lining and abdominal distention will be resolved immediately. Nishiwaki *et al*^[20] reported that pneumoperitoneum was

not observed in the CO₂ insufflation group. In our study, pneumoperitoneum might have occurred because of the leakage of remnant air in the stomach. Nishiwaki *et al.*^[20] performed a pull method of the PEG procedure, while in our study, a modified introducer method was performed. After the dilator was withdrawn, the PEG tube was inserted during the modified introducer method, and it was possible that intragastric gas (air) might have leaked into the abdominal cavity at this time. Thus we hypothesized that postprocedural pneumoperitoneum might be caused by the difference of the PEG procedure. Yamada *et al.*^[30] reported the potential safety of pneumoperitoneum under SPACE, because intra-gastric pressure was regulated within the preset pressure range to prevent excessive transmural insufflation. Nakajima *et al.*^[28] have reported that the migration of CO₂ over the proximal jejunum does not occur because of a pinch-cock phenomenon and intestinal surface tension. In this pinch-cock phenomenon, the distended upstream bowel (stomach and duodenum) acts as a cock that compresses the downstream bowel, resulting in the prevention of massive gas migration. The surface tension in the collapsed gut lumen may work as another pressure barrier. The insufflated gas volume was sufficiently low in each SPACE, suggesting no major gas migration into the downstream bowel during SPACE. In fact, CO₂ outflow stopped automatically whenever the stomach was insufflated.

Although conscious sedation is necessary during PEG procedure, most patients who undergo PEG have cerebrovascular diseases and aspiration pneumonia, which means they are at high risk for developing respiratory dysfunction. CO₂ narcosis might develop in patients with chronic pulmonary diseases, so they were excluded from this study. There was a tendency to an elevated PaCO₂ median after PEG compared with before PEG, but CO₂ narcosis did not occur in any cases. This elevation might be caused by PEG under SPACE, but it could also be caused by the administration of sedative drugs that suppress the respiratory function.

There were several limitations in this study. First, as this was a pilot study, the sample size was very small. We need to accumulate more clinical data such as a randomized controlled trial between PEG under conventional manual air or CO₂ insufflation and that under SPACE system in near future. There was a tendency to an elevated median PaCO₂ after PEG compared with previous values, indicating that a randomized controlled trial to compare PEG under SPACE and under manual air insufflation is necessary. We examined PaCO₂ only twice: once before and once after PEG. Ideally we should examine the course of PCO₂ during PEG using the monitor of transcutaneous measurement of PCO₂. Most patients cannot complain of abdominal pain or distention because of comorbid diseases such as cerebrovascular disease, so the complaints of all patients cannot be detected. We have to examine the gas volume in the small intestine and the pneumoperitoneum in the abdominal X-ray and/or CT scan. The channel is free during a modified introducer

procedure of PEG, therefore, the SPACE system is available during PEG procedure. The introduction of snares or forceps through the channel affects the SPACE system.

In conclusion, PEG under SPACE might be feasible and safe. SPACE might enable standardized pneumostomach which leads to easier and safer PEG procedures.

COMMENTS

Background

"On-demand" insufflation using atmospheric air has been a gold standard in performing percutaneous endoscopic gastrostomy (PEG), not only for optimal visualization but also for maintaining pneumostomach to keep puncture sites stabilized. However, excessive air insufflation may result in gaseous regurgitation, vomiting, and abdominal bloating.

Research frontiers

PEG under steady pressure automatically controlled endoscopy (SPACE) using carbon dioxide (CO₂) has not been reported.

Innovations and breakthroughs

PEG under SPACE was feasible and safe.

Applications

SPACE enables standardized pneumostomach which leads to easier and safer PEG procedures.

Peer-review

The authors evaluated the safety of PEG under SPACE using CO₂. PEG was completed under stable pneumostomach in all nine patients. Further clinical trials in a randomized controlled study between PEG under conventional manual air or CO₂ insufflation and that under SPACE system will be necessary.

REFERENCES

- 1 **Gauderer MW**, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; **15**: 872-875 [PMID: 6780678]
- 2 **Gottfried EB**, Plumser AB, Clair MR. Pneumoperitoneum following percutaneous endoscopic gastrostomy. A prospective study. *Gastrointest Endosc* 1986; **32**: 397-399 [PMID: 3803838]
- 3 **Wojtowycz MM**, Arata JA. Subcutaneous emphysema after percutaneous gastrostomy. *Am J Roentgenol* 1988; **151**: 311-312 [PMID: 3134806]
- 4 **Dulabon GR**, Abrams JE, Rutherford EJ. The incidence and significance of free air after percutaneous endoscopic gastrostomy. *Am Surg* 2002; **68**: 590-593 [PMID: 12079145]
- 5 **Wiesen AJ**, Sideridis K, Fernandes A, Hines J, Indaram A, Weinstein L, Davidoff S, Bank S. True incidence and clinical significance of pneumoperitoneum after PEG placement: a prospective study. *Gastrointest Endosc* 2006; **64**: 886-889 [PMID: 17140892]
- 6 **Schrag SP**, Sharma R, Jaik NP, Seamon MJ, Lukaszczuk JJ, Martin ND, Hoey BA, Stawicki SP. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. *J Gastrointest Liver Dis* 2007; **16**: 407-418 [PMID: 18193123]
- 7 **Blum CA**, Selander C, Ruddy JM, Leon S. The incidence and clinical significance of pneumoperitoneum after percutaneous endoscopic gastrostomy: a review of 722 cases. *Am Surg* 2009; **75**: 39-43 [PMID: 19213395]
- 8 **Rogers BH**. The safety of carbon dioxide insufflation during colonoscopic electrosurgical polypectomy. *Gastrointest Endosc* 1974; **20**: 115-117 [PMID: 4815026]
- 9 **Hussein AM**, Bartram CI, Williams CB. Carbon dioxide insufflation for more comfortable colonoscopy. *Gastrointest*

- Endosc* 1984; **30**: 68-70 [PMID: 6425108]
- 10 **Stevenson GW**, Wilson JA, Wilkinson J, Norman G, Goodacre RL. Pain following colonoscopy: elimination with carbon dioxide. *Gastrointest Endosc* 1992; **38**: 564-567 [PMID: 1397911]
 - 11 **Yamano HO**, Yoshikawa K, Kimura T, Yamamoto E, Harada E, Kudou T, Katou R, Hayashi Y, Satou K. Carbon dioxide insufflation for colonoscopy: evaluation of gas volume, abdominal pain, examination time and transcutaneous partial CO₂ pressure. *J Gastroenterol* 2010; **45**: 1235-1240 [PMID: 20635100 DOI: 10.1007/s00535-010-0286-5]
 - 12 **Uraoka T**, Kato J, Kuriyama M, Hori K, Ishikawa S, Harada K, Takemoto K, Hiraoka S, Fujita H, Horii J, Saito Y, Yamamoto K. CO₂ insufflation for potentially difficult colonoscopies: efficacy when used by less experienced colonoscopists. *World J Gastroenterol* 2009; **15**: 5186-5192 [PMID: 19891018]
 - 13 **Yasumasa K**, Nakajima K, Endo S, Ito T, Matsuda H, Nishida T. Carbon dioxide insufflation attenuates parietal blood flow obstruction in distended colon: potential advantages of carbon dioxide insufflated colonoscopy. *Surg Endosc* 2006; **20**: 587-594 [PMID: 16437273]
 - 14 **Bretthauer M**, Seip B, Aasen S, Kordal M, Hoff G, Aabakken L. Carbon dioxide insufflation for more comfortable endoscopic retrograde cholangiopancreatography: a randomized, controlled, double-blind trial. *Endoscopy* 2007; **39**: 58-64 [PMID: 17252462]
 - 15 **Maple JT**, Keswani RN, Hovis RM, Saddedin EZ, Jonnalagadda S, Azar RR, Hagen C, Thompson DM, Waldbaum L, Edmundowicz SA. Carbon dioxide insufflation during ERCP for reduction of postprocedure pain: a randomized, double-blind, controlled trial. *Gastrointest Endosc* 2009; **70**: 278-283 [PMID: 19523621 DOI: 10.1016/j.gie.2008.12.050]
 - 16 **Dellon ES**, Velayudham A, Clarke BW, Isaacs KL, Gangarosa LM, Galanko JA, Grimm IS. A randomized, controlled, double-blind trial of air insufflation versus carbon dioxide insufflation during ERCP. *Gastrointest Endosc* 2010; **72**: 68-77 [PMID: 20493485 DOI: 10.1016/j.gie.2010.01.041]
 - 17 **Nelson DB**, Freeman ML, Silvis SE, Cass OW, Yakshe PN, Vennes J, Stahnke LL, Herman M, Hodges J. A randomized, controlled trial of transcutaneous carbon dioxide monitoring during ERCP. *Gastrointest Endosc* 2000; **51**: 288-295 [PMID: 10699773]
 - 18 **Ueki T**, Mizuno M, Ota S, Ogawa T, Matsushita H, Uchida D, Numata N, Ueda A, Morimoto Y, Kominami Y, Nanba S, Kurome M, Ohe H, Nakagawa M, Araki Y. Carbon dioxide insufflation is useful for obtaining clear images of the bile duct during peroral cholangioscopy (with video). *Gastrointest Endosc* 2010; **71**: 1046-1051 [PMID: 20438891 DOI: 10.1016/j.gie.2010.01.015]
 - 19 **Domagk D**, Bretthauer M, Lenz P, Aabakken L, Ullerich H, Maaser C, Domschke W, Kucharzik T. Carbon dioxide insufflation improves intubation depth in double-balloon enteroscopy: a randomized, controlled, double-blind trial. *Endoscopy* 2007; **39**: 1064-1067 [PMID: 18072057]
 - 20 **Nishiwaki S**, Araki H, Hayashi M, Takada J, Iwashita M, Tagami A, Hatakeyama H, Hayashi T, Maeda T, Saito K. Inhibitory effects of carbon dioxide insufflation on pneumoperitoneum and bowel distension after percutaneous endoscopic gastrostomy. *World J Gastroenterol* 2012; **18**: 3565-3570 [PMID: 22826621 DOI: 10.3748/wjg.v18.i27.3565]
 - 21 **Maeda Y**, Hirasawa D, Fujita N, Obana T, Sugawara T, Ohira T, Harada Y, Yamagata T, Suzuki K, Koike Y, Kusaka J, Tanaka M, Noda Y. A prospective, randomized, double-blind, controlled trial on the efficacy of carbon dioxide insufflation in gastric endoscopic submucosal dissection. *Endoscopy* 2013; **45**: 335-341 [PMID: 23468193 DOI: 10.1055/s-0032-1326199]
 - 22 **Nonaka S**, Saito Y, Takisawa H, Kim Y, Kikuchi T, Oda I. Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation. *Surg Endosc* 2010; **24**: 1638-1645 [PMID: 20108154 DOI: 10.1007/s00464-009-0824-5]
 - 23 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Kozu T, Saito D. A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation. *Gastrointest Endosc* 2007; **65**: 537-542 [PMID: 17321264]
 - 24 **Kikuchi T**, Fu KI, Saito Y, Uraoka T, Fukuzawa M, Fukunaga S, Sakamoto T, Nakajima T, Matsuda T. Transcutaneous monitoring of partial pressure of carbon dioxide during endoscopic submucosal dissection of early colorectal neoplasia with carbon dioxide insufflation: a prospective study. *Surg Endosc* 2010; **24**: 2231-2235 [PMID: 20177925 DOI: 10.1007/s00464-010-0939-8]
 - 25 **Suzuki T**, Minami H, Komatsu T, Masusda R, Kobayashi Y, Sakamoto A, Sato Y, Inoue H, Serada K. Prolonged carbon dioxide insufflation under general anesthesia for endoscopic submucosal dissection. *Endoscopy* 2010; **42**: 1021-1029 [PMID: 21120775 DOI: 10.1055/s-0030-1255969]
 - 26 **Souma Y**, Nakajima K, Takahashi T, Nishimura J, Fujiwara Y, Takiguchi S, Miyata H, Yamasaki M, Doki Y, Nishida T. The role of intraoperative carbon dioxide insufflating upper gastrointestinal endoscopy during laparoscopic surgery. *Surg Endosc* 2009; **23**: 2279-2285 [PMID: 19184210 DOI: 10.1007/s00464-008-0309-y]
 - 27 **Nakajima K**, Nishida T, Milsom JW, Takahashi T, Souma Y, Miyazaki Y, Iijima H, Mori M, Doki Y. Current limitations in endoscopic CO₂ insufflation for NOTES: flow and pressure study. *Gastrointest Endosc* 2010; **72**: 1036-1042 [PMID: 20883992 DOI: 10.1016/j.gie.2010.07.002]
 - 28 **Nakajima K**, Moon JH, Tsutsui S, Miyazaki Y, Yamasaki M, Yamada T, Kato M, Yasuda K, Sumiyama K, Yahagi N, Saida Y, Kondo H, Nishida T, Mori M, Doki Y. Esophageal submucosal dissection under steady pressure automatically controlled endoscopy (SPACE): a randomized preclinical trial. *Endoscopy* 2012; **44**: 1139-1148 [PMID: 22932809 DOI: 10.1055/s-0032-1310093]
 - 29 **Kato M**, Nakajima K, Yamada T, Hirota M, Miyazaki Y, Yamasaki M, Nishida T, Mori M, Doki Y, Tsujii M, Takehara T. Esophageal submucosal dissection under steady pressure automatically controlled endoscopy (SPACE): a clinical feasibility study. *Endoscopy* 2014; **46**: 680-684 [PMID: 24770965 DOI: 10.1055/s-0034-1365465]
 - 30 **Yamada T**, Hirota M, Tsutsui S, Kato M, Takahashi T, Yasuda K, Sumiyama K, Tsujii M, Takehara T, Mori M, Doki Y, Nakajima K. Gastric endoscopic submucosal dissection under steady pressure automatically controlled endoscopy (SPACE): a multicenter randomized preclinical trial. *Surg Endosc* 2015; **29**: 2748-2755 [PMID: 25480619 DOI: 10.1007/s00464-014-4001-0]

P- Reviewer: Casadesus D, Kapetanios D, Trevisani L
S- Editor: Wang JL **L- Editor:** A **E- Editor:** Lu YJ



Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review

Elia Armellini, Stefano F Crinò, Marco Ballarè, Socrate Pallio, Pietro Occhipinti

Elia Armellini, Stefano F Crinò, Marco Ballarè, Socrate Pallio, Pietro Occhipinti, Gastroenterology Division, Azienda Ospedaliero Universitaria "Maggiore della Carità", 28100 Novara, Italy

Author contributions: Armellini E performed the endoscopic procedures; Ballarè M, Pallio S and Occhipinti P collected and analyzed the data; Armellini E and Crinò SF wrote the paper and contributed equally to this manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at our Institution.

Informed consent statement: The patient involved in this study gave his written informed consent authorizing use and disclosure of his protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Elia Armellini, MD, Gastroenterology Division, Azienda Ospedaliero Universitaria "Maggiore della Carità", Corso Mazzini 18, 28100 Novara, Italy. elia_armellini@hotmail.com
Telephone: +39-32-13733206
Fax: +39-32-13733345

Received: May 8, 2015
Peer-review started: May 11, 2015
First decision: July 25, 2015
Revised: August 20, 2015
Accepted: October 12, 2015

Article in press: October 13, 2015

Published online: February 10, 2016

Abstract

Here we offer a review of the literature regarding endoscopic ultrasound-guided ethanol ablation for pancreatic neuroendocrine tumours and describe the case of a cystic tumour completely ablated after a multisession procedure. A total of 35 PubMed indexed cases of treated functioning and non-functioning pancreatic neuroendocrine tumours resulted from our search, 29 of which are well-documented and summarised. Endoscopic ultrasound-guided ethanol ablation appears as a local, minimally invasive treatment of pancreatic neuroendocrine tumours, suitable for selected patients. This technique appears feasible, relatively safe and efficient, especially when applied to symptom relief in functioning tumours, aiming at loss of endocrine secretion. For non-functioning tumours, where the goal is complete tissue ablation, endoscopic ultrasound-guided ethanol ablation can provide good results for patients who are unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients requires assessment through further studies.

Key words: Endoscopic ultrasound; Pancreatic neuroendocrine tumour; Endoscopic ultrasound-guided injection; Ethanol; Tumour ablation

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We report a complete review of the literature about endoscopic ultrasound-guided ethanol ablation for pancreatic neuroendocrine tumours. The case of a cystic tumour completely ablated after a multisession procedure is described. On long term follow-up a durable

remission of the tumour was obtained; a complete image gallery showing the pre and post-treatment appearance is available. The technical aspects, clinical success and complication rates related to this kind of procedures are described.

Armellini E, Crinò SF, Ballarè M, Pallio S, Occhipinti P. Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review. *World J Gastrointest Endosc* 2016; 8(3): 192-197 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i3/192.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i3.192>

INTRODUCTION

In recent years the improvement of diagnostic and therapeutic technologies has led to less invasive treatments in any field of medicine with a shift from surgery to imaging guided treatments.

Endoscopic ultrasonography (EUS) has demonstrated excellent diagnostic accuracy for bilio-pancreatic district diseases and high safety and precision when applied for operative purposes. Along the years this peculiarity has made of EUS an optimal technique for imaging and cytological diagnosis, as well as for execution of more advanced procedures (*i.e.*, drainages and local treatments).

The current management of T1 and T2 pancreatic neuroendocrine tumours (pNETs) is somewhat similar to that of most pancreatic tumours (surgical resection), with a considerable economic burden and post-operative complications. However we are dealing with a pathology that offers a better prognosis and that is potentially responsive to local treatments^[1,2].

Neuroendocrine tumours arise from cells present in the diffuse endocrine system and can be found throughout the body. They are most commonly located in the gastrointestinal tract and lung but are also found in the pancreas^[3]. The 2010 World Health Organization (WHO) classification divides the pNETs in three grades (G1, G2 and G3) on the basis of Ki-67 nuclear antigen expression (< 2%; 2%-20% and > 20%) and mitotic rate (< 2; 2-20 and > 20). Biopsy is most commonly used to assess the grade of the tumour. According to the TNM, the tumour is classified as T1a (< 1 cm), T1b (1-2 cm) and T2 (larger than 2 cm); T3 and T4 are locally advanced tumours (Table 1).

Tumour grading and tumour stage are the main prognostic factors of pNETs. Well and moderately differentiated have a significantly better survival compared to poorly differentiated neuroendocrine carcinomas.

pNETs are also classified as functioning and non-functioning depending on the secretion of specific hormones. Functioning tumours are commonly associated with a specific hormonal syndrome directly related to a hormone secreted by the neoplasm such as insulinomas

Table 1 World Health Organization classification of pancreatic neuroendocrine tumors

Grade	Ki-67 index (%)	Mitotic count/10 HPF
G1	≤ 2	< 2
G2	3-20	2-20
G3	> 20	> 20
TNM	Size (cm)	Muscularis propria invasion
T1a	< 1	–
T1b	1-2	–
T2	> 2	+

Accordingly to the WHO classification 2010, the higher grade is assumed if the Ki-67 index and mitotic count differ; in the WHO 2010 TNM, the tumor is classified as T2 if it is larger than 2 cm in diameter or if it invades the muscularis propria. T3 and T4 tumors are locally aggressive tumors. WHO: World Health Organization; HPF: High-power field.

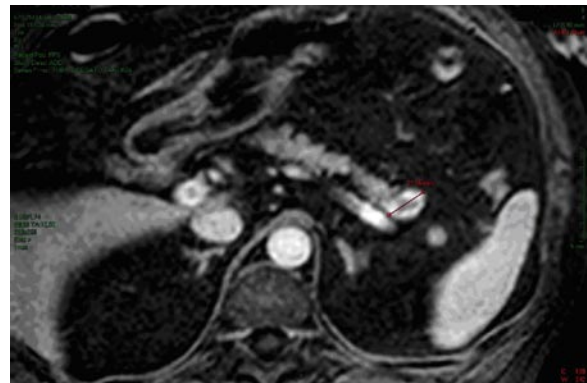


Figure 1 Abdominal magnetic resonance imaging demonstrating a round, well-demarcated nodule of the pancreatic tail. The 22 mm lesion (calipers) shows highly vascularised peripheral tissue.

with hypoglycemia, gastrinomas with Zollinger–Ellison or carcinoid syndrome. Most non-functioning tumours occur in the head of the pancreas and produce mass effect symptoms. When small, they are usually incidentally discovered due to the incremental use of high-level diagnostic imaging.

EUS is the optimal diagnostic modality and can provide a biopsy specimen for histological confirmation and differentiation grade. The EUS image is usually of a solid, ipoechoic, round and smooth nodule, sometimes with a cystic central component (bull's eye appearance).

To date, the management of pancreatic sporadic, small (< 2 cm), asymptomatic, low-grade (G1) NETs suggests a "wait and see" strategy. Surgical resection of non-functioning pNETs is actually recommended for large (> 2 cm) or G2-G3 lesions^[4]. For patients unfit for surgery due to high-risk comorbidity or for those who refuse resection, the EUS-guided ethanol ablation has been reported in a few cases^[5] as a local and minimally invasive therapy.

CASE REPORT

A 58-year-old man with essential hypertension and recent onset of glucose intolerance was referred for a

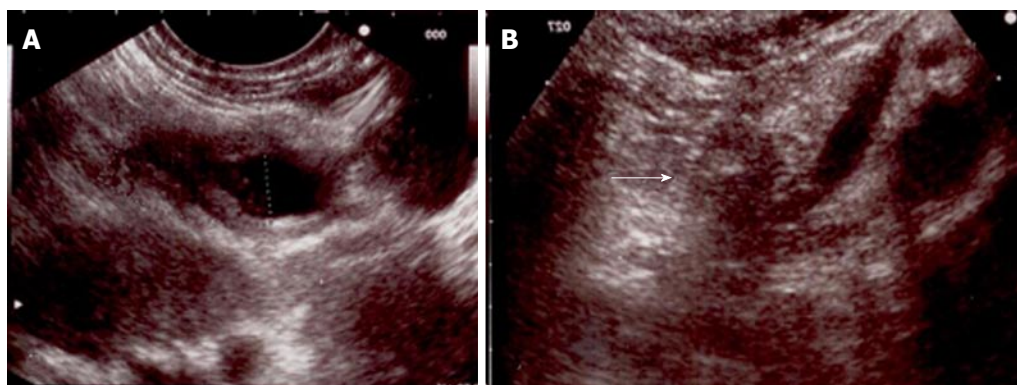


Figure 2 Endoscopic ultrasound appearances before (A) and after (B) treatment (white arrow).

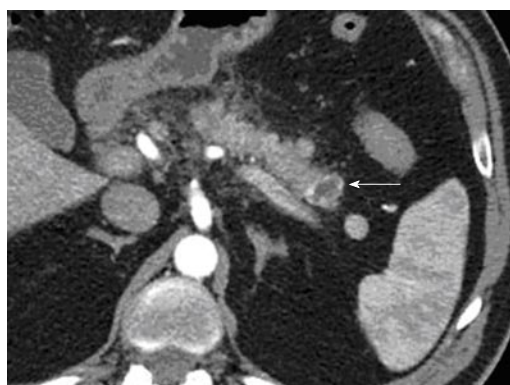


Figure 3 Computed tomography scan showing thin residual hypervascular tissue (white arrow) two months after the first treatment.

transabdominal ultrasonography (US). Other laboratory test results including levels of carcinoembryonic antigen and carbohydrate antigen were all within normal ranges. The US session diagnosed a focal lesion on the pancreatic tail. An abdominal magnetic resonance image showed a 22 mm nodule with peripheral hypervascularization (Figure 1), and EUS confirmed a “bull’s-eye” appearance nodule with peripheral hypervascular pattern *via* power Doppler and a central cystic component. The EUS-guided FNA of the lesion confirmed the diagnosis of pNET. The Ki67 proliferative index was > 5% to yield a G2 grade. However, because the patient adamantly refused surgical resection, we decided to ablate the lesion *via* EUS-guided ethanol injection.

After aspiration of the cystic component, a mean volume of 1.7 mL of 95% ethanol per session was injected into the tumour and re-aspirated using a 25-gauge needle (Echo-tip ultra, Cook, Limerick, Ireland) through a linear array echoendoscope (Figure 2). Three treatment sessions over six months were performed to ablate the nodule (Figure 3).

The hospitalization time was 2 d for each session. The patient experienced mild pancreatitis in 2 out of 3 sessions - that resolved with standard-of-care. No major or late complications were observed. After 24 mo, we achieved a durable and complete remission of

the tumour as shown by CT and EUS morphological imaging (Figure 4).

DISCUSSION

Most diagnosed pNETs are non-functioning tumours (90.8%); the remaining 9% are malignant functioning tumours such as gastrinomas (4.2%), insulinomas (2.5%), glucagonomas (1.6%), and VIPomas (0.9%). Although commonly perceived to be indolent tumours, they exhibit a broad range of growth rates, malignant potential, and overall prognosis. Most patients with pNETs (60%-70%) present with metastatic disease at diagnosis. Following surgical resection, the 5-year cumulative survival for pNETs other than insulinomas is roughly 65% with a 10-year survival of 45%^[6].

Patients with incidental diagnosis of pNETs with a tumour size < 2 cm and low-grade (G1) dysplasia have a 5-year overall survival of 100% with a minimal risk of recurrence^[6]. In this setting, a “wait and see” policy is recommended.

On the contrary, surgical resection is the standard treatment for functioning and non-functioning G2-G3 pNETs. However, this is associated with a high risk of complications. Even when performed in high-volume centres, typical pancreatic resections (pancreaticoduodenectomy or distal pancreatectomy) have a mortality rate of about 5% with complications ranging from 40% to 50%^[7]. This is particularly common in the elderly or patients with comorbidities. Typical pancreatic resections are also associated with a high incidence of exocrine and endocrine insufficiency.

In an attempt to reduce complications and pancreatic impairment, new parenchyma-sparing resection techniques such as enucleation and middle pancreatectomy (resection of the central part of the gland) have been applied to small tumours^[8]. Although pancreatic head tumour enucleation resulted in decreased operative time and length of hospitalization, the 5-year survival and overall morbidity and mortality were comparable to standard surgical resection even for small pNETs^[9]. To date, no alternative treatment has been standardized for patients unfit for surgery or for those who refuse

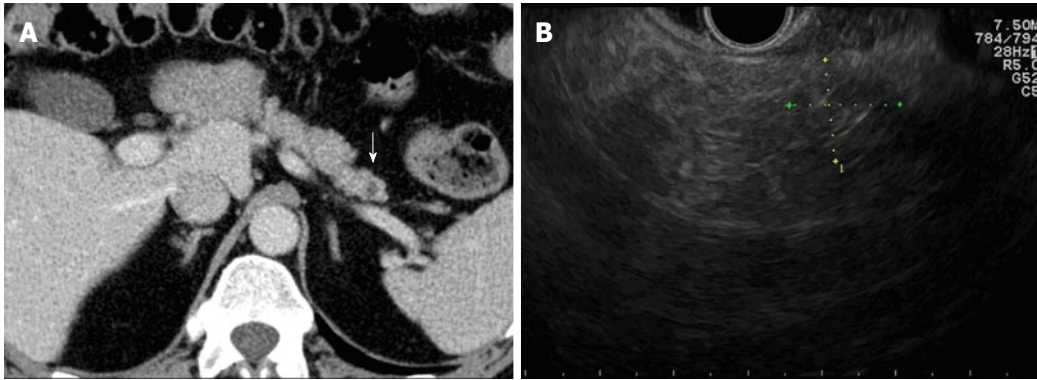


Figure 4 Twenty-four months follow-up. A: Computed tomography scan showing absence of hypervascular tissue around a small hypodense area (white arrow); B: Endoscopic ultrasound scan of the pancreatic tail demonstrating poorly defined hyperechoic tissue (fibrosis) with posterior shadow (caliper).

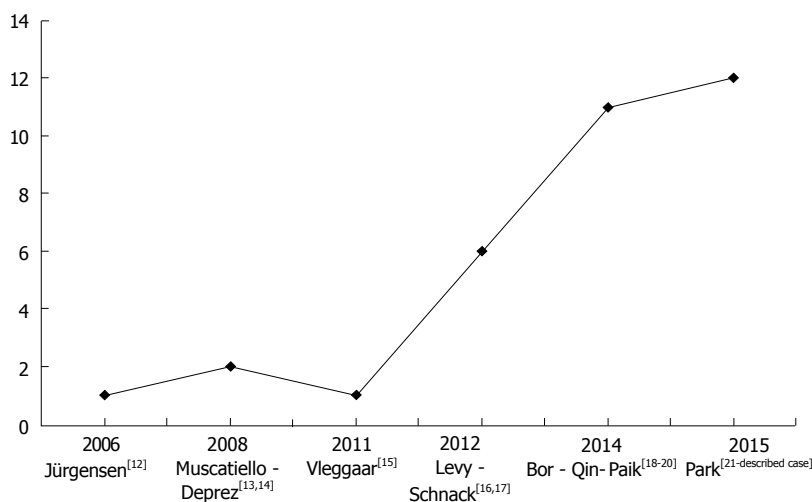


Figure 5 Reported endoscopic ultrasound-guided ethanol ablation procedures over time. Literature review showed a progressive increase of performed procedures from 2006 to 2015. Cases described in abstract form by Paik *et al.*^[20] were not included in the final results analysis.

resection.

In the recent decades, EUS has evolved into a useful therapeutic tool for treating a broad range of tumours. EUS-guided injection has been applied both as a pancreatic cancer treatment aimed at controlling pain through nerve blockade as well as a solid tumour therapy for the introduction of brachytherapy seeds and viral vectors or as a tool for ablation therapy^[10,11]. The pNET EUS-guided ethanol ablation is a new, less invasive therapeutic option although it remains rare.

A PubMed literature review showed 26 patients affected by small pNETs (maximum diameter of 21 mm) who underwent EUS-guided ethanol ablation^[12-21] including 19 functioning and 10 non-functioning tumours (Table 2). The number of patients treated by this technique progressively increased from 2006 to 2015 (Figure 5).

Conscious sedation is generally reported during the procedure. A mean hospitalization time of 2 d/session is usually necessary even in the absence of complications.

Technical success is reported in 100% of cases; a 22 or 25 gauge needle was generally used to inject a small volume of ethanol with a range between 0.2 and 8 mL per session. The choice of ethanol volume is a

function of tumour size. For small (≤ 20 mm) tumours, Qin *et al.*^[19] suggested that the volume be calculated as follows. For round tumours, the volume of ethanol corresponds to half the tumour size; for oval or irregular tumours, the volume of ethanol is (major axis + minor axis of the tumour)/2. A 1.0 mL syringe should be used for precise injection.

In terms of therapeutic outcomes, differentiation of functioning and non-functioning tumours seems to be very important. For small functioning symptomatic G1 tumours, the aim of the ablation is the symptom relief. For non-functioning tumours, the treatment goal is complete ablation of the lesion as confirmed by imaging.

Including the case here described, this technique achieved clinical success (complete symptom resolution) in 100% of 19 functioning tumours with a mean follow-up of 13.6 mo (range 2-38). Ethanol ablation is less effective for non-functioning tumours with a reported success (complete radiological ablation) of 70% (7/10 tumours were ablated, one lost to follow-up) with a mean follow-up of 13.4 mo (range 3-24) (Table 2). The reason is unclear but it might be due to a "debulking" effect in functioning ones, resulting in loss of endocrine

Table 2 Patient demographic information and baseline characteristics of the tumours

No. of patients ¹	27
Age, yr	
Mean (range)	59 (27-89)
Sex, male/female	10-17
No. of tumors	30
Functioning	19
Non functioning	11
Type of functioning tumor	
Insulinoma	18
Vipoma	1
Diameter, mm	
Mean (range)	12.5 (5-22)

¹Including described case.**Table 3 Procedural outcomes**

No. of treatment session per tumor	
Mean (range)	1.43 (1-3)
Alcohol volume, mL	
Mean (range)	1.83 (0.18-8)
Technical success, <i>n</i> (%)	30/30 (100)
Clinical success ¹ , <i>n</i> (%)	
Functioning	19/19 (100)
Non functioning ²	7/10 (70)
Adverse events ³ , <i>n</i> (%)	11 (25.5)
Early (within one week), <i>n</i> (%)	9 (21)
Pancreatic necrotic lesion	1 (2.3)
Mild pancreatitis	7 (16.2)
Abdominal pain	1 (2.3)
Late, <i>n</i> (%)	2 (4.6)
Hematoma and ulceration of the duodenal wall	1 (2.3)
Main pancreatic duct stricture	1 (2.3)
Follow-up, mo	
Mean (range)	13.4 (2-38)

¹Clinical success: Symptom resolution for functioning tumours and radiological ablation for non-functioning tumour; ²One non functioning tumor was lost to follow-up; ³Adverse events percentage is intended in relation to procedure number.

secretion, although with persistent viable tissue, or to a more aggressive histological grading of non-functioning tumours. Unfortunately, lesion grading was not available in most of the reviewed cases.

Few early complications (within one week) are reported: 7 mild pancreatitis cases were observed (16.2%) out of 43 procedures. One (2.3%) major early complication was described^[13]: A pancreatic necrotic lesion that was likely caused by ethanol effusion. It was managed by laparoscopic necrosectomy.

Two (4.6%) late complications occurred: One hematoma and ulceration of the duodenal wall^[14] and main pancreatic duct stricture^[21]. These were managed by endoscopic retrograde cholangiopancreatography and stent placement (Table 3).

In our case, we achieved a diagnosis of a non-functioning pNET with moderate dysplasia, grade (G2), established on the basis of biopsy (Ki67 > 5%) in a 58-year-old male who refused surgery. We decided to

ablate based both on the grading and the age of the patient. Moreover it is worth noting that FNA cytology may underestimate the staging based on surgical specimens. Physicians should be very cautious in using FNA specimens to classify a tumour as low-grade^[22]. Consequently our treatment aimed at the complete ablation of the lesion while sparing the pancreatic parenchyma. The nodule we treated had a cystic central component, which has not yet been described in the literature for pNET EUS-guidance ablation. A technique similar to that described for cystic neoplasm ablation (ethanol injection and reaspiration) was used.

In conclusion, based on our case study and literature review, we find that this technique is feasible, relatively safe and efficient when applied to symptom relief in functioning tumours. However, the long-term outcomes remain unknown. For non-functioning tumours, it can provide good results for patients unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients is still undefined and larger comparative studies with long-term follow-up are needed to assess its role.

COMMENTS

Case characteristics

The authors describe a procedure of eus guided ethanol ablation along three sessions for a cystic pancreatic neuroendocrine tumours (pNET).

Clinical diagnosis

Incidental focal lesion of the pancreatic tail with endoscopic ultrasound (EUS) "bull's eye appearance" and peripheral hypervascularization, suspicious for neuroendocrine tumour.

Differential diagnosis

Other focal lesions of the pancreas.

Laboratory diagnosis

No lab abnormality including levels of carcinoembryonic antigen and carbohydrate antigen, but recent onset of glucose intolerance.

Imaging diagnosis

Abdominal ultrasound, endoscopic ultrasound, magnetic resonance, EUS guided FNA.

Pathological diagnosis

Neuroendocrine tumor, G2, Ki67 proliferative index > 5%.

Treatment

The authors treated the patient by EUS-guided ethanol injection along three sessions.

Related reports

For patients unfit for surgery due to high-risk comorbidity or for those who refuse resection EUS-guided ethanol ablation has been reported in a few cases.

Term explanation

pNETS: Pancreatic neuroendocrine tumours; EUS: Endoscopic ultrasound.

Experiences and lessons

The authors find that EUS guided ethanol ablation is relatively safe and efficient

for the treatment of pNETs in patients unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients is still undefined.

Peer-review

A well written paper having a clear endpoint and objectives. The review of the literature is complete and presented in an attractive way.

REFERENCES

- 1 **Clift AK**, Frilling A. Management of patients with hepatic metastases from neuroendocrine tumors. *Ann Saudi Med* 2014; **34**: 279-290 [PMID: 25811199 DOI: 10.5144/0256-4947.2014.279]
- 2 **de Baere T**, Deschamps F, Tselikas L, Ducreux M, Planchard D, Pearson E, Berdelou A, Leboulleux S, Elias D, Baudin E. GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETS. *Eur J Endocrinol* 2015; **172**: R151-R166 [PMID: 25385817 DOI: 10.1530/EJE-14-0630]
- 3 **Metz DC**, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 2008; **135**: 1469-1492 [PMID: 18703061 DOI: 10.1053/j.gastro.2008.05.047]
- 4 **Partelli S**, Maurizi A, Tamburrino D, Baldoni A, Polenta V, Crippa S, Falconi M. GEP-NETS update: a review on surgery of gastroentero-pancreatic neuroendocrine tumors. *Eur J Endocrinol* 2014; **171**: R153-R162 [PMID: 24920289 DOI: 10.1530/EJE-14-0173]
- 5 **Zhang WY**, Li ZS, Jin ZD. Endoscopic ultrasound-guided ethanol ablation therapy for tumors. *World J Gastroenterol* 2013; **19**: 3397-3403 [PMID: 23801831 DOI: 10.3748/wjg.v19.i22.3397]
- 6 **de Wilde RF**, Edil BH, Hruban RH, Maitra A. Well-differentiated pancreatic neuroendocrine tumors: from genetics to therapy. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 199-208 [PMID: 22310917 DOI: 10.1038/nrgastro.2012.9]
- 7 **Bettini R**, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, Scarpa A, Falconi M. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery* 2011; **150**: 75-82 [PMID: 21683859 DOI: 10.1016/j.surg.2011.02.022]
- 8 **Falconi M**, Zerbi A, Crippa S, Balzano G, Boninsegna L, Capitanio V, Bassi C, Di Carlo V, Pederzoli P. Parenchyma-preserving resections for small nonfunctioning pancreatic endocrine tumors. *Ann Surg Oncol* 2010; **17**: 1621-1627 [PMID: 20162460 DOI: 10.1245/s10434-010-0949-8]
- 9 **Pitt SC**, Pitt HA, Baker MS, Christians K, Touzios JG, Kiely JM, Weber SM, Wilson SD, Howard TJ, Talamonti MS, Rikkers LF. Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? *J Gastrointest Surg* 2009; **13**: 1692-1698 [PMID: 19548038 DOI: 10.1007/s11605-009-0946-z]
- 10 **Wiechowska-Kozłowska A**, Boer K, Wójcicki M, Milkiewicz P. The efficacy and safety of endoscopic ultrasound-guided celiac plexus neurolysis for treatment of pain in patients with pancreatic cancer. *Gastroenterol Res Pract* 2012; **2012**: 503098 [PMID: 22474439 DOI: 10.1155/2012/503098]
- 11 **Jin Z**, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy* 2008; **40**: 314-320 [PMID: 18283622 DOI: 10.1055/s-2007-995476]
- 12 **Jürgensen C**, Schuppan D, Naser F, Ernstberger J, Junghans U, Stölzel U. EUS-guided alcohol ablation of an insulinoma. *Gastrointest Endosc* 2006; **63**: 1059-1062 [PMID: 16733126]
- 13 **Muscattello N**, Salcuni A, Macarini L, Cignarelli M, Prencipe S, di Maso M, Castriota M, D'Agnessa V, Ierardi E. Treatment of a pancreatic endocrine tumor by ethanol injection guided by endoscopic ultrasound. *Endoscopy* 2008; **40** Suppl 2: E258-E259 [PMID: 19090457 DOI: 10.1055/s-2007-966962]
- 14 **Deprez PH**, Claessens A, Borbath I, Gigot JF, Maitre D. Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma. *Acta Gastroenterol Belg* 2008; **71**: 333-337 [PMID: 19198582]
- 15 **Vleggaar FP**, Bij de Vaate EA, Valk GD, Leguit RJ, Siersema PD. Endoscopic ultrasound-guided ethanol ablation of a symptomatic sporadic insulinoma. *Endoscopy* 2011; **43** Suppl 2 UCTN: E328-E329 [PMID: 22020710 DOI: 10.1055/s-0030-1256775]
- 16 **Levy MJ**, Thompson GB, Topazian MD, Callstrom MR, Grant CS, Vella A. US-guided ethanol ablation of insulinomas: a new treatment option. *Gastrointest Endosc* 2012; **75**: 200-206 [PMID: 22078104 DOI: 10.1016/j.gie.2011.09.019]
- 17 **Schnack C**, Hansen CØ, Beck-Nielsen H, Mortensen PM. Treatment of insulinomas with alcoholic ablation. *Ugeskr Laeger* 2012; **174**: 501-502 [PMID: 22348674]
- 18 **Bor R**, Farkas K, Bálint A, Molnár T, Nagy F, Valkusz Z, Sepp K, Tiszlavicz L, Hamar S, Szepes Z. [Endoscopic ultrasound-guided ethanol ablation: an alternative option for the treatment of pancreatic insulinoma]. *Orv Hetil* 2014; **155**: 1647-1651 [PMID: 25282110 DOI: 10.1556/OH.2014.30012]
- 19 **Qin SY**, Lu XP, Jiang HX. EUS-guided ethanol ablation of insulinomas: case series and literature review. *Medicine (Baltimore)* 2014; **93**: e85 [PMID: 25255024 DOI: 10.1097/MD.0000000000000085]
- 20 **Paik WH**, Seo DW, Dhir VK, Wang HPO. Mo1373 EUS-Guided Ethanol Ablation of Small Solid Pancreatic Neoplasm. *Gastrointest Endosc* 2014; **79** Suppl 5: Page AB413 [DOI: 10.1016/j.gie.2014.02.550]
- 21 **Park do H**, Choi JH, Oh D, Lee SS, Seo DW, Lee SK, Kim MH. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. *Clin Endosc* 2015; **48**: 158-164 [PMID: 25844345 DOI: 10.5946/ce.2015.48.2.158]
- 22 **Vinayek R**, Capurso G, Larghi A. Grading of EUS-FNA cytologic specimens from patients with pancreatic neuroendocrine neoplasms: it is time move to tissue core biopsy? *Gland Surg* 2014; **3**: 222-225 [PMID: 25493252 DOI: 10.3978/j.issn.2227-684X.2014.07.03]

P- Reviewer: Ghosn M, Sadik R S- Editor: Ji FF
L- Editor: A E- Editor: Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 February 25; 8(4): 198-251





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

Contents

Biweekly Volume 8 Number 4 February 25, 2016

EDITORIAL

- 198 Role of colonic stents in the management of colorectal cancers
Sagar J

TOPIC HIGHLIGHT

- 205 Endoscopic hemostasis state of the art - Nonvariceal bleeding
Gölder SK, Brückner J, Messmann H
- 212 Endoscopic management of esophageal stenosis in children: New and traditional treatments
Dall'Oglio L, Caldaro T, Foschia F, Faraci S, Federici di Abriola G, Rea F, Romeo E, Torroni F, Angelino G, De Angelis P

REVIEW

- 220 Role of endoscopic retrograde cholangiopancreatography in the management of benign biliary strictures: What's new?
Ferreira R, Loureiro R, Nunes N, Santos AA, Maio R, Cravo M, Duarte MA

ORIGINAL ARTICLE

Prospective Study

- 232 Efficiency and patient experience with propofol vs conventional sedation: A prospective study
Thornley P, Al Beshir M, Gregor J, Antoniou A, Khanna N

SYSTEMATIC REVIEWS

- 239 Peroral endoscopic reduction of dilated gastrojejunal anastomosis after bariatric surgery: Techniques and efficacy
Changela K, Ofori E, Duddempudi S, Anand S, Singhal S

CASE REPORT

- 244 Gastric adenocarcinoma of fundic gland type: Endoscopic and clinicopathological features
Tohda G, Osawa T, Asada Y, Dochin M, Terahata S

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 4 February 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Erman Aytac, MD, Academic Fellow, Department of Colorectal Surgery, Cleveland Clinic, Digestive Disease Institute, Cleveland, OH 44106, United States

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Dan Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
February 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Role of colonic stents in the management of colorectal cancers

Jayesh Sagar

Jayesh Sagar, Department of Surgery, Medway Maritime Hospital, Gillingham ME7 5NY, United Kingdom

Author contributions: Sagar J conceived the issues which formed the contents of the manuscript and wrote the manuscript.

Conflict-of-interest statement: The author has no conflict of interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Jayesh Sagar, DNB, FRCS (Ed), MD, Surgeon, Department of Surgery, Medway Maritime Hospital, Windmill Rd, Gillingham ME7 5NY, United Kingdom. jsagar_2001@yahoo.com
Telephone: +44-7875-104480

Received: August 14, 2015
Peer-review started: August 22, 2015
First decision: October 13, 2015
Revised: December 7, 2015
Accepted: December 18, 2015
Article in press: December 21, 2015
Published online: February 25, 2016

Abstract

Colorectal cancer is one of the commonly encountered cancers across the Western World. In United Kingdom, this constitutes third most common ranked cancer and second most common ranked cause of cancer related deaths. Its acute presentation as a malignant colonic obstruction imposes challenges in its management. Colonic stent has been used for many years to alleviate

acute obstruction in such cases allowing optimisation of patient's physiological status and adequate staging of cancer. In this review, current literature evidence regarding use of colonic stent in acute malignant colonic obstruction is critically appraised and recommendations on the use of colonic stent are advocated.

Key words: Colorectal; Cancer; Surgery; Emergency; Stent

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Although colonic stents have been used for years to treat acute malignant colonic obstructions, current evidence based on the systematic review and randomised controlled trials do raise concerns about its impact on the long term outcomes. Its use has not been recommended in acute suspected malignant colonic obstruction as a bridge to surgery due to evidence of its impact on recurrence rates; however there is enough evidence to suggest its use as a palliation. In patients with multiple co-morbidities with high American Society of Anaesthesiologists grades, colonic stent may be considered as an alternative option to emergency surgical procedure as a bridge.

Sagar J. Role of colonic stents in the management of colorectal cancers. *World J Gastrointest Endosc* 2016; 8(4): 198-204
Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/198.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.198>

BACKGROUND

Colorectal cancer is one of the commonly encountered cancers across the Western World. In United Kingdom, it constitutes third most common ranked cancer and second most common ranked cause of cancer

related deaths. Although surgical intervention remains the mainstay of treatment for colorectal cancers, radiotherapy and chemotherapy do have role especially in locally advanced and metastatic disease. With the implementation of colorectal screening programme, presentation at an early stage is expected with better outcome. However, about 8%-13% of patients with colorectal cancers presents with acute colonic obstruction^[1-3]. In elective settings, individual would undergo adequate staging of cancer before initiation of treatment in a controlled environment, but acutely presenting patients with colonic obstruction need immediate intervention to relieve the obstruction. Thus this group of patients represents challenges to the colorectal team as emergency surgery in these patients either in the form of defunctioning stoma or primary resection is related with significantly high complications and mortality and in some cases, inadequate treatment. The alternative approach would be to stent the obstructing lesion to alleviate the obstruction. This would allow adequate time to stage the disease, achieve best optimal health status of the patient and initiation of any neoadjuvant treatment. However, there have been controversies about the use of stent in the management of acute suspected malignant colonic obstruction. Recently, European Society of Gastrointestinal Endoscopy has published the guidelines regarding the use of colonic stent in acute malignant colorectal obstruction^[4].

ANATOMICAL LIMITATIONS

Although colonic stents can be placed in any part of colon, considering the alternative surgical approach in the form of primary resection and anastomosis, colonic stents are usually preferred in left sided colonic obstructions. Until recently, the reported randomised controlled studies (RCT) comparing stenting vs emergency surgery for malignant colonic obstruction omitted colonic lesions proximal to splenic flexure except one^[5]. Similarly, all published RCTs except one^[5] had excluded rectal cancers from their study population due to known higher failure rates and complication rates. Apart from colonic obstruction from colorectal pathology, extra colonic pathology including carcinomatosis peritonei can also cause colonic obstruction. In these cases, colonic stenting may be considered for palliative purposes but this is associated with lower technical and clinical success rates and higher complication rates^[6-8]. Regarding presence of inflammatory bowel disease (IBD) in conjunction with malignant colonic obstruction requiring colonic stent, there is no evidence as IBD would change approach to deal with malignant colonic obstruction as management of malignant obstruction would override the management of IBD, however one needs to be aware of existing disease in proximal or distal colon when considering surgical or stent option in these cases. This review mainly focused on the obstruction caused by primary colonic malignant pathology.

COLONIC STENT

Although there is much published regarding the use of colonic stents in suspected malignant colonic obstruction, there is no evidence of colonic stenting as prophylaxis in asymptomatic patients. Prophylactic stenting is not recommended due to potential risks associated with stenting. There have been reports suggesting less effectiveness of colonic stents in peritoneal carcinomatosis cases although there has not been any major study published looking at the role of colonic stenting in these cases. There are generally no contraindications for the colonic stenting except perforation of colon. The only absolute contraindication for colonic stenting is colonic perforation. Outcomes following stent placement are not affected by patient's age and American Society of Anaesthesiologists (ASA)/physiological status^[9-14] as they are the main two risk factors predicting mortality and morbidity with any procedure. Pre-stenting investigation in the form of computed tomography (CT) with contrast enhancement is the investigation of choice with a sensitivity of 96% and specificity of 93%. It also helps to define the aetiology in 81% of cases and level of stenosis in 94% of cases. There is an added advantage of local lymphovascular and distant staging of tumour. Flexible sigmoidoscopy may be added in dubious diagnosis on CT scans. Synchronous colonic tumours are present in around 3%-4% of patients with colonic cancers^[15-18]. Knowledge of these synchronous lesions may change the definitive treatment of colonic cancers. However, routine adequate imaging with CT colonography or visualisation with colonoscopy to detect these synchronous lesions is not feasible in acute presentations and is not recommended. If patient receives successful colonic stent, colonoscopy through stent or CT colonography can be considered as a safe procedure^[19-22] to look for any synchronous lesions. In cohort of patients diagnosed with suspected malignant colonic obstructions, there would be few patients with benign cause of their obstructions. In two RCTs, the benign obstructive lesion was found in 4.6%^[23] and 8.2%^[24] of patients suspected of malignant obstructions. As definitive pathological confirmation in acute situation is not feasible, if indicated, stenting should be performed in suspected malignant obstruction without waiting for pathological diagnosis. Brush cytology or tissue biopsy can be obtained during stent placement if possible, however if there is any risk of obscuring views due to bleeding following biopsy, it can be deferred for a later time. In contrast to malignant pathology, stenting should be avoided in suspected diverticular strictures or obstruction due to high risk of perforation^[25]. However, the risk of having underlying malignant lesion in patients with diagnosed diverticulitis on CT scan was quoted to be 2.1% in one systematic review^[26].

Bowel preparation is debatable before stent placement considering the obstructive nature of the disease and there are no published reports related with the use of bowel preparation in such cases. In most of these

patients, although colon distal to obstruction is usually empty due to peristaltic movements, an enema can be used to facilitate visualisation before stent procedure. Antibiotic prophylaxis during stent placement is not indicated due to very low incidence of clinical manifestation of bacteraemia^[13,27]. Colonic stent placement can be achieved either endoscopically or radiologically but combination of endoscopy and fluoroscopy is recommended. Retrospective studies have reported similar success rates following endoscopic and radiologically placed stents but have shown greater technical success rates with combination technique^[14,28-30]. There is also definitive learning curve for an endoscopist to perform colonic stents. Couple of noncomparative studies suggested performance of at least 20 procedures with increased technical success rate and reduction in the number of used stents by endoscopist^[31,32]. There is some suggestion that endoscopists experienced in therapeutic endoscopic retrograde cholangiopancreatography would benefit from translating skills in stent placement procedures^[13]. Dilatation of colonic obstructing stricture is not recommended due to high risk of perforation^[29,33,34] but this recommendation is based on retrospective studies only.

The available colonic stents can be divided broadly in to two groups, covered and bare or uncovered stents. The potential factors responsible for success of stent insertion also include length and diameter of stent. Two met analysis comparing covered stents against bare stents showed no difference in technical and clinical success and complication rates, however, bare stents had significantly higher tumour ingrowth rates but had lower migration rates^[35,36]. Smaller body diameter stents (< 24 mm) are associated with higher migration rates^[13,37-39]. Considering the shortening after stent deployment, it is recommended to use long enough stent, in addition to the length of obstruction, to cover at least 2 cm on either ends^[40]. There is evidence of no difference in outcomes among different stent designs^[41-46]. The other major factor that affects stent outcomes is stentability of the obstruction. There is evidence that success rates are high in short segment obstructions with higher technical and clinical failures in obstructions > 4 cm^[38,47]. Similarly, although the clinical and technical success rates were similar in complete and impending (subtotal) obstruction, complication rates, especially perforation were higher in complete obstruction^[48].

COLONIC STENTS AS A BRIDGE TO SURGERY

Although colonic stenting seems to be an apparent management option for acute large bowel obstruction in potentially curable and resectable cases, there has always been controversy about their use as a bridge to surgery. Due to an ability to convert an emergency condition to elective situation permitting opportunities for staging and optimisation of patient's condition, stent

seems a viable option, however current evidence failed to show its superiority over traditional surgical options. Eight systematic reviews^[49-56] and seven randomised controlled trials^[23,24,57-61] have been published in last few years comparing emergency surgery with pre-operative colonic stenting for acute suspected malignant colonic obstruction. Two of the randomised controlled trials were closed prematurely due to higher complication rate in the stent group^[23,24] while one was closed early due to high complication rate in the surgical patients^[60].

The most recently published systematic review performed meta-analysis of all published seven randomised controlled trials covering more than 180 patients in each group^[49]. Mean technical success rate of 76.9% was achieved following stent placement. There was no difference in post procedure/surgical mortality in either group but overall complication rate and permanent stoma rate were noted to be lower in the stent group. The primary anastomosis rate was also high in stent group. The outcomes regarding cost effectiveness of stents were unclear. From this systematic review, it is clear that colonic stenting in acute setting has some definitive advantages compared to emergency surgery. However, one needs to consider long term impact of colonic stent insertion in terms of oncological outcomes, especially in cases of curable and resectable cancers at presentation.

There has been some trepidation raised regarding the impaired oncological outcomes following placement of colonic stents in patient having potentially curable cancer. This concern increases more so with potential complication in the form of perforation. Three randomised controlled trials have compared the medium term oncological outcomes subsequent to stent placement till the surgery vs primary surgical resection^[58,60,62]. All of these trials were of small sample size and comparatively shorter follow-up periods. The Chinese study included 48 patients; 24 offered stents till the surgery and 24 offered emergency surgical procedure^[58]. In this study, two of 13 patients in surgery arm and 11 of 22 patients in stent arm who had curative resection developed recurrent disease. However there was wide gap in the median follow-up period; 32 mo in open surgery group and 65 mo in stent group, this difference did not reach statistical significance. The 5-year overall survival rate was 27% and 48% in open surgery and stent groups respectively although it was statistically insignificant. The Spanish study included 28 patients; 15 in stent arm and 13 in surgery arm^[60]. Although this study was closed prematurely due to high rate of complications in the form of anastomotic leak in the surgical group, the disease recurrence was noted in eight out of 15 cases in stent arm and two out of 13 cases in surgical group at mean follow-up of 37.6 mo but this was not statistically significant. The third study represents outcomes of Dutch stent in 2 trial^[62]. This included follow-up of patients who had only curative treatment. It had 32 patients in emergency surgery arm and 26 in stent arm. The median follow-up was 36 and 38 mo respectively. Five-

year overall recurrence rate was 25% (8 patients of 32) in surgery arm and was 42% (11 of 26) in stent group. Local recurrence rate was 9% (3 out of 32) in surgery group and was 19% (5 out of 26) in stent group. Although overall five-year recurrence rate was statistically significant, local recurrence rate failed to reach that. The cumulative overall recurrence rate was 83% in patients with clinical or subclinical stent related perforation and was statistically significantly higher compared to emergency surgery group and non-perforated stent group.

The above findings made one to rethink about the use of these stent in acute suspected malignant colonic obstruction as a bridge till surgery in cases with potentially resectable and treatable tumours. Although the above studies had small number of patients and the follow-up period was variable and not long, it seems obvious that placement of these stent is not without its potential adverse impact in form of higher local and overall recurrence rates. These findings were supported by another large comparative prospective study showing higher local recurrence rates in stented patients aged ≤ 75 years^[63]. Until we have results from large number of patients with adequately designed randomised controlled trial, the oncological outcomes of stents needs to be weighed against the outcomes following emergency surgical intervention. As published studies did not reveal any significant difference in postoperative mortality and morbidity in either group, colonic stent cannot be recommended as a bridge till surgery in acute suspected malignant colonic obstruction. However, if surgical risks outweighs the long term benefits as in patients with increasing age, multiple co-morbidities and increasing ASA, stents can be considered as an alternative option. If colonic stent is used as a bridge till surgery, optimal time interval of five to ten days should be considered between stent placement and resection surgery^[52]. This is based on the facts that this time would allow patient to recover his/her physical and nutritional status. If resection surgery is delayed longer, it would impose more challenges performing surgical resection due to maturing of scar tissues, especially when considering laparoscopic resections.

COLONIC STENT AS A PALLIATION

It is getting clearer from above discussion that although colonic stent is not recommended as a bridge to surgery, it obviously has a role in the palliation. Two published meta-analysis including randomised and non-randomised comparative studies compared the colonic stent and emergency surgery as palliation^[64,65]. The clear advantages of lower postoperative mortality, reduced intensive and overall hospital stay with earlier start of chemotherapy were evident in the stent arm but the clinical success rate was statistically significantly higher in surgery arm. There was no statistically significant difference in the post-operative complications; early complications were more common in surgery arm while late complications were reported more frequently in stent arm. Although the

technical success rate in stent arm was 88% to 100%, colonic perforation, stent migration and re-obstruction were reported complications. These findings favour colonic stents in a palliative setting in acutely presented suspected malignant large bowel obstruction.

Successful deployment of colonic stents in these cases allows the advantage of starting chemotherapy at an earlier stage. However, chemotherapy also raises the suspicion of increased complication rates of stent placement, especially of colonic perforation. Several retrospective studies have reported increased stent related colonic perforation in patients who were treated with bevacizumab^[13,38,66]. Single meta-analysis published significantly higher rate of colonic perforation in patients who were on bevacizumab in comparison to those who were on chemotherapy without bevacizumab or not on chemotherapy at all^[34]. As the newer anti-angiogenic drugs such as regorafenib and aflibercept work alike bevacizumab, colonic stenting is not recommended in patients who are considered for treatment with anti-angiogenic agents. Clinically, this may impose difficulty as presentation of acute large bowel obstruction may be patients' first clinical presentation and it would be difficult to assess their suitability for chemotherapy with antiangiogenic agents at that time. However, patients presenting as an acute large bowel obstruction with known colonic cancer and on anti-angiogenic agents are not recommended to have colonic stent. There is limited evidence of increased stent related complications in patients who are already on chemotherapy without anti-angiogenic agents before stent placement however tumour shrinkage leading to stent migration due to chemotherapy may be a concern. Apart from stent related perforation, stent failure, re-obstruction and stent migration, other common potential complications include pain, tenesmus, incontinence and fistula formation. When used as a palliation, re-stenting is a viable option in expert hands in cases of stent migration or obstruction.

CONCLUSION

Colonic stents are associated with lower mortality and morbidity compared to emergency surgery in cases of acute suspected malignant large bowel obstruction. However, current evidence does not recommend use of colonic stent as a bridge till surgery in these cases but it is a preferred treatment to relieve obstruction in palliative settings. In patients with multiple medical co-morbidities, poor performance status and increased ASA, colonic stent can be considered as an alternative option as a bridge till surgery but careful discussion with patients about potential adverse impact on long term oncological outcomes is recommended.

REFERENCES

- 1 Winner M, Mooney SJ, Hershman DL, Feingold DL, Allendorf JD, Wright JD, Neugut AI. Incidence and predictors of bowel

- obstruction in elderly patients with stage IV colon cancer: a population-based cohort study. *JAMA Surg* 2013; **148**: 715-722 [PMID: 23740130 DOI: 10.1001/jamasurg.2013.1]
- 2 **Jullumstrø E**, Wibe A, Lydersen S, Edna TH. Colon cancer incidence, presentation, treatment and outcomes over 25 years. *Colorectal Dis* 2011; **13**: 512-518 [PMID: 20128833 DOI: 10.1111/j.1463-1318.2010.02191.x]
 - 3 **Cheyne N**, Cortet M, Lepage C, Benoit L, Faivre J, Bouvier AM. Trends in frequency and management of obstructing colorectal cancers in a well-defined population. *Dis Colon Rectum* 2007; **50**: 1568-1575 [PMID: 17687610 DOI: 10.1007/s10350-007-9007-4]
 - 4 **van Hooft JE**, van Halsema EE, Vanbiervliet G, Beets-Tan RG, DeWitt JM, Donnellan F, Dumonceau JM, Glynne-Jones RG, Hassan C, Jiménez-Perez J, Meisner S, Muthusamy VR, Parker MC, Regimbeau JM, Sabbagh C, Sagar J, Tanis PJ, Vandervoort J, Webster GJ, Manes G, Barthet MA, Repici A. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Gastrointest Endosc* 2014; **80**: 747-761.e1-e75 [PMID: 25436393 DOI: 10.1016/j.gie.2014.09.018]
 - 5 **Fiori E**, Lamazza A, De Cesare A, Bononi M, Volpino P, Schillaci A, Cavallaro A, Cangemi V. Palliative management of malignant rectosigmoidal obstruction. Colostomy vs. endoscopic stenting. A randomized prospective trial. *Anticancer Res* 2004; **24**: 265-268 [PMID: 15015606]
 - 6 **Kim JY**, Kim SG, Im JP, Kim JS, Jung HC. Comparison of treatment outcomes of endoscopic stenting for colonic and extracolonic malignant obstruction. *Surg Endosc* 2013; **27**: 272-277 [PMID: 22773238 DOI: 10.1007/s00464-012-2439-5]
 - 7 **Dronamraju SS**, Ramamurthy S, Kelly SB, Hayat M. Role of self-expanding metallic stents in the management of malignant obstruction of the proximal colon. *Dis Colon Rectum* 2009; **52**: 1657-1661 [PMID: 19690497 DOI: 10.1007/DCR.0b013e3181a8f4af]
 - 8 **Keswani RN**, Azar RR, Edmundowicz SA, Zhang Q, Ammar T, Banerjee B, Early DS, Jonnalagadda SS. Stenting for malignant colonic obstruction: a comparison of efficacy and complications in colonic versus extracolonic malignancy. *Gastrointest Endosc* 2009; **69**: 675-680 [PMID: 19251009 DOI: 10.1016/j.gie.2008.09.009]
 - 9 **Abbott S**, Eglinton TW, Ma Y, Stevenson C, Robertson GM, Frizelle FA. Predictors of outcome in palliative colonic stent placement for malignant obstruction. *Br J Surg* 2014; **101**: 121-126 [PMID: 24301218 DOI: 10.1002/bjs.9340]
 - 10 **Meisner S**, González-Huix F, Vandervoort JG, Goldberg P, Casellas JA, Roncero O, Grund KE, Alvarez A, García-Cano J, Vázquez-Astray E, Jiménez-Pérez J. Self-expandable metal stents for relieving malignant colorectal obstruction: short-term safety and efficacy within 30 days of stent procedure in 447 patients. *Gastrointest Endosc* 2011; **74**: 876-884 [PMID: 21855868 DOI: 10.1016/j.gie.2011.06.019]
 - 11 **Choi JH**, Lee YJ, Kim ES, Choi JH, Cho KB, Park KS, Jang BK, Chung WJ, Hwang JS. Covered self-expandable metal stents are more associated with complications in the management of malignant colorectal obstruction. *Surg Endosc* 2013; **27**: 3220-3227 [PMID: 23494513 DOI: 10.1007/s00464-013-2897-4]
 - 12 **Donnellan F**, Cullen G, Cagney D, O'Halloran P, Harewood GC, Murray FE, Patchett SE. Efficacy and safety of colonic stenting for malignant disease in the elderly. *Int J Colorectal Dis* 2010; **25**: 747-750 [PMID: 20213457 DOI: 10.1007/s00384-010-0917-6]
 - 13 **Small AJ**, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. *Gastrointest Endosc* 2010; **71**: 560-572 [PMID: 20189515 DOI: 10.1016/j.gie.2009.10.012]
 - 14 **Geraghty J**, Sarkar S, Cox T, Lal S, Willert R, Ramesh J, Bodger K, Carlson GL. Management of large bowel obstruction with self-expanding metal stents. A multicentre retrospective study of factors determining outcome. *Colorectal Dis* 2014; **16**: 476-483 [PMID: 24506142 DOI: 10.1111/codi.12582]
 - 15 **Kodeda K**, Nathanaelsson L, Jung B, Olsson H, Jestin P, Sjövall A, Glimelius B, Pahlman L, Syk I. Population-based data from the Swedish Colon Cancer Registry. *Br J Surg* 2013; **100**: 1100-1107 [PMID: 23696510 DOI: 10.1002/bjs.9166]
 - 16 **Mulder SA**, Kranse R, Damhuis RA, de Wilt JH, Ouwendijk RJ, Kuipers EJ, van Leerdam ME. Prevalence and prognosis of synchronous colorectal cancer: a Dutch population-based study. *Cancer Epidemiol* 2011; **35**: 442-447 [PMID: 21470938 DOI: 10.1016/j.canep.2010.12.007]
 - 17 **Latournerie M**, Jooste V, Cottet V, Lepage C, Faivre J, Bouvier AM. Epidemiology and prognosis of synchronous colorectal cancers. *Br J Surg* 2008; **95**: 1528-1533 [PMID: 18991301 DOI: 10.1002/bjs.6382]
 - 18 **Papadopoulos V**, Michalopoulos A, Basdanis G, Papapolychroniadis K, Paramythiotis D, Fotiadis P, Berovalis P, Harlaftis N. Synchronous and metachronous colorectal carcinoma. *Tech Coloproctol* 2004; **8** Suppl 1: s97-s100 [PMID: 15655657 DOI: 10.1007/s10151-004-0124-y]
 - 19 **Park SH**, Lee JH, Lee SS, Kim JC, Yu CS, Kim HC, Ye BD, Kim MJ, Kim AY, Ha HK. CT colonography for detection and characterisation of synchronous proximal colonic lesions in patients with stenosing colorectal cancer. *Gut* 2012; **61**: 1716-1722 [PMID: 22115824 DOI: 10.1136/gutjnl-2011-301135]
 - 20 **Cha EY**, Park SH, Lee SS, Kim JC, Yu CS, Lim SB, Yoon SN, Shin YM, Kim AY, Ha HK. CT colonography after metallic stent placement for acute malignant colonic obstruction. *Radiology* 2010; **254**: 774-782 [PMID: 20177092 DOI: 10.1148/radiol.09090842]
 - 21 **Lim SG**, Lee KJ, Suh KW, Oh SY, Kim SS, Yoo JH, Wi JO. Preoperative colonoscopy for detection of synchronous neoplasms after insertion of self-expandable metal stents in occlusive colorectal cancer: comparison of covered and uncovered stents. *Gut Liver* 2013; **7**: 311-316 [PMID: 23710312 DOI: 10.5009/gnl.2013.7.3.311]
 - 22 **Vitale MA**, Villotti G, d'Alba L, Frontespezi S, Iacopini F, Iacopini G. Preoperative colonoscopy after self-expandable metallic stent placement in patients with acute neoplastic colon obstruction. *Gastrointest Endosc* 2006; **63**: 814-819 [PMID: 16650544 DOI: 10.1016/j.gie.2005.12.032]
 - 23 **Pirlet IA**, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. *Surg Endosc* 2011; **25**: 1814-1821 [PMID: 21170659 DOI: 10.1007/s00464-010-1471-6]
 - 24 **van Hooft JE**, Bemelman WA, Oldenburg B, Marinelli AW, Lutke Holzik MF, Grubben MJ, Sprangers MA, Dijkgraaf MG, Fockens P. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol* 2011; **12**: 344-352 [PMID: 21398178 DOI: 10.1016/S1470-2045(11)70035-3]
 - 25 **Currie A**, Christmas C, Aldean H, Mobasher M, Bloom IT. Systematic review of self-expanding stents in the management of benign colorectal obstruction. *Colorectal Dis* 2014; **16**: 239-245 [PMID: 24033989 DOI: 10.1111/codi.12389]
 - 26 **Sai VF**, Velayos F, Neuhaus J, Westphalen AC. Colonoscopy after CT diagnosis of diverticulitis to exclude colon cancer: a systematic literature review. *Radiology* 2012; **263**: 383-390 [PMID: 22517956 DOI: 10.1148/radiol.12111869]
 - 27 **Chun YJ**, Yoon NR, Park JM, Lim CH, Cho YK, Lee IS, Kim SW, Choi MG, Choi KY, Chung IS. Prospective assessment of risk of bacteremia following colorectal stent placement. *Dig Dis Sci* 2012; **57**: 1045-1049 [PMID: 22057286 DOI: 10.1007/s10620-011-1962-x]
 - 28 **Kim JW**, Jeong JB, Lee KL, Kim BG, Jung YJ, Kim W, Kim HY, Ahn DW, Koh SJ, Lee JK. Comparison of clinical outcomes between endoscopic and radiologic placement of self-expandable metal stent in patients with malignant colorectal obstruction. *Korean J Gastroenterol* 2013; **61**: 22-29 [PMID: 23354346]
 - 29 **Sebastian S**, Johnston S, Geoghegan T, Torreggiani V, Buckley M. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. *Am J Gastroenterol* 2004; **99**: 2051-2057 [PMID: 15447772 DOI: 10.1111/j.1572-0241.2004.40017.x]

- 30 **de Gregorio MA**, Laborda A, Tejero E, Miguelena JM, Carnevale FC, de Blas I, Gimenez M, Maynar M, D'Agostino H. Ten-year retrospective study of treatment of malignant colonic obstructions with self-expandable stents. *J Vasc Interv Radiol* 2011; **22**: 870-878 [PMID: 21514839 DOI: 10.1016/j.jvir.2011.02.002]
- 31 **Williams D**, Law R, Pullyblank AM. Colorectal stenting in malignant large bowel obstruction: the learning curve. *Int J Surg Oncol* 2011; **2011**: 917848 [PMID: 22312531 DOI: 10.1155/2011/917848]
- 32 **Lee JH**, Yoon JY, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. The learning curve for colorectal stent insertion for the treatment of malignant colorectal obstruction. *Gut Liver* 2012; **6**: 328-333 [PMID: 22844560 DOI: 10.5009/gnl.2012.6.3.328]
- 33 **Khot UP**, Lang AW, Murali K, Parker MC. Systematic review of the efficacy and safety of colorectal stents. *Br J Surg* 2002; **89**: 1096-1102 [PMID: 12190673 DOI: 10.1046/j.1365-2168.2002.02148.x]
- 34 **van Halsema EE**, van Hooft JE, Small AJ, Baron TH, García-Cano J, Cheon JH, Lee MS, Kwon SH, Mucci-Hennekinne S, Fockens P, Dijkgraaf MG, Repici A. Perforation in colorectal stenting: a meta-analysis and a search for risk factors. *Gastrointest Endosc* 2014; **79**: 970-982.e7; quiz 983.e2, 983.e5 [PMID: 24650852 DOI: 10.1016/j.gie.2013.11.038]
- 35 **Zhang Y**, Shi J, Shi B, Song CY, Xie WF, Chen YX. Comparison of efficacy between uncovered and covered self-expanding metallic stents in malignant large bowel obstruction: a systematic review and meta-analysis. *Colorectal Dis* 2012; **14**: e367-e374 [PMID: 22540666 DOI: 10.1111/j.1463-1318.2012.03056.x]
- 36 **Yang Z**, Wu Q, Wang F, Ye X, Qi X, Fan D. A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. *Int J Med Sci* 2013; **10**: 825-835 [PMID: 23794946 DOI: 10.7150/ijms.5969]
- 37 **Kim BC**, Han KS, Hong CW, Sohn DK, Park JW, Park SC, Kim SY, Baek JY, Choi HS, Chang HJ, Kim DY, Oh JH. Clinical outcomes of palliative self-expanding metallic stents in patients with malignant colorectal obstruction. *J Dig Dis* 2012; **13**: 258-266 [PMID: 22500788 DOI: 10.1111/j.1751-2980.2012.00564.x]
- 38 **Manes G**, de Bellis M, Fuccio L, Repici A, Masci E, Ardizzone S, Mangiavillano B, Carlino A, Rossi GB, Occhipinti P, Cennamo V. Endoscopic palliation in patients with incurable malignant colorectal obstruction by means of self-expanding metal stent: analysis of results and predictors of outcomes in a large multicenter series. *Arch Surg* 2011; **146**: 1157-1162 [PMID: 22006874 DOI: 10.1001/archsurg.2011.233]
- 39 **Im JP**, Kim SG, Kang HW, Kim JS, Jung HC, Song IS. Clinical outcomes and patency of self-expanding metal stents in patients with malignant colorectal obstruction: a prospective single center study. *Int J Colorectal Dis* 2008; **23**: 789-794 [PMID: 18443807 DOI: 10.1007/s00384-008-0477-1]
- 40 **Baron TH**, Wong Kee Song LM, Repici A. Role of self-expandable stents for patients with colon cancer (with videos). *Gastrointest Endosc* 2012; **75**: 653-662 [PMID: 22341111 DOI: 10.1016/j.gie.2011.12.020]
- 41 **Yoon JY**, Jung YS, Hong SP, Kim TI, Kim WH, Cheon JH. Clinical outcomes and risk factors for technical and clinical failures of self-expandable metal stent insertion for malignant colorectal obstruction. *Gastrointest Endosc* 2011; **74**: 858-868 [PMID: 21862005 DOI: 10.1016/j.gie.2011.05.044]
- 42 **Kim JH**, Song HY, Li YD, Shin JH, Park JH, Yu CS, Kim JC. Dual-design expandable colorectal stent for malignant colorectal obstruction: comparison of flared ends and bent ends. *AJR Am J Roentgenol* 2009; **193**: 248-254 [PMID: 19542421 DOI: 10.2214/AJR.08.2003]
- 43 **Cheung DY**, Kim JY, Hong SP, Jung MK, Ye BD, Kim SG, Kim JH, Lee KM, Kim KH, Baik GH, Kim HG, Eun CS, Kim TI, Kim SW, Kim CD, Yang CH. Outcome and safety of self-expandable metallic stents for malignant colon obstruction: a Korean multicenter randomized prospective study. *Surg Endosc* 2012; **26**: 3106-3113 [PMID: 22609981 DOI: 10.1007/s00464-012-2300-x]
- 44 **Park JK**, Lee MS, Ko BM, Kim HK, Kim YJ, Choi HJ, Hong SJ, Ryu CB, Moon JH, Kim JO, Cho JY, Lee JS. Outcome of palliative self-expanding metal stent placement in malignant colorectal obstruction according to stent type and manufacturer. *Surg Endosc* 2011; **25**: 1293-1299 [PMID: 20976501 DOI: 10.1007/s00464-010-1366-6]
- 45 **Small AJ**, Baron TH. Comparison of Wallstent and Ultraflex stents for palliation of malignant left-sided colon obstruction: a retrospective, case-matched analysis. *Gastrointest Endosc* 2008; **67**: 478-488 [PMID: 18294511 DOI: 10.1016/j.gie.2007.08.043]
- 46 **García-Cano J**, González-Huix F, Juzgado D, Igea F, Pérez-Miranda M, López-Rosés L, Rodríguez A, González-Carro P, Yuguero L, Espinós J, Ducóns J, Orive V, Rodríguez S. Use of self-expanding metal stents to treat malignant colorectal obstruction in general endoscopic practice (with videos). *Gastrointest Endosc* 2006; **64**: 914-920 [PMID: 17140898 DOI: 10.1016/j.gie.2006.06.034]
- 47 **Jung MK**, Park SY, Jeon SW, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH, Kim GC, Ryeon HK. Factors associated with the long-term outcome of a self-expandable colon stent used for palliation of malignant colorectal obstruction. *Surg Endosc* 2010; **24**: 525-530 [PMID: 19597776 DOI: 10.1007/s00464-009-0604-2]
- 48 **Song HY**, Kim JH, Shin JH, Kim HC, Yu CS, Kim JC, Kang SG, Yoon CJ, Lee JY, Koo JH, Lee KH, Kim JK, Kim DH, Shin TB, Jung GS, Han YM. A dual-design expandable colorectal stent for malignant colorectal obstruction: results of a multicenter study. *Endoscopy* 2007; **39**: 448-454 [PMID: 17516352 DOI: 10.1055/s-2007-966270]
- 49 **Huang X**, Lv B, Zhang S, Meng L. Preoperative colonic stents versus emergency surgery for acute left-sided malignant colonic obstruction: a meta-analysis. *J Gastrointest Surg* 2014; **18**: 584-591 [PMID: 24170606 DOI: 10.1007/s11605-013-2344-9]
- 50 **Cennamo V**, Luigiano C, Coccolini F, Fabbri C, Bassi M, De Caro G, Ceroni L, Maimone A, Ravelli P, Ansaloni L. Meta-analysis of randomized trials comparing endoscopic stenting and surgical decompression for colorectal cancer obstruction. *Int J Colorectal Dis* 2013; **28**: 855-863 [PMID: 23151813 DOI: 10.1007/s00384-012-1599-z]
- 51 **Cirocchi R**, Farinella E, Trastulli S, Desiderio J, Listorti C, Boselli C, Parisi A, Noya G, Sagar J. Safety and efficacy of endoscopic colonic stenting as a bridge to surgery in the management of intestinal obstruction due to left colon and rectal cancer: a systematic review and meta-analysis. *Surg Oncol* 2013; **22**: 14-21 [PMID: 23183301 DOI: 10.1016/j.suronc.2012.10.003]
- 52 **De Ceglie A**, Filiberti R, Baron TH, Ceppi M, Conio M. A meta-analysis of endoscopic stenting as bridge to surgery versus emergency surgery for left-sided colorectal cancer obstruction. *Crit Rev Oncol Hematol* 2013; **88**: 387-403 [PMID: 23845505 DOI: 10.1016/j.critrevonc.2013.06.006]
- 53 **Tan CJ**, Dasari BV, Gardiner K. Systematic review and meta-analysis of randomized clinical trials of self-expanding metallic stents as a bridge to surgery versus emergency surgery for malignant left-sided large bowel obstruction. *Br J Surg* 2012; **99**: 469-476 [PMID: 22261931 DOI: 10.1002/bjs.8689]
- 54 **Ye GY**, Cui Z, Chen L, Zhong M. Colonic stenting vs emergent surgery for acute left-sided malignant colonic obstruction: a systematic review and meta-analysis. *World J Gastroenterol* 2012; **18**: 5608-5615 [PMID: 23112555 DOI: 10.3748/wjg.v18.i39.5608]
- 55 **Zhang Y**, Shi J, Shi B, Song CY, Xie WF, Chen YX. Self-expanding metallic stent as a bridge to surgery versus emergency surgery for obstructive colorectal cancer: a meta-analysis. *Surg Endosc* 2012; **26**: 110-119 [PMID: 21789642 DOI: 10.1007/s00464-011-1835-6]
- 56 **Sagar J**. Colorectal stents for the management of malignant colonic obstructions. *Cochrane Database Syst Rev* 2011; **(11)**: CD007378 [PMID: 22071835 DOI: 10.1002/14651858.CD007378.pub2]
- 57 **Ghazal AH**, El-Shazly WG, Bessa SS, El-Riwini MT, Hussein AM. Colonic endolumenal stenting devices and elective surgery versus emergency subtotal/total colectomy in the management of malignant obstructed left colon carcinoma. *J Gastrointest Surg* 2013; **17**: 1123-1129 [PMID: 23358847 DOI: 10.1007/s11605-013-2152-2]
- 58 **Tung KL**, Cheung HY, Ng LW, Chung CC, Li MK. Endo-

- laparoscopic approach versus conventional open surgery in the treatment of obstructing left-sided colon cancer: long-term follow-up of a randomized trial. *Asian J Endosc Surg* 2013; **6**: 78-81 [PMID: 23601995 DOI: 10.1111/ases.12030]
- 59 **Ho KS**, Quah HM, Lim JF, Tang CL, Eu KW. Endoscopic stenting and elective surgery versus emergency surgery for left-sided malignant colonic obstruction: a prospective randomized trial. *Int J Colorectal Dis* 2012; **27**: 355-362 [PMID: 22033810 DOI: 10.1007/s00384-011-1331-4]
 - 60 **Alcántara M**, Serra-Aracil X, Falcó J, Mora L, Bombardó J, Navarro S. Prospective, controlled, randomized study of intraoperative colonic lavage versus stent placement in obstructive left-sided colonic cancer. *World J Surg* 2011; **35**: 1904-1910 [PMID: 21559998 DOI: 10.1007/s00268-011-1139-y]
 - 61 **Cheung HY**, Chung CC, Tsang WW, Wong JC, Yau KK, Li MK. Endolaparoscopic approach vs conventional open surgery in the treatment of obstructing left-sided colon cancer: a randomized controlled trial. *Arch Surg* 2009; **144**: 1127-1132 [PMID: 20026830 DOI: 10.1001/archsurg.2009.216]
 - 62 **Sloothaak D**, van den Berg MM, Dijkgraaf M. Recurrences after endoscopic stenting as treatment for acute malignant colonic obstruction in the Dutch Stent-In 2 trial. Presented at the 21st UEG Week, Berlin, 2013
 - 63 **Gorissen KJ**, Tuynman JB, Fryer E, Wang L, Uberoi R, Jones OM, Cunningham C, Lindsey I. Local recurrence after stenting for obstructing left-sided colonic cancer. *Br J Surg* 2013; **100**: 1805-1809 [PMID: 24227368 DOI: 10.1002/bjs.9297]
 - 64 **Liang TW**, Sun Y, Wei YC, Yang DX. Palliative treatment of malignant colorectal obstruction caused by advanced malignancy: a self-expanding metallic stent or surgery? A system review and meta-analysis. *Surg Today* 2014; **44**: 22-33 [PMID: 23893158 DOI: 10.1007/s00595-013-0665-7]
 - 65 **Zhao XD**, Cai BB, Cao RS, Shi RH. Palliative treatment for incurable malignant colorectal obstructions: a meta-analysis. *World J Gastroenterol* 2013; **19**: 5565-5574 [PMID: 24023502 DOI: 10.3748/wjg.v19.i33.5565]
 - 66 **Cennamo V**, Fuccio L, Mutri V, Minardi ME, Eusebi LH, Ceroni L, Laterza L, Ansaloni L, Pinna AD, Salfi N, Martoni AA, Bazzoli F. Does stent placement for advanced colon cancer increase the risk of perforation during bevacizumab-based therapy? *Clin Gastroenterol Hepatol* 2009; **7**: 1174-1176 [PMID: 19631290 DOI: 10.1016/j.cgh.2009.07.015]

P- Reviewer: Sergi C S- Editor: Ji FF
L- Editor: A E- Editor: Li D



2016 Gastrointestinal Endoscopy: Global view

Endoscopic hemostasis state of the art - Nonvariceal bleeding

Stefan Karl Goelder, Juliane Brueckner, Helmut Messmann

Stefan Karl Goelder, Juliane Brueckner, Helmut Messmann,
Department of Internal Medicine III, Klinikum Augsburg, 86159
Augsburg, Germany

Author contributions: Goelder SK conceived and drafted the manuscript, prepared the tables and figures; Brueckner J and Messmann H contributed to the final draft revisions and editing of the paper.

Conflict-of-interest statement: The authors confirm that they have no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Stefan Karl Goelder, Department of Internal Medicine III, Klinikum Augsburg, Stenglinstraße 2, 86159 Augsburg, Germany. stefan.goelder@klinikum-augsburg.de
Telephone: +49-82-14002351
Fax: +49-82-14003331

Received: April 30, 2015

Peer-review started: May 7, 2015

First decision: July 22, 2015

Revised: September 30, 2015

Accepted: December 17, 2015

Article in press: December 18, 2015

Published online: February 25, 2016

Abstract

New endoscopic techniques for hemostasis in nonvariceal bleeding were introduced and known methods further improved. Hemospray and Endoclot are two new compounds for topical treatment of bleeding. Initial

studies in this area have shown a good hemostatic effect, especially in active large scale oozing bleeding, *e.g.*, tumor bleedings. For further evaluation larger prospective studies comparing the substances with other methods of endoscopic hemostasis are needed. For localized active arterial bleeding primary injection therapy in the area of bleeding as well as in the four adjacent quadrants offers a good method to reduce bleeding activity. The injection is technically easy to learn and practicable. After bleeding activity is reduced the bleeding source can be localized more clearly for clip application. Today many different through-the-scope (TTS) clips are available. The ability to close and reopen a clip can aid towards good positioning at the bleeding site. Even more important is the rotatability of a clip before application. Often multiple TTS clips are required for secure closure of a bleeding vessel. One model has the ability to use three clips in series without changing the applicator. Severe arterial bleeding from vessels larger than 2 mm is often unmanageable with these conventional methods. Here is the over-the-scope-clip system another newly available method. It is similar to the ligation of esophageal varices and involves aspiration of tissue into a transparent cap before closure of the clip. Thus a greater vascular occlusion pressure can be achieved and larger vessels can be treated endoscopically. Patients with severe arterial bleeding from the upper gastrointestinal tract have a very high rate of recurrence after initial endoscopic treatment. These patients should always be managed in an interdisciplinary team of interventional radiologist and surgeons.

Key words: Gastrointestinal bleeding; Endoscopic treatment; Intestinal hemorrhage; Endoscopic clips; Topical hemostatic substances

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: An increasing rate of patients who present

with nonvariceal hemorrhage present with an anticoagulative or antithrombotic medication. Often the patient suffers from concomitant disease. In the recent years new methods for flexible endoscopic treatment of hemorrhage have been developed. The following article discusses the current literature of the new endoscopic methods in the context of every day practice in endoscopic treatment for nonvariceal hemorrhage.

Goelder SK, Brueckner J, Messmann H. Endoscopic hemostasis state of the art - Nonvariceal bleeding. *World J Gastrointest Endosc* 2016; 8(4): 205-211 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/205.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.205>

INTRODUCTION

Endoscopic hemostatic treatment is the gold standard for active gastrointestinal bleeding, as well as for recent bleeding with stigmata of a high recurrence rate. International treatment guidelines recommend an early risk stratification by immediate endoscopic diagnosis and treatment^[1]. Injection therapy, clip application and thermal hemostasis are well established methods of mono therapies. However a combination of two hemostatic methods have been found to be superior to an individual method alone and should therefore be preferred^[2]. Mechanical hemostasis with clips can be limited due to poor angulation and mobility of the endoscope, *e.g.*, in the duodenal bulb. Also some conventional clips cannot be reopened after closing even after poor placement.

In this review we highlight recent innovations in the field of endoscopic hemostasis in nonvariceal bleeding in the upper gastrointestinal tract with a focus on new topically applied substances (*e.g.*, Ankafer, Hemospray and EndoClot) and newly developed clips [instinct clip and over-the-scope-clip (OTSC)].

Before endoscopic treatment of a nonvariceal bleeding certain factors that correlate with a high rate of re-bleeding, should be considered. Interdisciplinary solutions should be evaluated at an early stage. Ogasawara *et al*^[3] described in a single center retrospective study the parameters: Age > 70 years, hemorrhagic shock on admission, hemoglobin < 8 mg/dL, serum albumin < 3.3 g/dL, vessels > 2 mm and Forrest I a and I b ulcers as negative predictors. The strongest predictors of failure of endoscopic therapy is a vessel diameter > 2 mm (OR = 4:38; 95%CI: 1.25-7.01) and the presence of hemorrhagic shock (OR = 5.26, 95%CI: 2.43-11.6)^[3].

The authors describe precisely the approach when initial hemostasis fails. From 2000-2010, *n* = 428 patients were treated with Forrest I a/ I b (F I a/F I b) and Forrest II a/b (F II a/F II b) lesions. The authors describe a standardized second-look endoscopy after 24 h in all patients. A recurrent bleeding occurred in 69 (16%) of the patients. Twelve percent of those

received surgery, 4% died. For the entire population of 428 patients with F I a/F I b and F II a/F II b bleeding endoscopic failure rate of 17/428 (4%).

The second endoscopic hemostasis was successful in 46/69 (66.7%). A third intervention was successful in 11/23 (47.8%) of the patients. With this approach, the authors were able to treat 57/69 (82%) recurrences during follow-up.

This work shows that by endoscopic hemostasis a large proportion of patients with upper nonvariceal gastrointestinal bleeding can be permanently treated with the first endoscopic hemostasis.

Attention should be paid to the special situation of a large visible vessel (> 2 mm). Especially arterial vessels on the posterior wall of the duodenal bulb should gain attention. Surprisingly, the proportion of intractable bleeding in the study of Ogasawara *et al*^[3] were more frequent in the duodenal bulb, but this did not reach statistical significance.

Another crucial parameter before starting any endoscopic therapy in the presence of bleeding is the fact that especially non-bleeding-related comorbidities cause the mortality of non variceal bleeding^[4]. The number of comorbidities and the probably of taking anticoagulative or antithrombotic drugs will affect decisively the prognosis in the individual cases.

NEW HEMOSTASIS METHODS - TOPICALLY APPLIED SUBSTANCES

Surface bleeding provides a problem for common hemostatic methods. Injections work better with localized active bleeding sources. Also, after injection of NaCl or diluted epinephrine solution a decongestion of the injected volume cause a reactivation of bleeding. Mechanical hemostatic methods can cannot easily be used for diffuse mucosal bleeding. Hemostasis with argon plasma coagulation would be the method of choice but a High Frequency (HF) Generator is required, which must be frequently initially activated in emergency examinations or on the intensive care unit.

Over the past 50 years, various substances for topical hemostasis were developed especially in open surgery. Bergel in 1909 described the application of fibrin to accelerate hemostasis. Other locally applied substances include thrombin clotting factors and sucralfate, which have been described with differing results in small case series^[5].

Currently the literature describes three substances, used for endoscopic hemostasis (Table 1). Hemospray (Cook Medical, Limerik, Ireland) and EndoClot (EPI, Santa Clara CA, United States) are eligible for endoscopic treatment of nonvariceal bleeding. The preparation of ankaferd [ankaferd blood stopper (ABS)] is not available for endoscopic hemostasis in Germany.

ABS

ABS is a preparation of Turkish medicine, specified by

Table 1 Overview on the commercially available substances for topical application^[5]

	Contains	Mechanism of action	Approved human application	Formulation
Ankaferd blood stopper	Herbal mixture	Forms protein networks, activates clotting cascade	Dental procedures, first aid services	Tampons, sprays, ampoules
Hemospray	Mineral powder	Absorbs H ₂ O, mechanical tamponade, activates clotting cascade	Nonvariceal GI bleeding	CO ₂ pressurized handheld canister (20 g)
EndoClot	Absorbable polymers	Absorbs H ₂ O and concentrate cells, activates clotting cascade	Adjuvant hemostatic therapy	Pressurized air compressor

GI: Gastrointestinal.

the manufacturer as a blend of vegetable ingredients. A preparation of 100 mL of ABS is composed of a standardized mixture of plants, including 5 mg *Thymus vulgaris* (dried grass extract), 9 mg *Glycyrrhiza glabra* (dried leaf extract), 8 mg *Vitis vinifera* (dried leaf extract), 7 mg *Alpinia officinarum* (dried leaf extract), and 6 mg *Urtica dioica* (dried root extract)^[6].

The endoscopic application of ABS is published in case reports and series for treatment of Mallory-Weiss tears, Dieulafoy ulcers, GAVE, anastomotic bleeding, post sphincterotomy and tumor bleeding^[7]. Prospective randomized trials comparing ABS to other endoscopic hemostasis procedures are lacking.

HEMOSPRAY TC-325

Hemospray (also named TC-325) is a mineral-based powder from Cook Medical Limerick Ireland. It was developed by the armed forces for control of bleeding in military operations. The powder is applied *via* a CO₂ pressurized handle. The powder is sprayed onto the source of bleeding and it is important for the application that an active bleeding is present. Only then the effect of the substance can occur.

In an animal model with an artificial arterial bleeding in the stomach, endoscopic hemostasis could successfully be achieved^[8]. There was no evidence for an embolic removal of the substance into the circulatory system or local reactions at the site of bleeding. Sung *et al*^[9] reported 2011 on the first application of hemostasis for $n = 20$ patients with peptic ulcer bleeding. The acute hemostasis rate was 95% (19/20). One patient with a F I a hemorrhage had to be embolized radiologically due to a pseudoaneurysm. Out of the patients with a successful initial treatment, 2/10 (11%) showed a recurrence of bleeding within 72 h, however these could again be treated endoscopically^[9].

In 2013, the results of the "Evaluate Survey of the Application of Hemospray in the luminal tract", a European database, were published^[10]. The authors report on $n = 30$ patients with peptic ulcers and $n = 33$ patients with other nonvariceal bleeding sources (e.g., post EMR, tumor bleeding, Dieulafoy ulcer). Monotherapy with Hemospray was carried out in 87%. The primary hemostasis rate was 85%. A rebleeding within 7 d occurred in 15% of all treated patients. In 8

cases Hemospray was applied adjuvantly after ineffective primary hemostasis with other methods. In all eight cases, treatment with Hemospray was successful, however, rebleeding occurred in 25%.

Another typical indication for Hemospray are large diffuse tumor bleedings. Chen *et al*^[11] described the successful treatment of $n = 5$ patients with different tumor bleedings. Binkau *et al*^[12] successfully treated two cases of an ulcerated carcinoma of the stomach and one case of small cell lung cancer, with bleeding from a metastasis in the stomach. The advantage of Hemospray is the contact-free application of the substance to a diffusely bleeding tumor surface. Upon blood contact, local hemostasis is accelerated (Figure 1).

ENDOCLOT

EndoClot contains absorbable polysaccharide particles, which are polysaccharides that absorb the blood fluid and form a gel to accelerate coagulation.

The substance is applied over a catheter with an air compressor. During application, the catheter tip has to be held at a distance from the bleeding source in order to prevent blockage of the catheter.

Müller-Gerbes *et al*^[13] report their experience of treating 22 patients either with EndoClot alone (17 patients) or in combination with other hemostatic methods (5 patients). Overall, hemostasis was successful in 21/22 patients. Out of these cases 8 involved diffuse tumor bleeding which could be stopped.

However, Holster *et al*^[14] could report sufficient hemostasis in patients with active arterial bleeding who were under anticoagulants.

Overall topically applied substances are particularly helpful for diffuse bleedings with low activity and without a clearly localized source. Also, patients taking anticoagulants or antithrombotic medication can well be treated with the new substances. Other indications such as arterial bleeding have shown less favorable results. In order to more firmly establish topically applied substances in the algorithm of endoscopic hemostatic therapy, larger studies comparing them to conventional methods are at need.

If positioning of the endoscope is adequate and the endoscopic team is clip-experienced, a mechanical method for hemostasis could be preferred. For this



Figure 1 Hemospray (Cook Medical, Ireland) with a CO₂ pressurized handle the mineral powder is applied with a catheter introduced through the working channel of the endoscope.



Figure 2 Over the scope clip (Oversco, Tübingen, Germany). The clip is preloaded on a transparent cap that can be fixed on the distal end of the endoscope. After suctioning of the bleeding source into the cap the clip is placed over the bleeding site.



Figure 4 Clip Master 3 (Medwork, Höchstädt/Aisch, Germany) is a through the scope clip with three consecutively preloaded clips. The clips can be applied without changing the device.

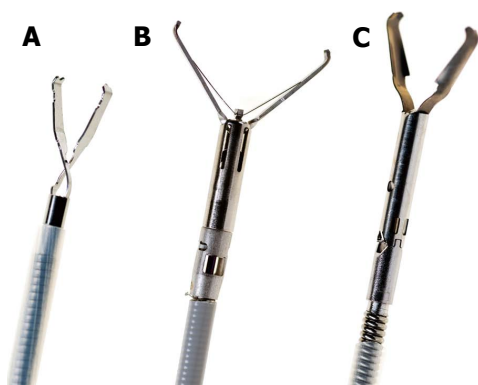


Figure 3 Different types of through the scope clips. A: Quick clip, (Olympus, Hamburg, Deutschland); B: Instinct clip (Cook Medical, Limerick, Ireland); C: Resolution clip (Boston Scientific Germany, Ratingen, Germany).

modality new clip models were presented in recent years.

CLIPS FOR MECHANICAL ENDOSCOPIC HEMOSTASIS

There are two groups of clips: Clips applied through the working channel of an endoscope [Through-the-

Scope (TTS)] and clips pre-loaded with a transparent detachable cap at the distal end of the endoscope (over the scope OTSC) (Figure 2).

The TTS clips are available from different manufacturers and with different opening lengths (Table 2, Figures 3 and 4). A clip with three branches (TriClip, Cook Medical, Ireland) is now no longer available. Prospective studies with the TriClip compared to the Quick Clip (Olympus, Hamburg, Germany) showed a slightly worse outcome for the TriClip. Another study showed more recurrent bleeding with the TriClip (15% vs 29%). The primary hemostasis rate was also significantly lower with the TriClip (94% vs 76%, $P = 0.01$)^[15].

Meanwhile the company has improved the clip model and offers a clip with two branches. It is called "instinct clip", opens at a very wide angle, can be rotated and reopened. However it is a single use clip, requiring a complete application set for each application. So far there are no published clinical trials. However, an *ex vivo* study showed a good application even in full inversion of the endoscope and a durable tissue closure (Figure 5)^[16].

The mechanical hemostasis is the only endoscopic procedure that offers a safe and permanent closure of larger vessels^[17]. However, the exact placement on the bleeding source and the durability of the clip until hemostasis has occurred are important.

Table 2 Currently available through the scope clips for endoscopic hemostasis

Clip	Manufacturer	Opening with	Special
Clipmaster 3	Medwork, Höchststadt/ Aisch, Germany	12 mm	3 clips in a row - no change of the applicator required
Quick clip 2	Olympus, Hamburg, Germany	9 mm	Multiple use applicator
Quick clip 2 long	Olympus, Hamburg, Germany	11 mm	Multiple use applicator
Resolution clip	Boston Scientific, Ratingen, Germany	11 mm	Reopenable after placement
Instinct clip	Cook Medical, Limerick, Ireland	16 mm	Reopenable after placement

With the clipmaster 3 clips can be applied with one applicator. The quick clip applicator is a multiple use device but every clip has to be separately loaded. The instinct and the resolution clip can be closed and reopened until a proper position could be achieved.

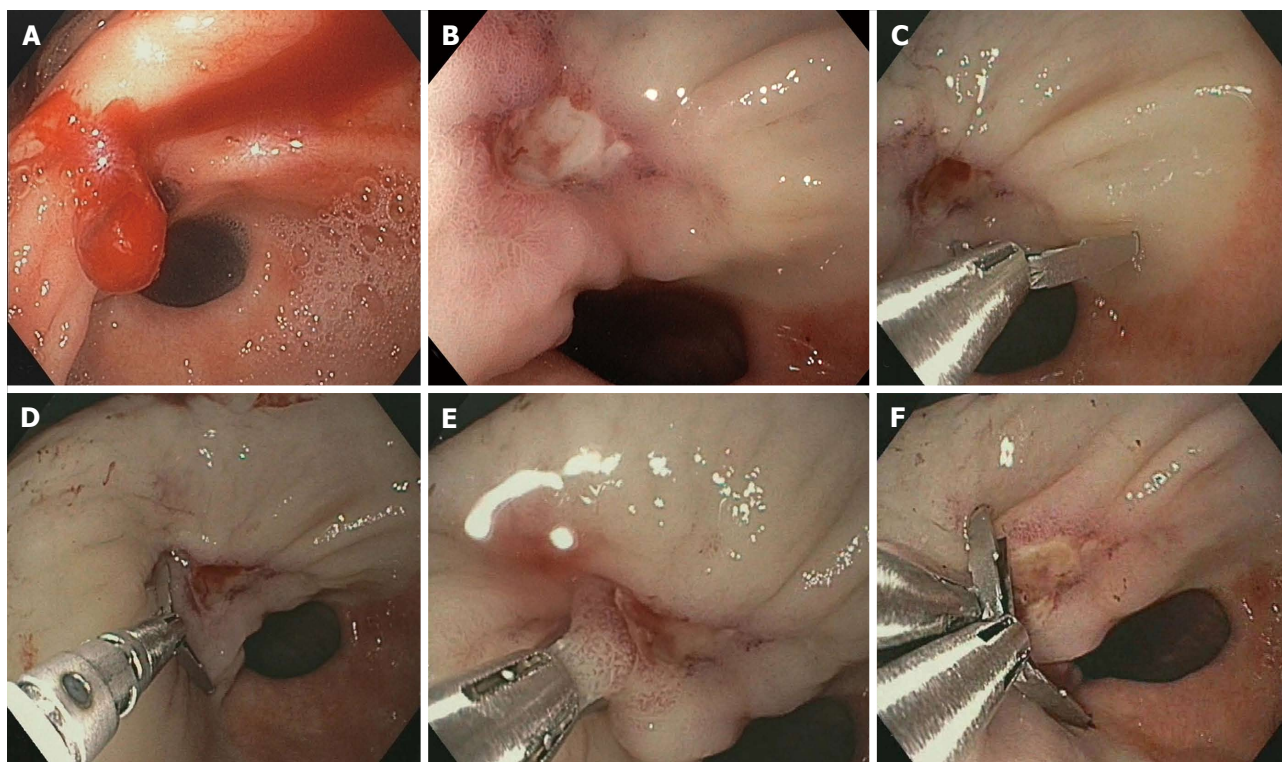


Figure 5 Instinct clip. A: Forrest Ib ulcer in the prepyloric antrum; B: After injection of diluted epinephrine solution and clearing of the blood clot a small feeding vessel is identified; C: The instinct clip (Cook Medical, Ireland) is positioned close to the lesion and then the branches are rotated to the desired angle; D: The clip is placed at the basis of the ulcer; E: The clip is closed in a proper position; F: The clip is released and a second clip is positioned on the opposite position.

Hepworth *et al.*^[18] compared the methods of endoscopic injection, heater probe thermal treatment, and clip application in an animal model on arterial vessels of different diameter. The injection could not achieve permanent hemostasis in any vessel diameter (1-3 mm). But even with the state of the art hemostasis clips, the authors were only able to achieve permanent hemostasis in 10%-15% of the cases. The attempt to achieve a higher hemostasis rate with an endoscopic suture or an endoloop achieved more durable vascular occlusion. Another *ex vivo* study was performed on the "Erlangen Active Simulator for Interventional Endoscopy" and measured the closing pressure after endoscopic application of different clip models. The maximum closure pressure of 200 mmHg was achieved in 59% with the OTSC system. The resolution clip (Boston Scientific, Ratingen, Germany) accomplished this in 10%, quick clip (Olympus, Hamburg, Germany) 3% and in TriClip

(Cook, Limerick, Ireland) in 10%. With injection alone, the maximum occlusion pressure has been reached in 5% of the tests. The authors conclude from their experimental results that arterial vessels greater than 2 mm can only be closed with the OTSC System^[19].

Another benefit of the OTSC System could be a circular grasp of the bleeding source and the surrounding tissue containing the supplying blood vessels. Kirschniak *et al.*^[20] reported the first clinical experience with the OTSC clip for hemostasis.

The clip was used for primary or postoperative bleeding in the gastrointestinal tract. In all seven patients in whom the clip was used for endoscopic hemostasis, the primary hemostasis was successful and there was no recurrent bleeding. Another series of 30 cases in which the conventional methods of endoscopic hemostasis had failed, use of the OTSC system achieved a success rate of 97% of primary hemostasis^[21]. In two cases there was

recurrent bleeding, which could be treated with repeated endoscopic treatment. In a recent case series, a technical success rate of 100% for hemostasis with the OTSC clip is reported. In two cases a rebleeding occurred, in one of which the source of bleeding was a multiply pretreated tumor^[22].

HEMOSTASIS STATE OF THE ART - NONVARICEAL BLEEDING

In recent years, new techniques for endoscopic hemostasis were introduced and known methods further improved.

With Hemospray and EndoClot two new compounds for topical treatment are available. Initial studies in this area have shown a good hemostatic effect, especially in active large scale oozing bleeding, *e.g.*, tumor bleedings. For further evaluation larger prospective studies comparing the substance with other methods of endoscopic hemostasis are needed.

For localized active arterial bleeding, primary injection therapy in the area of bleeding as well as in the four adjacent quadrants offers a good method to reduce bleeding activity. The injection is technically quite easy to learn and practicable. After bleeding activity is reduced the bleeding source can be localized more easily for clip application. Today many different TTS clips are available. The ability to close and reopen a clip can aid towards good positioning at the bleeding site. Even more important is the rotatability of a clip before application. Often multiple TTS clips are required for secure closure of a bleeding vessel. One model has the ability to use three clips in series without changing the applicator.

Severe arterial bleeding from vessels larger than 2 mm is often unmanageable with these conventional methods. Here the OTSC system is a newly available method. Its mechanism is similar to the ligation of esophageal varices and involves aspiration of tissue into a transparent cap before closure of the clip. Thus a greater vascular occlusion pressure can be achieved and larger vessels can be treated endoscopically. Patients with severe arterial bleeding from the upper gastrointestinal tract have a very high rate of recurrence after initial endoscopic treatment. These patients should always be managed in an interdisciplinary team of interventional radiologist and surgeons.

REFERENCES

- 1 **Barkun AN**, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; **152**: 101-113 [PMID: 20083829 DOI: 10.7326/0003-4819-152-2-201001190-00009]
- 2 **Vergara M**, Calvet X, Gisbert JP. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. *Cochrane Database Syst Rev* 2007; (2): CD005584 [PMID: 17443601 DOI: 10.1002/14651858.cd005584.pub2]
- 3 **Ogasawara N**, Mizuno M, Masui R, Kondo Y, Yamaguchi Y, Yanamoto K, Noda H, Okaniwa N, Sasaki M, Kasugai K. Predictive factors for intractability to endoscopic hemostasis in the treatment of bleeding gastroduodenal peptic ulcers in Japanese patients. *Clin Endosc* 2014; **47**: 162-173 [PMID: 24765599 DOI: 10.5946/ce.2014.47.2.162]
- 4 **Sung JJ**, Tsoi KK, Ma TK, Yung MY, Lau JY, Chiu PW. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. *Am J Gastroenterol* 2010; **105**: 84-89 [PMID: 19755976 DOI: 10.1038/ajg.2009.507]
- 5 **Barkun AN**, Moosavi S, Martel M. Topical hemostatic agents: a systematic review with particular emphasis on endoscopic application in GI bleeding. *Gastrointest Endosc* 2013; **77**: 692-700 [PMID: 23582528 DOI: 10.1016/j.gie.2013.01.020]
- 6 **Goker H**, Haznedaroglu IC, Ercetin S, Kirazli S, Akman U, Ozturk Y, Firat HC. Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper. *J Int Med Res* 2008; **36**: 163-170 [PMID: 18304416 DOI: 10.1177/147323000803600121]
- 7 **Wong Kee Song LM**, Banerjee S, Barth BA, Bhat Y, Desilets D, Gottlieb KT, Maple JT, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Wang A, Rodriguez SA. Emerging technologies for endoscopic hemostasis. *Gastrointest Endosc* 2012; **75**: 933-937 [PMID: 22445927 DOI: 10.1016/j.gie.2012.01.024]
- 8 **Giday SA**, Kim Y, Krishnamurthy DM, Ducharme R, Liang DB, Shin EJ, Dray X, Hutcheon D, Moskowicz K, Donatelli G, Rueben D, Canto MI, Okolo PI, Kalloo AN. Long-term randomized controlled trial of a novel nanopowder hemostatic agent (TC-325) for control of severe arterial upper gastrointestinal bleeding in a porcine model. *Endoscopy* 2011; **43**: 296-299 [PMID: 21384319 DOI: 10.1055/s-0030-1256125]
- 9 **Sung JJ**, Luo D, Wu JC, Ching JY, Chan FK, Lau JY, Mack S, Ducharme R, Okolo P, Canto M, Kalloo A, Giday SA. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy* 2011; **43**: 291-295 [PMID: 21455870 DOI: 10.1055/s-0030-1256311]
- 10 **Smith LA**, Stanley AJ, Bergman JJ, Kiesslich R, Hoffman A, Tjwa ET, Kuipers EJ, von Holstein CS, Oberg S, Brullet E, Schmidt PN, Iqbal T, Mangiavillano B, Masci E, Prat F, Morris AJ. Hemospray application in nonvariceal upper gastrointestinal bleeding: results of the Survey to Evaluate the Application of Hemospray in the Luminal Tract. *J Clin Gastroenterol* 2013; **48**: e89-e92 [PMID: 24326829 DOI: 10.1097/MCG.0000000000000054]
- 11 **Chen YI**, Barkun AN, Soulellis C, Mayrand S, Ghali P. Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience (with video). *Gastrointest Endosc* 2012; **75**: 1278-1281 [PMID: 22482923 DOI: 10.1016/j.gie.2012.02.009]
- 12 **Binkau J**, Nötzel E, Hartmann D. TC-325-Applikation (Hemospray®-Device) zur endoskopischen Blutstillung bei Tumorblutungen - zwei Kasuistiken. *Endo heute* 2013; **26**: 259-262 [DOI: 10.1055/s-0033-1356204]
- 13 **Müller-Gerbes D**, Beeck A, Dormann A. Hämostase mit Pulver - Erfahrungen mit EndoClot™ bei schwierigen oberen GI-Blutungen. *Endo heute* 2013; **26**: 254-258 [DOI: 10.1055/s-0033-1355954]
- 14 **Holster IL**, Kuipers EJ, Tjwa ET. Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy. *Endoscopy* 2013; **45**: 63-66 [PMID: 23208778]
- 15 **Lin HJ**, Lo WC, Cheng YC, Perng CL. Endoscopic hemoclip versus triclclip placement in patients with high-risk peptic ulcer bleeding. *Am J Gastroenterol* 2007; **102**: 539-543 [PMID: 17100962 DOI: 10.1111/j.1572-0241.2006.00962.x]
- 16 **Daram SR**, Tang SJ, Wu R, To SD. Benchtop testing and comparisons among three types of through-the-scope endoscopic clipping devices. *Surg Endosc* 2013; **27**: 1521-1529 [PMID: 23292554 DOI: 10.1007/s00464-012-2679-4]
- 17 **Jensen DM**, Machicado GA. Hemoclippling of chronic canine ulcers: a randomized, prospective study of initial deployment success, clip retention rates, and ulcer healing. *Gastrointest Endosc* 2009; **70**: 969-975 [PMID: 19640519 DOI: 10.1016/j.gie.2009.04.052]
- 18 **Hepworth CC**, Kadirkamanathan SS, Gong F, Swain CP. A

- randomised controlled comparison of injection, thermal, and mechanical endoscopic methods of haemostasis on mesenteric vessels. *Gut* 1998; **42**: 462-469 [PMID: 9616305 DOI: 10.1136/gut.42.4.462]
- 19 **Naegel A**, Bolz J, Zopf Y, Matthes K, Mueller B, Kraus F, Neurath MF, Maiss J. Hemodynamic efficacy of the over-the-scope clip in an established porcine cadaveric model for spurting bleeding. *Gastrointest Endosc* 2012; **75**: 152-159 [PMID: 22100298 DOI: 10.1016/j.gie.2011.08.009]
 - 20 **Kirschniak A**, Subotova N, Zieker D, Königsrainer A, Kratt T. The Over-The-Scope Clip (OTSC) for the treatment of gastrointestinal bleeding, perforations, and fistulas. *Surg Endosc* 2011; **25**: 2901-2905 [PMID: 21424197 DOI: 10.1007/s00464-011-1640-2]
 - 21 **Manta R**, Galloro G, Mangiavillano B, Conigliaro R, Pasquale L, Arezzo A, Masci E, Bassotti G, Frazzoni M. Over-the-scope clip (OTSC) represents an effective endoscopic treatment for acute GI bleeding after failure of conventional techniques. *Surg Endosc* 2013; **27**: 3162-3164 [PMID: 23436101 DOI: 10.1007/s00464-013-2871-1]
 - 22 **Chan SM**, Chiu PW, Teoh AY, Lau JY. Use of the Over-The-Scope Clip for treatment of refractory upper gastrointestinal bleeding: a case series. *Endoscopy* 2014; **46**: 428-431 [PMID: 24505017 DOI: 10.1055/s-0034-1364932]

P- Reviewer: Yan SL **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Li D



2016 Gastrointestinal Endoscopy: Global view

Endoscopic management of esophageal stenosis in children: New and traditional treatments

Luigi Dall'Oglio, Tamara Caldaro, Francesca Foschia, Simona Faraci, Giovanni Federici di Abriola, Francesca Rea, Erminia Romeo, Filippo Torroni, Giulia Angelino, Paola De Angelis

Luigi Dall'Oglio, Tamara Caldaro, Francesca Foschia, Simona Faraci, Giovanni Federici di Abriola, Francesca Rea, Erminia Romeo, Filippo Torroni, Giulia Angelino, Paola De Angelis, Digestive Endoscopy and Surgery Unit, Bambino Gesù Children Hospital, IRCCS, 00165 Roma, Italy

Author contributions: Dall'Oglio L wrote the paper and was the coordinator of these therapeutic procedures; Angelino G provided the review activity; the other authors contributed equally to this work supporting the paper with references and their clinical activity.

Conflict-of-interest statement: The authors have no conflict of interest to report.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Luigi Dall'Oglio, MD, Digestive Endoscopy and Surgery Unit, Bambino Gesù Children Hospital, IRCCS, Piazza Sant'Onofrio 4, 00165 Roma, Italy. luigi.dalloglio@opbg.net
Telephone: +39-06-68592841
Fax: +39-06-68593910

Received: May 25, 2015

Peer-review started: May 26, 2015

First decision: August 31, 2015

Revised: October 14, 2015

Accepted: December 16, 2015

Article in press: December 18, 2015

Published online: February 25, 2016

Abstract

Post-esophageal atresia anastomotic strictures and post-corrosive esophagitis are the most frequent types of cicatricial esophageal stricture. Congenital esophageal stenosis has been reported to be a rare but typical disease in children; other pediatric conditions are peptic, eosinophilic esophagitis and dystrophic recessive epidermolysis bullosa strictures. The conservative treatment of esophageal stenosis and strictures (ES) rather than surgery is a well-known strategy for children. Before planning esophageal dilation, the esophageal morphology should be assessed in detail for its length, aspect, number and level, and different conservative strategies should be chosen accordingly. Endoscopic dilators and techniques that involve different adjuvant treatment strategies have been reported and depend on the stricture's etiology, the availability of different tools and the operator's experience and preferences. Balloon and semirigid dilators are the most frequently used tools. No high-quality studies have reported on the differences in the efficacies and rates of complications associated with these two types of dilators. There is no consensus in the literature regarding the frequency of dilations or the diameter that should be achieved. The use of adjuvant treatments has been reported in cases of recalcitrant stenosis or strictures with evidence of dysphagic symptoms. Corticosteroids (either systemically or locally injected), the local application of mitomycin C, diathermy and laser ES sectioning have been reported. Some authors have suggested that stenting can reduce both the number of dilations and the treatment length. In many cases, this strategy is effective when either metallic or plastic stents are utilized. Treatment complications, such as esophageal perforations, can be conservatively managed, considering surgery only in cases with severe pleural cavity involvement. In cases of stricture relapse,

even if such relapses occur following the execution of well-conducted conservative strategies, surgical stricture resection and anastomosis or esophageal substitution are the only remaining options.

Key words: Esophageal stenosis; Esophageal stricture; Esophageal dilation; Esophageal stent; Caustic stricture

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The paper reviews the conservative treatment of esophageal stenosis and strictures (ES) in children. Different types of ES are discussed, including post-esophageal atresia anastomotic strictures, congenital esophageal stenosis and dystrophic recessive epidermolysis bullosa strictures. Endoscopic techniques are reviewed, including balloon and semirigid dilators, esophageal stents and different adjuvant treatment strategies, like corticosteroids (either systemically or locally injected), the local application of mitomycin C, and ES incision. Conservative management must be considered also for complications, such esophageal perforations, except for patients with severe pleural cavity involvement, who require surgery.

Dall'Oglio L, Caldaro T, Foschia F, Faraci S, Federici di Abriola G, Rea F, Romeo E, Torroni F, Angelino G, De Angelis P. Endoscopic management of esophageal stenosis in children: New and traditional treatments. *World J Gastrointest Endosc* 2016; 8(4): 212-219 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/212.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.212>

INTRODUCTION

The endoscopic treatment of esophageal strictures or stenosis (ES) has been reported to be the most frequently used strategy in children and adults. Improvements in endoscopes and accessories have supported an increase in the number of patients who are conservatively treated with endoscopic dilations (ED) rather than surgical treatment.

In the past, patients with severe cicatricial strictures, particularly cases that occurred following the ingestion of caustic agents, have generally undergone esophageal substitutions with or without esophagectomy. The conservative option was complicated by the difficulty of passing the bougie through the stricture without clear endoscopic control and without a guide wire. The mortality risks of these procedures was elevated because of high incidence of complicated esophageal perforations and consequently severe mediastinal infections.

Safe and effective ED performed with flexible endoscopes, guide wires with differing stiffnesses, balloon dilators or semirigid bougie dilators have drastically improved the outcomes and the quality of life of these

patients. Further, the rates of ES resolution with a stable esophageal caliber that is suitable for normal food intake without dysphagia are high.

Normal food intake is the only achievable target of conservative treatment because there are no treatments that can achieve a true normal esophagus with normal motility at the level of the cicatricial tissue.

ESOPHAGEAL DILATIONS

Conservative treatments of ES with ED utilizing different strategies have been reported, and the indications for each treatment depend on the operator's experience and preferences and the etiology of the ES.

General anesthesia represents a widespread strategy that is used in children both to reduce patient discomfort and to allow for proper airway protection during dilation maneuvers. In teenagers, repeated ED under conscious sedation can be used. In indwelling balloon dilation program, the patient requires neither sedation nor anesthesia^[1].

A guide wire that is inserted under endoscopic control through the stricture represents an important and effective tool for avoiding an incorrect path of the preferred dilator tip.

Different dilators are now available; for example, reusable dilators that are applied over the wire such as semirigid Savary-Giliard bougies and disposable balloon dilators have been used. Balloon dilators pass over a guide wire or through the channel of the endoscope. All of these dilators are available in different lengths and diameters.

There is no consensus regarding the use of balloon dilators or semirigid Savary-Giliard bougies. No prospective studies have directly compared the safety and efficacy of these types of dilators. However, retrospective studies have reported different results regarding perforation rates^[2,3].

Based on our more than thirty-five years of experience with thousands of dilations, we generally use balloon dilators in cases that involve inflammatory strictures, *e.g.*, in the early treatment of caustic, epidermolysis bullosa and peptic strictures.

Savary dilators are safer and more effective than balloon dilators in the treatment of consolidated and old cicatricial strictures and in cases of resistant esophageal narrowing due to, *e.g.*, congenital esophageal stenosis (CES) with cartilaginous remnants^[4].

The advantages of balloon dilators include the radial force that is applied to the ES and the avoidance of the application of axial force^[5]. Balloon dilators can be advanced through the endoscope channel and carefully pushed forward into and through the ES under direct vision. Balloon dilators may also be inserted, on the side of the endoscope itself or under fluoroscopic control, over a guide wire that has previously been inserted through the scope.

Inflating balloon devices allow for the application of a standard force (PSI or ATM) at a standard diameter

Table 1 How to prevent esophageal perforation

Accurate stricture/stenosis morphology with X-ray-esophagram, MEUS
Stricture/stenosis etiology
General anesthesia
Fluoroscopy available
Guide wire in correct position
Correct dilator type and size
Carefully dilator passage or inflation
Endoscopic/contrast X-ray evaluation for possible perforation

MEUS: Miniprobe ultrasonography.

and with one specific pressure. The balloon filled with contrast medium allows for the verification of the disappearance of the hourglass image or the waist in the balloon caused by the stricture, under the fluoroscopic control^[5]. The persistence of a portion of the "waist" is an indication that the procedure was partially successful^[6].

There is no consensus regarding the duration, which can range from 10 to 120 s, that the balloon should remain inflated, and there are no published pediatric studies on this topic. An adult study^[7] revealed no difference in the outcomes of patient regardless of whether the balloon was dilated for 10 or 120 s.

Semirigid Savary-Giliard dilators require an expert operator to conduct progressive dilations and thus avoid esophageal perforation by carefully inserting the dilators without excessive force or hastiness.

The problem of the optimum dilator is difficult to solve, because of the different esophageal size during the pediatric age. The "tumble rule" was proposed, comparing the size of the thumb with the esophageal size. The most frequently used rule in children is to dilate no more than two sizes for each dilation session. Dilation can be repeated, with increasing diameter, after at least 3 d. Only the tissue damage after the previous dilation could represent a guide for the treatment. Personal experience plays a fundamental role in the choice of the optimal dilator size.

In patients operated for esophageal atresia (EA) the opportunity and the timing of the first endoscopic control of esophageal anastomosis is debated. Due to the absence of evidence of routine endoscopic control utility, the most used strategy is to evaluate with barium swallow or endoscopy only the patient that are not able to eat the normal food for the age. In case of dysphagia and stricture evidence the patient starts with a dilations program.

There is no consensus regarding the interval between repeated ED with either a balloon or a bougie. An average of two to three weeks is the most frequently reported interval^[2,3]. This interval should be individualized based on the stricture size, the resistance against the dilations, the post-dilation bleeding, the symptoms and the local or patient's logistical environment. Patients who require treatment in a level III endoscopic center may request a special dilation setting and an increased frequency of dilations to reduce difficult or expensive travel from the country of origin, if they are located far

Table 2 Type of esophageal strictures in children

Caustic
Anastomotic
Congenital stenosis
Epidermolysis bullosa
Peptic
Eosinophilic esophagitis
Actinic
Neoplastic

from the level III center. In many cases the interval between ED can be progressively elongated, according with symptoms relapse, to reduce the patient's stress.

The steps to reduce the risk of esophageal perforation are listed in Table 1.

TYPE OF STRICTURES

Table 2 shows the most frequent ES in children listed in order of frequency.

In EA anastomotic strictures, there are no clear indications for dilations, as a routine post-operative procedures^[8]; indeed, the only indication is the presence of dysphagia symptoms.

This second strategy has been reported to be as effective as the first one and with fewer dilations^[9-11].

Due to the high risk of severe stricture that has reportedly been associated with long gaps EA with anastomotic tension^[12,13], patients with this condition require strict clinical follow-up to prevent sudden, full and potentially dramatic anastomotic occlusions that can only be dilated with special strategies. In very difficult situations that lack evidence of an anastomotic lumen, the simultaneous insertion of two endoscopes, one *via* the mouth and the second through a preexisting gastrostomy, could provide an opportunity to reestablish esophageal patency^[14].

In very thin anastomotic stricture it may be impossible to pass the guide wire through. Under fluoroscopy, using an ERCP cannula and strategy, filling water-soluble contrast medium it is possible to verify the correct way and then the correct wire passage through the cannula into the stricture.

In CES, different subtypes have been described. The two most important subtypes in terms of frequency are the fibromuscular (FMS CES) and tracheal cartilaginous remnant (TBR CES) subtypes.

The differential diagnosis, to rule out other esophageal narrowing etiologies, is necessary for selecting the correct therapeutic strategy. Miniprobe ultrasonography (MEUS) currently represents the only diagnostic tool that can provide an accurate evaluation of esophageal wall thickness and can differentiate the CES subtype^[4,15,16]. Different therapeutic options have been reported for CES. In case of TBR, some authors have suggested surgical stenosis resection and anastomosis^[15-17]. The conservative treatment with ED has been reported to be effective^[4] in a large series of 47 patients. An overall

success rate of 95% has also been reported in cases of TBR CES.

The reported incidences of perforation following stenosis dilation in CES are higher than those reported for other types of ES and range from 10%^[4] to 33%^[18] and 44%^[19]. These higher incidences are likely due to the high resistance of the stenosis and the risk of the sudden cracking of the stenosis during dilations, particularly with balloon dilators^[4]. In the reviews of Michaud *et al.*^[16] and Takamizawa *et al.*^[17], the authors reported many cases and studies of the surgical resection of TBR CES as the first option when diagnoses of TBR CES were obtained; but in many reported cases^[16] the TBR diagnosis was based only on post-operative histology and not preoperatively. Indeed, the surgical option has been reported to be the first option in surgical environments, whereas dilation options are more frequently employed in gastroenterological centers^[16]. The numbers of patients with diagnoses of cartilaginous remnants on endoscopic ultrasound with miniprbes that were reported in these two reviews were low, even if this tool is currently the only diagnostic tool that can identify cartilaginous remnants.

Romeo published results supporting conservative strategy as an effective treatment for CES, either FMS or TBR CES. Special care must be taken, in particular in previously MEUS detected TBR CES, to prevent esophageal perforation. Surgery should be reserved only for cases in which conservative treatment has been ineffective^[4].

In recessive dystrophic epidermolysis bullosa, the ES result from bullous lesions and tend to relapse. In these patients, it is important to reduce the esophageal trauma to avoid new blisters and the resultant risk of strictures^[20,21]. To minimize these risks, balloon dilation under only fluoroscopic control allows for ED without a high risk of blisters in non-stenotic esophageal areas^[21-23]. The first step is to pass a soft guide wire through the nostril, the pharynx and the esophageal stricture into the stomach. Under fluoroscopic control, the passage of the guide wire (0.032-0.035 mm hydrophilic wire) through the cricopharyngeal junction can occasionally be very difficult, but this difficulty can be resolved by using a thin tube, over-the-wire. In rare cases, the only option is endoscopic control. An over-the-wire-balloon dilator is then progressively introduced to reach the stomach. The balloon is partially filled with water and contrast medium and is slowly retracted to identify the stricture *via* the appearance of an "hourglass shape" that disappears with progressive balloon inflation. The balloon is then deflated and pulled back to identify any possible additional strictures. It is very important that the completely inflated balloon is not pulled back, to prevent the formation of blisters and new scars^[21-23]. Adjuvant treatment with dexamethasone (2 mg/kg per day for 3 d) reduces patient discomfort and can reduce the formation of scar tissue^[21].

Oral budesonide was recently reported in a short

series as adjuvant treatment in these special patients^[24].

In children during chemotherapy for leukemia or other hematologic diseases ES have been reported^[25,26], due to deep mucositis and esophageal wall damage. Conservative treatment with ED and stenting represents the first option but esophageal substitution could be necessary because of the stricture length and its recurrence. In our experience two, out three, ES resolved with stenting; the other underwent jejune esophageal substitution.

ADJUVANT TREATMENTS

Different adjuvant treatments have been proposed for cases of refractory or recurrent ES. These solutions can reduce fibroblastic activity in scar tissue production and reduce the damage to the injured esophageal wall due to acid gastro esophageal reflux. The role of these treatments is very important because they could give the chance to avoid a surgical procedure, with esophageal resection and anastomosis, a partial or total esophageal substitution or a gastric pull-up procedure. Before planning a surgical strategy in a refractory or relapsed ES a treatment with one or more combined adjuvant strategies is mandatory.

Proton pump inhibitors (PPI) are commonly used, although there are no studies of their efficacy in the prevention of stricture relapse. In one prospective study^[27], the authors reported no prophylactic effect of omeprazole (2 mg/kg) on post-esophageal atresia ES and no effect on reducing the number of ED.

In contrast, severe gastro esophageal reflux disease (GERD) is frequently observed in cases of severe ES due to corrosive esophagitis or long-gap esophageal atresia anastomosis strictures. Cicatricial shortening of the esophagus represents an important cause of GERD and consequent stricture worsening. In these patients, PPI treatment is very helpful to treat esophagitis and acid damage on the stricture wall; a correct evaluation is necessary for potential anti reflux surgery.

Mitomycin C is an antineoplastic antibiotic with *in vivo* and *in vitro* anti fibroblastic activities that has been described to exert inconsistent results at different drug concentrations. Good results in two patients with caustic ES and two patients with anastomotic ES who were treated with ED plus 1 mg/mL mitomycin C have been reported^[28]. The authors of one study reported results that were similar to those of an ED-only treated group in 11/21 anastomotic ES patients who were treated with ED plus mitomycin C (0.1 mg/mL)^[29]. In a review of 11 papers with 31 patients with ES, no direct or indirect side effects were reported. The mitomycin C concentrations varied from 0.1 mg/mL to 1 mg/mL. After a mean follow-up of 22 mo, good results in terms of symptom relief were reported for 21 children (67.7%), and 6 (19.4%) children experienced partial relief. In four children (12.9%), the mitomycin C treatment failed^[30].

In a recent prospective study, the authors described significant improvements in dysphagia in 18/30 corrosive ES patients who were treated with ED plus mitomycin C at 0.4 mg/mL^[31]. In two papers by El-Asmar *et al.*^[32,33], the authors described a significant effectiveness of 0.4 mg/mL of mitomycin C in caustic stricture.

No direct or indirect adverse effects were reported in any of these series.

Different techniques for the topical application of mitomycin C application have been reported. Cotton pledgets soaked in mitomycin C solution have generally been used. Other techniques, such as drug-eluting stents or, in our own experience, the local instillation of a mitomycin C solution at the stricture level with a cotton swab, have produced accurate solution aspiration and lavage after 4-5 min.

Until larger prospective studies are published, topical mitomycin C solutions (0.4 mg/mL) may help improve symptoms and reduces both the number of dilations and their frequency. There are no reports of direct or indirect adverse effects of the topical use of mitomycin C topical, but additional long-term follow-up studies are needed.

The use of corticosteroids, both systemically and intralesionally, has been described. In two ES patients, one post-anastomotic and one corrosive, who were previously treated with repeated intralesional dexamethasone injections, the systemic intravenous administration of prednisolone (2, 1, and 0.5 mg/kg daily for 1 wk each) improved the dysphagia in both patients^[34].

Adjuvant dexamethasone (2 mg/kg for 3 d, tapered over six additional days) has been used in the successful treatment of patients with "dynamic" custom plastic stents^[35,36].

Intralesional triamcinolone acetonide (TAC) injection has been described in adults and children. A prospective study of 60 adult patients with post-esophagectomy esophagogastric anastomotic strictures described non-significant improvement in the number of ED and the dysphagia-free period^[37]. Ten patients with intractable corrosive ES received 2 mL of TAC (40 mg/mL) injected in 3 or 4 quadrants and achieved symptom resolution^[38].

No direct or indirect adverse effects were reported in any of these series, and despite the lack of prospective pediatric studies, local TAC injections could aid the treatment of ES.

STENTING

Surgical ES resection and anastomosis with partial or total esophageal substitution may represent the only therapeutic option for refractory or recurrent ES.

Intra- and post-operative complications, anastomotic strictures, severe GERD, bronchopulmonary disease, chronic dysphagia due to esophageal motility disorders and frequent long-term low quality of life have prompted the use of more aggressive conservative strategies in the

treatment of ES with the goal of avoiding surgery and the goal to save the own patient's esophagus.

Two different strategies for stenting have been described. The metal and plastic stents press against the esophageal wall, with food and secretions that pass through the stent itself. The stents pressing against the cicatricial ES allow for the ES healing.

The second stenting strategy consists of a plastic or silicon tube, customized in different length and diameter according with the stricture size and level, affixed to a nasogastric tube. This type of stent allows the food and secretions to pass in the space between the ES and the stent itself. Such continuous passages seem to effectively maintaining lumen patency^[35,36,39-41]. In one review^[42], experiences with different stents were reported. There are three studies that have reported on second type PTFE or silicon custom stents and three that have reported on self-expanding metallic or plastic stents. Migration of the first type stent was the most commonly cited complication of metallic stents and occurred in 0% to 29% of the patients^[43,44]. The softening of the esophageal wall allowed for the distal displacement of the stent. Plastic stents affixed to nasogastric tubes are associated with a reduced risk of dislocation risks but are also associated with the increased discomfort of a nasal tube.

Results related to one of the second type of stent, the custom "dynamic stent", have been reported in two retrospective studies^[35,36] of patients with post-anastomotic (25 patients) and corrosive (55 patients) ES. The implantation of the stents was followed by high-dose dexamethasone therapy (2 mg/kg per day for 3 d tapered in 6 d more). This stenting strategy was reported to be effective in 88% of the patients. The authors underlined that this type of stent allows for continuous swallowing and food passage, which resulted in a type of gym for the esophageal wall. These dynamic custom stents might aid in stricture healing, but at a minimum, they aid in stricture shortening. This aspect has been reported to be important with respect to possible surgical resection and anastomosis. Indeed, total or long esophageal resection with partial or total esophageal substitution can be avoided^[35].

In a study of plastic and metallic stents^[45], the authors reported stent appositions in refractory ES and esophageal perforation of 23 and 14, respectively. These authors reported that the stents were effective in all patients with esophageal perforations. In the treatment of ES, the stents were effective in 6 of the 23 patients who did not receive further treatment following stent removal. The authors concluded that in anastomotic ES, self-expanding stents are very effective for treating post-dilation perforations and post-anastomotic leaks but are not effective in the treatment of ES with ES relapse after stent removal.

In a recent paper^[46], the authors reported on eleven patients with perforations or anastomotic strictures (7 and 4 patients, respectively) who were treated with

covered metal stents. No stent-related complications were observed during stent insertion or removal. Two patients underwent one additional ED. These authors concluded that stenting represents a safe and effective strategy for healing esophageal perforations.

Severe stent related complication has been described in esophageal atresia patients with post anastomotic ES. In three patients with stent (metallic and dynamic custom stent) massive bleeding from arterial-esophageal fistula has been reported. One patient with metallic stent had fatal outcome and two, with dynamic custom stent, needed thoracic surgery for subclavian anomaly^[47]. Because of the higher incidence of vascular anomalies in patients with post esophageal atresia, it is mandatory to rule out vascular anomalies with CT or MR angiography before implanting a stent.

Biodegradable esophageal stent use was described in children^[48]. The opportunity of progressive reduction of stent compression on the esophageal wall represents an important advantage of this special stent. The published inconstant results in children didn't show a significant advantage in the treatment of recalcitrant esophageal stricture. The most frequent described complications are the gastric dislocations and the mucosal overgrowth with consequent stent obstruction^[49].

ES incision has been reported in some case reports. In a recent retrospective paper, the authors reported on seven anastomotic ES patients.

In two patients ES relapsed and patients underwent one more successful incision. Three patients with ES longer than 1.5 cm underwent metallic stenting after the incision^[50].

This strategy, as the others above reported, should be performed only in III level referral centers in a pediatric medical-surgical setting, for individualized conservative strategy. Before planning surgery, in refractory or recurrent ES, all these conservative strategies must be considered.

ACKNOWLEDGMENTS

The medico-surgical endoscopic team thanks the patients, and their families, that, during the last thirty-five years, followed the difficult conservative strategy for their esophageal diseases. We thank all nurses that had a fundamental role in the treatment of these difficult patients.

REFERENCES

- van der Zee D, Hulscher C. Indwelling esophageal balloon catheter for benign esophageal stenosis in infants and children. *Surg Endosc* 2014; **28**: 1126-1130 [PMID: 24202711 DOI: 10.1007/s00464-013-3288-6]
- Lan LC, Wong KK, Lin SC, Sprigg A, Clarke S, Johnson PR, Tam PK. Endoscopic balloon dilatation of esophageal strictures in infants and children: 17 years' experience and a literature review. *J Pediatr Surg* 2003; **38**: 1712-1715 [PMID: 14666449 DOI: 10.1016/j.jpedsurg.2003.08.040]
- Poddar U, Thapa BR. Benign esophageal strictures in infants and children: results of Savary-Gilliard bougie dilation in 107 Indian children. *Gastrointest Endosc* 2001; **54**: 480-484 [PMID: 11577311 DOI: 10.1067/mge.2001.118253]
- Romeo E, Foschia F, de Angelis P, Caldaro T, Federici di Abriola G, Gambitta R, Buoni S, Torroni F, Pardi V, Dall'oglio L. Endoscopic management of congenital esophageal stenosis. *J Pediatr Surg* 2011; **46**: 838-841 [PMID: 21616237 DOI: 10.1016/j.jpedsurg.2011.02.010]
- Tam PK, Sprigg A, Cudmore RE, Cook RC, Carty H. Endoscopy-guided balloon dilatation of esophageal strictures and anastomotic strictures after esophageal replacement in children. *J Pediatr Surg* 1991; **26**: 1101-1103 [PMID: 1941489 DOI: 10.1016/0022-3468(91)90682-J]
- Antoniu D, Soutis M, Christopoulos-Geroulanos G. Anastomotic strictures following esophageal atresia repair: a 20-year experience with endoscopic balloon dilatation. *J Pediatr Gastroenterol Nutr* 2010; **51**: 464-467 [PMID: 20562719 DOI: 10.1097/MPG.0b013e3181d682ac]
- Wallner O, Wallner B. Balloon dilation of benign esophageal rings or strictures: a randomized clinical trial comparing two different inflation times. *Dis Esophagus* 2014; **27**: 109-111 [PMID: 23621385 DOI: 10.1111/dote.12080]
- Parolini F, Leva E, Morandi A, Macchini F, Gentilino V, Di Cesare A, Torricelli M. Anastomotic strictures and endoscopic dilatations following esophageal atresia repair. *Pediatr Surg Int* 2013; **29**: 601-605 [PMID: 23519549 DOI: 10.1007/s00383-013-3298-4]
- Koivusalo A, Turunen P, Rintala RJ, van der Zee DC, Lindahl H, Bax NM. Is routine dilatation after repair of esophageal atresia with distal fistula better than dilatation when symptoms arise? Comparison of results of two European pediatric surgical centers. *J Pediatr Surg* 2004; **39**: 1643-1647 [PMID: 15547826 DOI: 10.1016/j.jpedsurg.2004.07.011]
- Koivusalo A, Pakarinen MP, Rintala RJ. Anastomotic dilatation after repair of esophageal atresia with distal fistula. Comparison of results after routine versus selective dilatation. *Dis Esophagus* 2009; **22**: 190-194 [PMID: 19207547 DOI: 10.1111/j.1442-2050.2008.00902.x]
- Michaud L, Guimber D, Sfeir R, Rakza T, Bajja H, Bonneville M, Gottrand F, Turck D. [Anastomotic stenosis after surgical treatment of esophageal atresia: frequency, risk factors and effectiveness of esophageal dilatations]. *Arch Pediatr* 2001; **8**: 268-274 [PMID: 11270250 DOI: 10.1016/S0929-693X(00)00193-7]
- Lilja HE, Wester T. Outcome in neonates with esophageal atresia treated over the last 20 years. *Pediatr Surg Int* 2008; **24**: 531-536 [PMID: 18351365 DOI: 10.1007/s00383-008-2122-z]
- Chang EY, Chang HK, Han SJ, Choi SH, Hwang EH, Oh JT. Clinical characteristics and treatment of esophageal atresia: a single institutional experience. *J Korean Surg Soc* 2012; **83**: 43-49 [PMID: 22792533 DOI: 10.4174/jkss.2012.83.1.43]
- Pane A, Foschia F, Caldaro T, De Angelis P, Torroni F, Federici G, Servedio D, Dall'Oglio L. Esophageal anastomotic severe stenosis after atresia repair: effectiveness of a multi-step strategy for an unusual endoscopic recanalization. *Endoscopy* 2008; **40** Suppl 2: E254-E255 [PMID: 18991228 DOI: 10.1055/s-2008-1077650]
- Terui K, Saito T, Mitsunaga T, Nakata M, Yoshida H. Endoscopic management for congenital esophageal stenosis: A systematic review. *World J Gastrointest Endosc* 2015; **7**: 183-191 [PMID: 25789088 DOI: 10.4253/wjge.v7.i3.183]
- Michaud L, Coutenier F, Podevin G, Bonnard A, Becmeur F, Khen-Dunlop N, Auber F, Maurel A, Gelas T, Dassonville M, Borderon C, Dabadie A, Weil D, Piolat C, Breton A, Djeddi D, Morali A, Bastiani F, Lamireau T, Gottrand F. Characteristics and management of congenital esophageal stenosis: findings from a multicenter study. *Orphanet J Rare Dis* 2013; **8**: 186 [PMID: 24289834 DOI: 10.1186/1750-1172-8-186]
- Takamizawa S, Tsugawa C, Mouri N, Satoh S, Kanegawa K, Nishijima E, Muraji T. Congenital esophageal stenosis: Therapeutic strategy based on etiology. *J Pediatr Surg* 2002; **37**: 197-201 [PMID: 11819198 DOI: 10.1053/jpsu.2002.30254]
- Newman B, Bender TM. Esophageal atresia/tracheoesophageal fistula and associated congenital esophageal stenosis. *Pediatr Radiol* 1997; **27**: 530-534 [PMID: 9174027 DOI: 10.1007/s002470050174]

- 19 **Kawahara H**, Imura K, Yagi M, Kubota A. Clinical characteristics of congenital esophageal stenosis distal to associated esophageal atresia. *Surgery* 2001; **129**: 29-38 [PMID: 11150031 DOI: 10.1067/msy.2001.109064]
- 20 **Azizkhan RG**, Stehr W, Cohen AP, Wittkugel E, Farrell MK, Lucky AW, Hammelman BD, Johnson ND, Racadio JM. Esophageal strictures in children with recessive dystrophic epidermolysis bullosa: an 11-year experience with fluoroscopically guided balloon dilatation. *J Pediatr Surg* 2006; **41**: 55-60; discussion 55-60 [PMID: 16410108 DOI: 10.1016/j.jpedsurg.2005.10.007]
- 21 **De Angelis P**, Caldaro T, Torroni F, Romeo E, Foschia F, di Abriola GF, Rea F, El Hachem M, Genovese E, D'Alessandro S, Dall'Oglio L. Esophageal stenosis in epidermolysis bullosa: a challenge for the endoscopist. *J Pediatr Surg* 2011; **46**: 842-847 [PMID: 21616238 DOI: 10.1016/j.jpedsurg.2011.02.017]
- 22 **Spiliopoulos S**, Sabharwal T, Krokidis M, Gkoutzios P, Mellerio J, Dourado R, Adam A. Fluoroscopically guided dilation of esophageal strictures in patients with dystrophic epidermolysis bullosa: long-term results. *AJR Am J Roentgenol* 2012; **199**: 208-212 [PMID: 22733914 DOI: 10.2214/AJR.11.8159]
- 23 **Uygun I**, Arslan MS, Aydogdu B, Okur MH, Otcu S. Fluoroscopic balloon dilatation for caustic esophageal stricture in children: an 8-year experience. *J Pediatr Surg* 2013; **48**: 2230-2234 [PMID: 24210191 DOI: 10.1016/j.jpedsurg.2013.04.005]
- 24 **Zanini A**, Guez S, Salera S, Farris G, Morandi A, Gentilino V, Leva E, Manzoni F, Pavesi MA, Esposito S, Macchini F. Oral viscous budesonide as a first-line approach to esophageal stenosis in epidermolysis bullosa: an open-label trial in six children. *Paediatr Drugs* 2014; **16**: 391-395 [PMID: 25138121 DOI: 10.1007/s40272-014-0086-0]
- 25 **Kelly K**, Storey L, O' Sullivan M, Butler K, McDermott M, Corbally M, McMahon C, Smith OP, O' Marcaigh A. Esophageal strictures during treatment for acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2010; **32**: 124-127 [PMID: 20168244 DOI: 10.1097/MPH.0b013e3181ced25c]
- 26 **Karadağ-Öncel E**, Keleş S, Aytaç S, Aydemir Y, Hızal G, Yüce A, Kara A. Esophageal stricture due to recurrent mucositis in a patient with acute lymphoblastic leukemia. *Türk J Pediatr* 2013; **55**: 116-117 [PMID: 23692846]
- 27 **Hagander L**, Muszynska C, Arnbjörnsson E, Sandgren K. Prophylactic treatment with proton pump inhibitors in children operated on for oesophageal atresia. *Eur J Pediatr Surg* 2012; **22**: 139-142 [PMID: 22517521 DOI: 10.1055/s-0032-1308698]
- 28 **Uhlen S**, Fayoux P, Vachin F, Guimber D, Gottrand F, Turck D, Michaud L. Mitomycin C: an alternative conservative treatment for refractory esophageal stricture in children? *Endoscopy* 2006; **38**: 404-407 [PMID: 16586239 DOI: 10.1055/s-2006-925054]
- 29 **Chapuy L**, Pomerleau M, Faure C. Topical mitomycin-C application in recurrent esophageal strictures after surgical repair of esophageal atresia. *J Pediatr Gastroenterol Nutr* 2014; **59**: 608-611 [PMID: 24590215 DOI: 10.1097/MPG.0000000000000352]
- 30 **Berger M**, Ure B, Lacher M. Mitomycin C in the therapy of recurrent esophageal strictures: hype or hope? *Eur J Pediatr Surg* 2012; **22**: 109-116 [PMID: 22517516 DOI: 10.1055/s-0032-1311695]
- 31 **Sweed AS**, Fawaz SA, Ezzat WF, Sabri SM. A prospective controlled study to assess the use of mitomycin C in improving the results of esophageal dilatation in post corrosive esophageal stricture in children. *Int J Pediatr Otorhinolaryngol* 2015; **79**: 23-25 [PMID: 25465445 DOI: 10.1016/j.ijporl.2014.10.024]
- 32 **El-Asmar KM**, Hassan MA, Abdelkader HM, Hamza AF. Topical mitomycin C application is effective in management of localized caustic esophageal stricture: a double-blinded, randomized, placebo-controlled trial. *J Pediatr Surg* 2013; **48**: 1621-1627 [PMID: 23895984 DOI: 10.1016/j.jpedsurg.2013.04.014]
- 33 **El-Asmar KM**, Hassan MA, Abdelkader HM, Hamza AF. Topical mitomycin C can effectively alleviate dysphagia in children with long-segment caustic esophageal strictures. *Dis Esophagus* 2015; **28**: 422-427 [PMID: 24708423 DOI: 10.1111/dote.12218]
- 34 **Morikawa N**, Honna T, Kuroda T, Watanabe K, Tanaka H, Takayasu H, Fujino A, Tanemura H, Matsukubo M. High dose intravenous methylprednisolone resolves esophageal stricture resistant to balloon dilatation with intralesional injection of dexamethasone. *Pediatr Surg Int* 2008; **24**: 1161-1164 [PMID: 18704454 DOI: 10.1007/s00383-008-2224-7]
- 35 **Caldaro T**, Torroni F, De Angelis P, Federici di Abriola G, Foschia F, Rea F, Romeo E, Dall'Oglio L. Dynamic esophageal stents. *Dis Esophagus* 2013; **26**: 388-391 [PMID: 23679029 DOI: 10.1111/dote.12048]
- 36 **Foschia F**, De Angelis P, Torroni F, Romeo E, Caldaro T, di Abriola GF, Pane A, Fiorenza MS, De Peppo F, Dall'Oglio L. Custom dynamic stent for esophageal strictures in children. *J Pediatr Surg* 2011; **46**: 848-853 [PMID: 21616239 DOI: 10.1016/j.jpedsurg.2011.02.014]
- 37 **Hirides MM**, van Hooft JE, Koornstra JJ, Timmer R, Leenders M, Weersma RK, Weusten BL, van Hillegersberg R, van Berge Henegouwen MI, Plukker JT, Wiersema RJ, Bergman JG, Vleggaar FP, Fockens P, Siersema PD. Endoscopic corticosteroid injections do not reduce dysphagia after endoscopic dilation therapy in patients with benign esophagogastric anastomotic strictures. *Clin Gastroenterol Hepatol* 2013; **11**: 795-801.e1 [PMID: 23376318 DOI: 10.1016/j.cgh.2013.01.016]
- 38 **Bicakci U**, Tander B, Deveci G, Rizalar R, Ariturk E, Bernay F. Minimally invasive management of children with caustic ingestion: less pain for patients. *Pediatr Surg Int* 2010; **26**: 251-255 [PMID: 19936762 DOI: 10.1007/s00383-009-2525-5]
- 39 **Atabek C**, Surer I, Demirbag S, Caliskan B, Ozturk H, Cetinkursun S. Increasing tendency in caustic esophageal burns and long-term polytetrafluorethylene stenting in severe cases: 10 years experience. *J Pediatr Surg* 2007; **42**: 636-640 [PMID: 17448758 DOI: 10.1016/j.jpedsurg.2006.12.012]
- 40 **Mutaf O**. Treatment of corrosive esophageal strictures by long-term stenting. *J Pediatr Surg* 1996; **31**: 681-685 [PMID: 8861481 DOI: 10.1016/S0022-3468(96)90674-0]
- 41 **De Peppo F**, Zaccara A, Dall'Oglio L, Federici di Abriola G, Ponticelli A, Marchetti P, Lucchetti MC, Rivosocchi M. Stenting for caustic strictures: esophageal replacement replaced. *J Pediatr Surg* 1998; **33**: 54-57 [PMID: 9473100 DOI: 10.1016/S0022-3468(98)90361-X]
- 42 **Kramer RE**, Quiros JA. Esophageal stents for severe strictures in young children: experience, benefits, and risk. *Curr Gastroenterol Rep* 2010; **12**: 203-210 [PMID: 20425474 DOI: 10.1007/s11894-010-0105-4]
- 43 **Broto J**, Asensio M, Vernet JM. Results of a new technique in the treatment of severe esophageal stenosis in children: poliflex stents. *J Pediatr Gastroenterol Nutr* 2003; **37**: 203-206 [PMID: 12883312 DOI: 10.1097/00005176-200308000-00024]
- 44 **Zhang C**, Yu JM, Fan GP, Shi CR, Yu SY, Wang HP, Ge L, Zhong WX. The use of a retrievable self-expanding stent in treating childhood benign esophageal strictures. *J Pediatr Surg* 2005; **40**: 501-504 [PMID: 15793725 DOI: 10.1016/j.jpedsurg.2004.11.041]
- 45 **Manfredi MA**, Jennings RW, Anjum MW, Hamilton TE, Smithers CJ, Lightdale JR. Externally removable stents in the treatment of benign recalcitrant strictures and esophageal perforations in pediatric patients with esophageal atresia. *Gastrointest Endosc* 2014; **80**: 246-252 [PMID: 24650853 DOI: 10.1016/j.gie.2014.01.033]
- 46 **Lange B**, Kubiak R, Wessel LM, Kähler G. Use of fully covered self-expandable metal stents for benign esophageal disorders in children. *J Laparoendosc Adv Surg Tech A* 2015; **25**: 335-341 [PMID: 25768949 DOI: 10.1089/lap.2014.0203]
- 47 **Lo A**, Baird R, De Angelis P, Lévesque D, Morinville V, di Abriola GF, Caldaro T, Laberge JM, Dall'Oglio L. Arterioesophageal fistula after stenting for esophageal atresia. *J Pediatr Gastroenterol Nutr* 2013; **56**: e30-e31 [PMID: 22357121 DOI: 10.1097/MPG.0b013e31824ffd7f]
- 48 **Vandenplas Y**, Hauser B, Devreker T, Urbain D, Reynaert H. A biodegradable esophageal stent in the treatment of a corrosive esophageal stenosis in a child. *J Pediatr Gastroenterol Nutr* 2009; **49**: 254-257 [PMID: 19561544 DOI: 10.1097/MPG.0b013e31819de871]
- 49 **Karakan T**, Utku OG, Dorukoz O, Sen I, Colak B, Erdal H, Karatay E, Tahtaci M, Cengiz M. Biodegradable stents for caustic esophageal

strictures: a new therapeutic approach. *Dis Esophagus* 2013; **26**: 319-322 [PMID: 22974043 DOI: 10.1111/j.1442-2050.2012.01418.x]
50 **Tan Y**, Zhang J, Zhou J, Duan T, Liu D. Endoscopic Incision for

the Treatment of Refractory Esophageal Anastomotic Strictures in Children. *J Pediatr Gastroenterol Nutr* 2015; **61**: 319-322 [PMID: 25844710 DOI: 10.1097/MPG.0000000000000801]

P- Reviewer: El-Asmar KM, Uygun I
S- Editor: Kong JX **L- Editor:** A **E- Editor:** Li D



Role of endoscopic retrograde cholangiopancreatography in the management of benign biliary strictures: What's new?

Rosa Ferreira, Rui Loureiro, Nuno Nunes, António Alberto Santos, Rui Maio, Marília Cravo, Maria Antónia Duarte

Rosa Ferreira, Rui Loureiro, António Alberto Santos, Marília Cravo, Gastroenterology Department, Hospital Beatriz Ângelo, 2674-514 Loures, Portugal

Nuno Nunes, Maria Antónia Duarte, Gastroenterology Department, Hospital Divino Espírito Santo, 9500-370 São Miguel-Açores, Portugal

Rui Maio, Surgery Department, Hospital Beatriz Ângelo, 2674-514 Loures, Portugal

Author contributions: Ferreira R designed research; Ferreira R, Loureiro R, Nunes N, Santos AA wrote the paper; Ferreira R, Loureiro R, Nunes N, Santos AA, Maio R, Cravo M and Duarte MA performed the collected data.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Rosa Ferreira, MD, Gastroenterology Department, Hospital Beatriz Ângelo, Avenida Carlos Teixeira, 3, 2674-514 Loures, Portugal. rosa.l.ferreira@gmail.com
Telephone: +351-966-510601
Fax: +351-219-847090

Received: June 2, 2015

Peer-review started: June 3, 2015

First decision: August 7, 2015

Revised: September 25, 2015

Accepted: December 13, 2015

Article in press: December 15, 2015

Published online: February 25, 2016

Abstract

Benign biliary strictures comprise a heterogeneous group of diseases. The most common strictures amenable to endoscopic treatment are post-cholecystectomy, post-liver transplantation, related to primary sclerosing cholangitis and to chronic pancreatitis. Endoscopic treatment of benign biliary strictures is widely used as first line therapy, since it is effective, safe, noninvasive and repeatable. Endoscopic techniques currently used are dilation, multiple plastic stents insertion and fully covered self-expandable metal stents. The main indication for dilation alone is primary sclerosing cholangitis related strictures. In the vast majority of the remaining cases, temporary placement of multiple plastic stents with/without dilation is considered the treatment of choice. Although this approach is effective, it requires multiple endoscopic sessions due to the short duration of stent patency. Fully covered self-expandable metal stents appear as a good alternative to plastic stents, since they have an increased radial diameter, longer stent patency, easier insertion technique and similar efficacy. Recent advances in endoscopic technique and various devices have allowed successful treatment in most cases. The development of novel endoscopic techniques and devices is still ongoing.

Key words: Benign biliary strictures; Bile duct stricture; Endoscopic retrograde cholangiopancreatography; Stents; Cholecystectomy; Liver transplantation; Primary sclerosing cholangitis; Chronic pancreatitis

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic treatment of benign biliary strictures has been evolved in the last decades and is widely considered as first line therapy. Among endoscopic techniques, multiple plastic stents placement is an

effective method but requires multiple endoscopic sessions. Fully covered self-expandable metal stents appear as a reasonable alternative due to their larger lumen and longer patency. Emergent data proved their efficacy, their low complications rate and cost-effectiveness. We herein discuss the endoscopic management of benign biliary strictures and focus on the outcomes, advantages and disadvantages of each endoscopic technique.

Ferreira R, Loureiro R, Nunes N, Santos AA, Maio R, Cravo M, Duarte MA. Role of endoscopic retrograde cholangiopancreatography in the management of benign biliary strictures: What's new? *World J Gastrointest Endosc* 2016; 8(4): 220-231 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/220.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.220>

INTRODUCTION

Endoscopic treatment for benign biliary strictures (BBS) has been evolving in the last decade. The vast majority of BBS are caused by postoperative biliary injuries [mainly post-cholecystectomy and orthotopic liver transplantation (OLT)] or chronic inflammatory disorders [such as chronic pancreatitis and primary sclerosing cholangitis (PSC)]. Less frequent causes of BBS include ischemia, trauma, autoimmune pancreatitis, radiation therapy, as listed in Table 1^[1-7].

Although BBS comprise a heterogeneous group of disorders with variable natural history, its etiology plays an important role in predicting endoscopic treatment success. Post-cholecystectomy BBS, whose incidence has increased 2-3 fold since the increment of laparoscopic cholecystectomy, are very responsive to endoscopic therapy^[8,9]. Bile duct strictures related to OLT can occur in 3% to 6% of patients. Among these, anastomotic strictures are more amenable to endoscopic treatment as compared to nonanastomotic strictures caused by ischemic injury^[5]. Approximately 10%-30% of patients with chronic pancreatitis will develop a symptomatic biliary stricture. However, these BBS are more resistant to endoscopic treatment with an overall lower success rate. On the other hand, BBS related to PSC showed a good response to endoscopic treatment^[5].

The diagnosis of BBS should lead to prompt treatment in order to avoid serious complications such as secondary biliary cirrhosis and end-stage liver failure^[3]. Treatment options for BBS include surgery, percutaneous approach, and endoscopic therapy. Endoscopic treatment is widely accepted as first line treatment option due to its efficacy and less invasiveness. The techniques currently used are dilation; single plastic stent; multiple large-bore plastic stents; and self-expandable metal stent (SEMS)^[1-3,5,6]. Recent advances in these endoscopic techniques and devices have allowed successful treatment of most BBS cases. When endoscopic treat-

ment fails, percutaneous and endoscopic combined approach may be attempted. Surgery is usually reserved for complete transections, prior endoscopic failure and refractory cases. Nevertheless, a consensus regarding the adequate management of BBS has not yet been established.

In this review, the authors will discuss the endoscopic management of BBS and focus on the outcomes, advantages and disadvantages of each endoscopic technique.

DIAGNOSIS

Diagnosis of BBS is usually based on the correlation between clinical, epidemiological, laboratorial data and imaging findings. Patients with biliary strictures can be completely asymptomatic or present with clinical and laboratory evidence of biliary obstruction, such as jaundice, abdominal pain, cholangitis and abnormal liver function tests^[10]. Clinical manifestations can also be related to the underlying cause of obstruction and its location. According to the distance from the stricture to the hepatic hilum, several classification systems for BBS have been proposed; most commonly used are Bismuth classification, which differs from malignant biliary strictures, and Strasberg classification (Table 2)^[11,12].

Abdominal ultrasound is typically the initial method for the evaluation of patients with biliary strictures. Accuracy levels over 90% in the detection of biliary dilation and the level of obstruction have been found. However, its accuracy for detecting the underlying cause is low and the results are operator dependent^[13].

Cross-sectional imaging modalities obtained both by computerized tomography and particularly magnetic resonance cholangiopancreatography (MRCP) can accurately delineate the biliary anatomy, location and length of the stricture. MRCP is therefore very useful before endoscopic retrograde cholangiopancreatography (ERCP) for treatment planning^[14]. Furthermore these imaging methods play a key role in differentiating benign from malignant biliary strictures and, in malignant disease, staging can be performed. Malignancy exclusion is indeed of utmost importance during the diagnostic evaluation of BBS and can be challenging. In a meta-analysis, including 4711 patients with suspected biliary obstruction, MRCP showed a sensitivity and specificity of 98% in determining the level of obstruction and 88% and 95%, respectively, in the detection of malignancy^[15]. Recent advances in magnetic resonance imaging (MRI), such as diffusion weighted MRI, have shown an improvement in the differentiation between benign and malignant lesions^[16].

The diagnostic role of ERCP in biliary obstruction evaluation has decreased with the wider availability of MRCP. However, unlike MRCP, ERCP enables tissue sampling, using biliary brushings or biopsies. A review of 16 studies including 1556 patients with biliary brushings and biopsies obtained during ERCP found an overall

Table 1 Etiology of benign biliary strictures

Post-operative injuries	Cholecystectomy Liver transplantation Hepatic resection Biliary anastomosis Biliary reconstruction Biliary enteric anastomosis
Inflammatory	Chronic pancreatitis Primary sclerosing cholangitis Autoimmune pancreatitis Choledocholithiasis Immunoglobulin G4 cholangiopathy Infections (recurrent bacterial cholangitis, tuberculosis, histoplasmosis, schistosomiasis, HIV, parasites) Postradiation therapy
Others	Ischemic (hypotension, hepatic artery thrombosis, portal biliopathy) Trauma Mirizzi syndrome Postbiliary sphincterotomy Endoscopic sclerotherapy for duodenal ulcer bleeding

HIV: Human immunodeficiency virus.

sensitivity of 41.6% and a negative predictive value of 58%^[17]. One of the reasons for this low sensitivity is the low cellularity of samples obtained; a recent study demonstrated that the identification of drunken honeycomb cells, loosely cohesive clusters of round cells and large atypical cells with foamy cytoplasm may significantly increase sensitivity^[18].

Endoscopic ultrasound (EUS) and intraductal ultrasonography (IDUS) have good accuracy in discriminating benign from malignant strictures in the extra-hepatic bile duct, but some strictures in the common duct and hilar region are difficult to identify. With the introduction of EUS guided fine needle aspiration (FNA) histological diagnosis is also possible. However, the sensitivity of EUS-FNA in distinguishing benign from malignant strictures is widely variable ranging from 43% to 86%^[19-22]. The possibility of peritoneal seeding during EUS-FNA is a limiting factor of this technique^[23].

Intraductal ultrasonography provides high-resolution images of the ductal wall and periductal structures. A review of 397 patients with indeterminate biliary strictures who performed ERCP with IDUS showed a sensitivity, specificity and accuracy of 97.6%, 98% and 92% respectively^[24].

Emerging technologies such as fluorescence *in-situ* hybridization (FISH), confocal laser endomicroscopy and direct cholangioscopy have yielded promising results in the differential diagnosis of biliary strictures. Furthermore measurement of volatile organic compounds in the bile duct fluid can help in the differentiation of benign vs malignant strictures^[25].

Fluorescence *in situ* hybridization uses fluorescently

Table 2 Classification for benign biliary strictures

Bismuth classification	
I	Low CHD stricture, > 2 cm distal to hilum
II	Proximal CHD stricture, < 2 cm distal to hilum
III	Hilar involvement up to proximal extent of CHD, but confluence preserved
IV	Confluence involved, no communication between left and right ducts
V	Type I, II or III plus stricture of an isolated (aberrant) right duct
Strasberg classification	
A	Small duct injury in continuity with biliary system, with cystic duct leak
B	Injury to sectoral duct with consequent obstruction
C	Injury to sectoral duct with consequent bile leak from a duct not in continuity with biliary system
D	Injury lateral to extrahepatic ducts
E1	Stricture located > 2 cm from bile duct confluence
E2	Stricture located < 2 cm from bile duct confluence
E3	Stricture located at bile duct confluence
E4	Stricture involving right and left bile ducts
E5	Complete occlusion of all bile ducts

CHD: Common hepatic duct.

labeled DNA probes to detect chromosomal abnormalities that can be indicative of tumor. One prospective study compared sensitivity and specificity of cytology with FISH in patients with cholangiocarcinoma and found that sensitivity of cytology was 15% compared to 34% for FISH and specificity was 91% and 98% respectively^[26]. The use of cholangioscopy-directed intraductal biopsies and FISH of brush cytology samples was shown to increase the diagnostic yield^[27,28].

Digital image analysis (DIA) uses Feulgen dye and spectrophotometric principles to quantify abnormalities in nuclear DNA that allow measuring ploidy within the cell. When FISH and DIA are used in combination a malignant diagnosis can be predicted in 67% of the cases compared with 62% and 14% for FISH and DIA when used separately^[29].

Cholangioscopy enables direct visualization and targeted biopsies. However, the sensitivity of its histologic biopsies was only 49% in the diagnosis of malignancy^[30].

Confocal laser endomicroscopy is a new diagnostic tool that uses an intravenous injected contrast agent like fluoresceine. It showed promising results in the diagnosis of biliary stenosis by using a catheter probe, which can be inserted through the working channel of an endoscope, or through a FNA needle. Several studies have shown that this new technique is rather useful in the differentiation between benign and malignant strictures of the bile duct with a high sensitivity of 73%-83%, but a low specificity of 33%-50%^[31-36].

Despite the development of these new diagnostic tools, the majority is still under evaluation in clinical trials.

ENDOSCOPIC THERAPY OF BBS

The objectives of BBS endoscopic treatment include biliary decompression with maintenance of the bile duct patency and prevention of recurrent stricture formation. This can be achieved by using expandable or graduating dilators; inserting single or multiple biliary plastic stents; inserting SEMS or, in some circumstances, by the combination of two modalities. Multiple endoscopic sessions are usually necessary before complete and sustained resolution is achieved. For those patients who may need surgery, endoscopic treatment can be considered as bridging therapy^[7].

During ERCP, there are three main technical decisions that should be made, namely the guide wire choice, the need for dilation and the stent choice. After endoscopic sphincterotomy, the crucial step is to overcome the stricture with a guide wire. The stricture can be negotiated only if there is no common bile duct complete transection. In postoperative stricture this step can be particularly difficult because the stenotic tract, even if short, can be asymmetric, angulated and rich in fibrous tissue. The choice for the adequate guide wire according to the morphology of the stricture is critical. Several types of ERCP guide wires are commercially available with different characteristics and wire tips (straight, tapered, J shaped or looped). Although there is a paucity of comparative studies, hydrophilic guide wires with a straight or J shaped tip are the preferred ones in this clinical setting^[1,37]. In a recent randomized trial involving 197 patients, a novel stiff-shaft flexible guide wire showed higher success rate in stricture cannulation (94% vs 79%, $P = 0.00041$) and lower procedure time (8.1 vs 11.2 min, $P < 0.0001$) when compared to a standard angle-tip hydrophilic wire in combination with a nitinol wire^[38]. Manipulation of guide wires demands patience, skill and optimal fluoroscopic imaging. The direction of the catheter and the wire should also be in the same axis as the stricture. Sometimes straightening the common bile duct by pulling an inflated stone extraction balloon just below the stricture or using the bending capabilities of the papilotome can be helpful. Other devices that can be used to overcome the stricture include tapered tip steerable catheters (3.9-4.9 Fr), a screw drill (7-8.5 Fr Soehendra stent extractor)^[39], angioplasty balloons mounted on 3 Fr catheters^[40], or a 6 Fr wire guided diathermic dilator^[41,42].

After overcoming the stricture with a guide wire, BBS dilation can be considered using either a balloon or bougie system. Although there is no head-to-head comparison between these two techniques, an elevated restenosis rate (up to 47%) has been consistently observed^[43-45]. Balloon dilation alone is therefore considered inappropriate in vast majority of cases. It should be performed only if necessary and during the first endoscopic procedure, because of the forceful disruption of the scar may add further traumatic damage to the tissue with subsequently development of a new

fibrotic reaction. Even so, the underlying cause of BBS should be taken into account in the final decision. According to retrospective studies, balloon dilation alone in BBS in the context of PSC can achieve a clinical and biochemical response in approximately 80% of non-cirrhotic patients^[46-49].

The next step, the choice of the stent, is currently the most contentious decision. Insertion of one plastic stent is easy to perform and cheap, but has short patency and a low rate of long-term success. A widely used alternative is a multiple plastic stent insertion method, where multiple large bore plastic stents (10 to 11.5 Fr) are inserted in the biliary tract at regular time intervals (every 3 to 6 mo) throughout one year^[50-52]. The rationale is that the gradual and continuous dilation of the stricture area may induce tissue remodeling and consolidation. Although it is a very effective technique, it requires multiple endoscopic procedures. SEMS due to its larger lumen and longer patency appear as a reasonable alternative. Bare SEMS, commonly used in malignant biliary obstruction, are not suitable for BBS since stent itself can create irreversible tissue hyperplasia and stent embedment, precluding its removal. With the evolution of stent design, partially covered and fully covered stents have been developed. These stents allow temporary placement and can therefore be used in BBS^[53].

These endoscopic techniques will be individually discussed, focusing on outcomes, advantages, disadvantages and complications.

Dilation

Dilation of BBS is mostly used as a complementary technique before stent placement and rarely as a single method. Actually, PSC is the main indication for dilation alone, when a dominant stricture (defined as a stenosis with < 1.5 mm in the main biliary duct or < 1 mm in the intra-hepatic duct) is present. Even so, the best endoscopic management is not yet defined.

In retrospective studies, dilation alone showed clinical and biochemical response in approximately 80% of non-cirrhotic PSC patients^[46-49]. There is no consensus on the method of dilation to be used, either rigid dilators or balloon dilators. If the stenosis is too tight some authors recommend rigid dilation from 5 Fr to 7 Fr followed by balloon dilators to obtain dilation up to 18 Fr to 24 Fr^[54]. In one prospective uncontrolled study involving 96 patients in which a total of 500 hundred dilations were performed over a 20-year period, the survival free of liver transplantation was 81% at 5 years and 52% after 10 years of follow-up^[55]. The use of stents in BBS related to PSC is still controversial since it was shown to be associated with increased complication rates when compared to balloon dilation. Previous studies with plastic stents showed a high risk of ascending cholangitis (up to 50%)^[56,57]. Although there are no prospective randomized controlled trials comparing dilation with dilation and stenting, a retrospective, single-center study compared endoscopic

Table 3 Studies reporting on the treatment of benign biliary strictures with multiple plastic stent

Ref.	Etiology	Total number (completed treatment) (n)	ERCP number	Balloon dilation	Maximal number of stents	Stenting duration (mo)	Follow-up after stent removal (mo)	Success after end of follow-up (%)
Bourke <i>et al</i> ^[99]	Sphincterotomy	6 (6)	5.2	-	2.2	13	27	100
Costamagna <i>et al</i> ^[51]	Various surgical procedures	45 (42)	4.1	40% of patients	3.2	12	164	89
Draganov <i>et al</i> ^[44]	Surgery (n = 19) Chronic pancreatitis (n = 9) Idiopathic (n = 1)	29 (27)	4	-	2.7	14	48	Surgery 68 Chronic pancreatitis 44
Pozsár <i>et al</i> ^[69]	Chronic pancreatitis	29 (24)	4.2	-	2.4	21	12	62
Catalano <i>et al</i> ^[68]	Chronic pancreatitis	12 (12)	4.7	-	4.3	14	47	92
Kuzela <i>et al</i> ^[100]	Cholecystectomy	43 (43)	6	In some	3.4	12	16	100
Morelli <i>et al</i> ^[101]	OLT	38 (38)	3.5	+	2.5	3.6	12	87
Tabibian <i>et al</i> ^[102]	OLT	83 (69)	4.1	+	NA	15	11	91

ERCP: Endoscopic retrgrade cholangio pancreatograph; NA: Not available; OLT: Orthotopic liver transplantation.

balloon dilation with either percutaneous or endoscopic dilation with stent placement. Stent placement did not achieve any additional benefit and was associated with more infectious complications^[58].

Based on these studies most of authors prefer dilation to stenting in patients with PSC. Stent placement should be reserved for patients with cholangitis and in patients not responding to balloon dilation. Optimal endoscopic intervention is still unclear and results from randomized trials are necessary to answer these questions.

Plastic stents

By keeping the stricture open for a prolonged period of time, plastic stents placement may allow a continuous calibration of the stenosis diameter, with tissue remodeling around the stent and a more sustained stricture resolution.

Various stenting protocols (single stent, two or multiple stents) have been described with different short and long-term results^[1,52].

Single plastic stent placement usually does not achieve good results in terms of BBS resolution or long-term follow-up. Due to their limited stent diameter, single plastic stents have only short-term patency rates, and so multiple endoscopic sessions are required. Furthermore, most of the previous studies are retrospective and heterogeneous with different patient selection criteria, dilation methods, sent diameters, follow-up periods and success definitions. For these reasons, this technique has limited clinical applications^[59].

An aggressive multiple stent strategy described by Costamagna *et al*^[50,51] for the treatment of post-operative biliary strictures is associated with better results than the Amsterdam protocol described by Bergman *et al*^[60] and, thus, is the preferred approach. After the placement of one or two plastic 10 Fr stents at the initial ERCP the maximum number of 10 Fr plastic stents (up to six) are placed at the each subsequent ERCP with stent exchange being performed every 3-4

mo until complete stricture disappearance occurs usually 12-18 mo later^[50,51]. This maximal multiple stenting was also adapted for the treatment of chronic pancreatitis and post-cholecystectomy strictures.

The placement of multiple large bore plastic stents in BBS is achieved in over 90% of patients. However, the long-term patency varies according to BBS etiology. Table 3 summaries clinical trials reported the treatment of BBS with multiple plastic stents.

In post-cholecystectomy BBS, endoscopic treatment can be performed in patients in whom the bile duct has not been transected or ligated. The maximal stent insertion strategy (1 to 6, 10 Fr stents) with 3 monthly exchanges during one year or until complete morphologic disappearance of the stricture has consistently shown good long-term results with success rates over 90% in some series even after prolonged follow-up^[61]. A recurrence rate of 20%-30% within 2 years of stent removal has been reported^[5], but these patients can be successfully retreated endoscopically. The maximal multiple stent strategy is therefore often considered the first line treatment in most cases^[5,52,61,62]. Treatment of peri-hilar stricture are, in turn, more challenging, technically difficult, and with worse success rates than distal strictures (Bismuth III 25% vs 80% in Bismuth I / II)^[5,44,63].

Similarly, in post-OLT strictures multistenting technique is considered the first line treatment. Better results are seen in early anastomotic strictures with resolution achieved within 3 mo whereas those presenting later, usually associated with fibrosis, required longer stenting periods, up to 12 to 24 mo^[64]. Balloon dilation and maximal stent placement every 3 mo seems the most effective strategy with an 80% to 90% success rate. A recently published prospective study by Kaffes *et al*^[65] which compared plastic stents with fully covered self-expandable metal stents (FCSEMS) in anastomotic strictures showed similar stricture resolution between groups after a median follow-up of 23 mo (100% in

FCSEMS group vs 80% in plastic group, $P = \text{ns}$). On the other hand, in non-anastomotic strictures endoscopic treatment can be considered either as the first line treatment or as a bridge to retransplantation^[64]. These strictures, vascular in origin, are usually multiple, proximal and its endoscopic treatment associated with low long-term success rate (50%-75%), requiring retransplantation in up to 25%-50% of patients^[5,7,62,64].

Distal common bile duct strictures in chronic pancreatitis are, in turn, more resistant to endoscopic treatment. As many remain symptomless for years its true incidence is unknown. However, 10%-30% of patients with advanced chronic pancreatitis develop a symptomatic biliary stricture^[1]. Treatment is recommended when symptoms occur; in the presence of secondary biliary cirrhosis or bile duct stones; and for persistent (more than 1 mo) asymptomatic elevation of serum alkaline phosphatase (levels greater than twice the upper limit of normal values) and/or serum bilirubin^[66]. The long-term success of single biliary plastic stent strategies has been disappointing specially in the presence of pancreatic head calcifications^[67], whereas multiple stenting for 12 or more mo led to an overall success in 65.2% of patients (60%-92% of cases)^[5,68,69]. Recurrent stricture rates reaching 17% after stent removal have been reported during a mean follow-up period of 42 mo^[5] and can be retreated by ERCP. Recently, Haapamäki *et al.*^[70] published a prospective randomized multicenter study comparing the placement of multiple plastic stents with a FCSEMS. During a stenting period of 6 mo, either strategy showed good long-term relief of the stricture, with 2-year stricture-free success of 90% for plastic stent and 92% in the FCSEMS group and no difference in stent related complications. These results need to be followed-up and the results of upcoming trials (NCT01543256) are awaited especially in this population where non-compliance is of serious concern. Due to limited efficacy, need for repeated endoscopic therapy and risk of severe septic complications associated with non-compliance, the choice between endoscopic and surgical options should rely on patient co-morbidities, expected compliance and local expertise^[5,66].

Although some authors suggested that multistenting strategy has a low rate of premature symptomatic stent occlusion and a longer occlusion free survival^[71], these stenting strategies have shown some shortcomings. It is hindered by the need of patient compliance with multiple ERCP sessions over 1-year or more; its inherent costs; and its possible adverse events like cholangitis and other stent related complications. Fully covered SEMs are therefore gaining an increasing role in the treatment of BBS, but there is a lack of published head-to-head comparisons and the results of several on-going randomized trials are awaited.

SEMS

Among endoscopic treatments of BBS, stent placement

has emerged as a less invasive therapeutic option, with lower morbidity and mortality compared to surgery^[72].

In order to overcome major limitations of plastic stents, such as suboptimal stricture resolution and need for frequent ERCPs, SEMs appeared as a good alternative. Besides the initial enthusiasm with the use of partially covered SEMs (PCSEMS), further studies revealed high rates of stent migration (up to 23%), mucosal hyperplasia (up to 36%) and stent occlusion (up to 67%)^[73-80]. Like uncovered SEMs, the clinical use of PCSEMS has been therefore abandoned^[81].

The relative ease removal of FCSEMS triggered the attention of many investigators, leading to an increased use in benign biliary conditions. FCSEMS have, in fact, a covering membrane to prevent ingrowth and hyperplastic reaction, and to improve removability. FCSEMS do not embed into the mucosa, provided that the covering membrane remains intact^[82,83]. Other advantages include an increased radial diameter, longer stent patency, and easy insertion technique^[84-86]. Therefore, FCSEMS have emerged as a promising therapeutic option in the treatment of BBS, and have largely replaced their uncovered, partially covered counterparts, as well as plastic stents. Even so, before its use can be widely recommended the following questions need to be answered. Are FCSEMS-related outcomes significantly better than plastic multistenting procedures? What is the immediate, and long-term clinical success? Can FCSEMS be effectively removed at the end of treatment? Are FCSEMS complications serious enough to preclude their use? Several studies have been published trying to address all these issues.

FCSEMS efficiency in stricture resolution has been demonstrated in several studies that range from relatively small size with less than 10 patients^[83] to more recent and larger ones with over 100 patients^[72,79,87].

In a multicenter, prospective study of 133 patients, Kahaleh *et al.*^[72] found a high response rate of stricture resolution, ranging from 61% for anastomotic strictures to 91% for post-surgical strictures, and 81% for chronic pancreatitis related strictures. FCSEMS were removed after a mean time of 95.5 ± 48.7 d. Two predictors for stricture resolution were found, namely longer indwell time (OR = 4.3, 95%CI: 1.24-15.09) and absence of migration (OR = 5.4, 95%CI: 1.001-29.29).

Most recently, Devière *et al.*^[87] evaluated the ability to remove FCSEMS after extended indwell and the frequency and durability of stricture resolution. In this prospective, nonrandomized, multinational study of 187 patients stent removal was scheduled at 10-12 mo for patients with chronic pancreatitis or cholecystectomy related strictures, and at 4-6 mo for patients who received liver transplant. Stricture resolution occurred in 76.3% of patients (95%CI: 69.3%-82.3%). Removal success was accomplished in 74.6% (95%CI: 67.5%-80.8%) and it was more frequent in the chronic pancreatitis group (80.5%) than in the liver transplantation (63.4%) or cholecystectomy (61.1%) groups

($P = 0.017$). Endoscopic removal of FCSEMS was accomplished in all patients in whom this procedure was attempted. As such, in some types of BBS, FCSEMS can be left *in situ* for 1-year without compromising removability.

Although FCSEMS feasibility has been well established, comparative studies on the efficacy of multiple plastic stents are still lacking. To the best of our knowledge, only two prospective randomized trials comparing FCSEMS to plastic stents have been published. Kaffes *et al.*^[65], in a study of 32 patients with anastomotic post-liver transplant, showed that FCSEMS reduced the number of ERCPs needed to achieve stricture resolution (median 2 vs 4, $P = 0.0001$) with similar recurrence rates. There was no significant statistical difference between groups neither in stricture resolution (100% in FCSEMS group vs 80% in plastic group, $P = ns$), nor in complication rate (10% in FCSEMS group vs 50% in plastic group, $P = 0.051$). No cases of migration were observed in FCSEMS group. Cost analyses showed that FCSEMS was more cost effective. In the other multicenter, randomized trial, 60 patients with BBS caused by chronic pancreatitis were included. At 6 mo after randomization, all stents were removed and the patients were followed at 6 mo and 2 years after stent removal. The stricture-free success rate after 2 years was 90% (95%CI: 72%-97%) in the plastic group and 92% (95%CI: 70%-98%) in the FCSEMS group ($P = 0.405$). Stent migration was similar in both groups (10% in plastic group vs 7% in FCSEMS group, $P = 1$)^[70]. Recently a systematic review showed a tendency to successful use of FCSEMS in BBS related to chronic pancreatitis [77% (95%CI: 61%-94%) vs 33% (95%CI: 4%-63%), $P = 0.06$] with fewer endoscopic sessions (1.5 vs 3.9, $P = 0.0002$) and subsequently fewer complications. However, these results were not observed in other BBS etiologies other than chronic pancreatitis^[88].

Interestingly, in BBS related to chronic pancreatitis (particularly in calcified pancreatitis) the previous studies with multiple plastic stents showed inferior response to endoscopic therapy. On the contrary, as stated before, there is increasing evidence of a better success rate and lower recurrence rate with FCSEMS. It is thought that both the diameter of the FCSEMS and the duration of indwell may contribute to these findings^[82,87].

Among the available literature, stent duration is not homogeneous or standardized. Even so, it seems that a short stenting period might not be enough to allow for adequate tissue repair. Longer stenting duration should be therefore considered, as it has been independently associated with stricture resolution^[72,87,89].

The drawbacks of FCSEMS include stent migration, duodenal reflux and tissue hyperplasia^[2]. These issues should be addressed in the development of new stents in order to reinforce stent quality. Stent migration is, in fact, the major obstacle of FCSEMS. To minimize stent migration, the concept of flared ends (FE) and anchoring flaps has been introduced. Park *et al.*^[90], compared 2 stents, both with FE at the distal portion and with either

4 anchoring-fins (AF) or FE at the proximal end, in 43 BBS patients. Stents remained *in situ* for a median of 6 mo (interquartile range, 4 to 6) and no migrations were seen in the AF group, whereas a 33% migration was seen in the FE group ($P = 0.004$). Immediate stricture resolution was noted in 91% of patients with AF and 88% of those with FE. Recurrence during the median 4 mo follow-up period after stent removal occurred in 7 patients in total (16%) with no significant difference between the 2 groups. All nonmigrated stents were successfully removed without complications. The authors concluded that the AF design might be superior to the FE regarding antimigration effect for BBS. More recently, Walter *et al.*^[91] conducted a prospective, multicenter cohort study with a novel Niti-S biliary bumpy stent with bilateral FE and a high conformability at the middle part of the stent. In this study, involving 38 patients, the stent was removed after 3 mo. Despite the initial clinical success rate of 80%, the long-term clinical success rate was only 63% and stent migration occurred in 31% of patients. Regarding duodenal reflux issue, some studies using SEMS with antireflux valve have been conducted. However, only cases of malignant biliary obstruction were included^[92-94].

Besides stent migration, acute cholangitis, cholecystitis and pancreatitis have also been reported with FCSEMS placement^[65,70,87,88]. Even so, complications did not preclude its use in the treatment of BBS^[72,82].

After FCSEMS placement, clinical, laboratory and radiological follow-up has not yet been defined. Some authors advocate clinical follow-up for symptom recurrence and liver function tests every 3-6 mo for a minimum of 2 years after stent removal, then yearly with a baseline transabdominal ultrasound or MRCP^[79].

Based on these more recent data, FCSEMS might be recommended as the first line option for BBS, particularly in certain groups of patients, like chronic pancreatitis. Table 4 outlines the main prospective trials regarding FCSEMS use in BBS endoscopic treatment.

NEW AREAS OF RESEARCH

Bioabsorbable self-expandable stent is a growing area of interest in BBS treatment. This type of stent has a larger lumen than plastic stents, which allows better patency rate and reduced biofilm formation. Unlike FCSEMS, it does not require removal of stent and can reduce biliary mucosal hyperplasia. It is a braided structure of filaments made of absorbent polydioxanone or polylactide^[3]. After sent insertion, balloon dilation may be required to promote additional expansion of lumen, because of its radial force is weaker than FCSEMS. In animal models, biostents showed endoscopically deployment with success, expansion to full diameter, and maintenance of patency up to 9 mo^[95-97]. To the best of our knowledge, biodegradable stent have been currently experimented only in animal models^[95-97].

Recently, is has been published some early and

Table 4 Prospective trials reporting placement of self-expandable metal stents in benign biliary strictures

Ref.	No. patients	Etiology	Type of stent	Clinical success (%)	Adverse events (%)	Migration rate (%)	Median follow-up
Park do <i>et al</i> ^[90]	33	CP, BDS, OLT, postsurgical	FCSEMS with 4 AF; FCSEMS with both FE	91 with AF; 88 with FE	3	0 with AF; 33 with FE	6 mo (IQR 4-6)
Wagh <i>et al</i> ^[82]	23	CP, BDS, OLT, idiopathic	Wallflex	96-short term 83-long term	4.3	39	18.8 mo (IQR 14.1-21.3)
Kahaleh <i>et al</i> ^[72]	133	CP, OLT	FCSEMS flared	67	3.1	10.5	95.5 ± 48.7 d
Devrière <i>et al</i> ^[87]	187	CP, OLT, CCY	Wallflex	76.3	27.3	29.4	20.3 mo (IQR 12.9-24.3)
Kaffes <i>et al</i> ^[65]	32	OLT	10 FCSEMS; 10 plastic stent	100 in FCSEMS; 80 in plastic stent	1 in FCSEMS, 5 in plastic stent	0 in FCSEMS	24.5 mo (range 4-38) in FCSEMS; 23 (range 1-42) in plastic stent
Haapamäki <i>et al</i> ^[70]	60	CP	30 FCSEMS; 30 plastic stent	92 in FCSEMS; 90 in plastic stent	29	10 in FCSEMS; 7 in plastic stent	40 mo (range-66)

AF: Anchoring fins; BDS: Bile duct stones; CCY: Cholecystectomy; CP: Chronic pancreatitis; FE: Fared ends; FCSEMS: Fully covered self-expandable metal stents; IQR: Interquartile range; OLT: Orthotic liver transplantation.

exciting work looking at intraductal radiofrequency ablation (RFA) in the treatment of BBS. In a pilot study, Hu *et al*^[98] performed intraductal bipolar radiofrequency at power 10W for 90 s/stricture, followed by balloon dilation with/without stent placement, in 9 BBS patients. Seven of them were refractory at endoscopic or percutaneous interventions. The treatment concept is aimed to using ablation power rather than using boogie effect to treat the structure. After RFA, stricture of all patients showed immediate improvement and five patients (55%) achieved stricture resolution during a follow-up of 12.6 mo. Three of the nine patients required no further stenting. Thus, RFA therapy is a new method that appears promising particularly in refractory cases.

CONCLUSION

Over the past 20 years, the progress and development of endoscopic devices and therapeutic options in the management of BBS have been really remarkable. Several prospective randomized trials have been recently published; including the most waited which compare FCSEMS with plastic stents.

Although multiple plastic stent insertion remains a very effective method in the vast majority of patients, there are emergent data suggesting that FCSEMS may be a reasonable alternative treatment option. The most recent studies support its efficacy, its relative low migration rate and low complications rate, and cost-effectiveness. However, data that clearly demonstrate the superiority of FCSEMS over plastic multistenting procedures are lacking. Thus, randomized, controlled trials assessing stent efficacy, complications, and cost-effectiveness are needed before a routine use of FCSEMS can be recommended. Also new functional SEMS are waited; the ideal stent characteristics have not been yet defined. In the near future, not only new techniques, like RFA, but also other therapies involving new devices will be available in clinical practice.

REFERENCES

- 1 **Costamagna G**, Boskoski I. Current treatment of benign biliary strictures. *Ann Gastroenterol* 2013; **26**: 37-40 [PMID: 24714594]
- 2 **Pausawasadi N**, Soontornmanokul T, Rerknimitr R. Role of fully covered self-expandable metal stent for treatment of benign biliary strictures and bile leaks. *Korean J Radiol* 2012; **13** Suppl 1: S67-S73 [PMID: 22563290 DOI: 10.3348/kjr.2012.13.S1.S67]
- 3 **Kwon CI**, Ko KH, Hahm KB, Kang DH. Functional self-expandable metal stents in biliary obstruction. *Clin Endosc* 2013; **46**: 515-521 [PMID: 24143314 DOI: 10.5946/ce.2013.46.5.515]
- 4 **Singh A**, Gelrud A, Agarwal B. Biliary strictures: diagnostic considerations and approach. *Gastroenterol Rep (Oxf)* 2015; **3**: 22-31 [PMID: 25355800 DOI: 10.1093/gastro/gou072]
- 5 **Chathadi KV**, Chandrasekhara V, Acosta RD, Decker GA, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fanelli RD, Fisher DA, Foley K, Fonkalsrud L, Hwang JH, Jue TL, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Shaikat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The role of ERCP in benign diseases of the biliary tract. *Gastrointest Endosc* 2015; **81**: 795-803 [PMID: 25665931 DOI: 10.1016/j.gie.2014.11.019]
- 6 **Pfau PR**, Pleskow DK, Banerjee S, Barth BA, Bhat YM, Desilets DJ, Gottlieb KT, Maple JT, Siddiqui UD, Tokar JL, Wang A, Song LM, Rodriguez SA. Pancreatic and biliary stents. *Gastrointest Endosc* 2013; **77**: 319-327 [PMID: 23410693 DOI: 10.1016/j.gie.2012.09.026]
- 7 **Chan CH**, Telford JJ. Endoscopic management of benign biliary strictures. *Gastrointest Endosc Clin N Am* 2012; **22**: 511-537 [PMID: 22748246 DOI: 10.1016/j.giec.2012.05.005]
- 8 **Archer SB**, Brown DW, Smith CD, Branum GD, Hunter JG. Bile duct injury during laparoscopic cholecystectomy: results of a national survey. *Ann Surg* 2001; **234**: 549-558; discussion 558-559 [PMID: 11573048 DOI: 10.1097/0000658-200110000-00014]
- 9 **Nuzzo G**, Giuliani F, Giovannini I, Ardito F, D'Acapito F, Vellone M, Murazio M, Capelli G. Bile duct injury during laparoscopic cholecystectomy: results of an Italian national survey on 56 591 cholecystectomies. *Arch Surg* 2005; **140**: 986-992 [PMID: 16230550 DOI: 10.1001/archsurg.140.10.986]
- 10 **Warshaw AL**, Schapiro RH, Ferrucci JT, Galdabini JJ. Persistent obstructive jaundice, cholangitis, and biliary cirrhosis due to common bile duct stenosis in chronic pancreatitis. *Gastroenterology* 1976; **70**: 562-567 [PMID: 943356]
- 11 **Bismuth H**. Postoperative strictures of the biliary tract. In: Blumgart L, editor. *The biliary tract clinical surgery international*. Edinburgh: Churchill Livingstone, 1982: 209-218

- 12 **Strasberg SM**, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *J Am Coll Surg* 1995; **180**: 101-125 [PMID: 8000648]
- 13 **Saini S**. Imaging of the hepatobiliary tract. *N Engl J Med* 1997; **336**: 1889-1894 [PMID: 9197218 DOI: 10.1056/NEJM.199706263362607]
- 14 **Khalid TR**, Casillas VJ, Montalvo BM, Centeno R, Levi JU. Using MR cholangiopancreatography to evaluate iatrogenic bile duct injury. *AJR Am J Roentgenol* 2001; **177**: 1347-1352 [PMID: 11717081 DOI: 10.2214/ajr.177.6.1771347]
- 15 **Romagnuolo J**, Bardou M, Rahme E, Joseph L, Reinhold C, Barkun AN. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. *Ann Intern Med* 2003; **139**: 547-557 [PMID: 14530225 DOI: 10.7326/0003-4819-139-7-200310070-00006]
- 16 **Lee NK**, Kim S, Seo HI, Kim DU, Woo HY, Kim TU. Diffusion-weighted MR imaging for the differentiation of malignant from benign strictures in the peripapillary region. *Eur Radiol* 2013; **23**: 1288-1296 [PMID: 23223836 DOI: 10.1007/s00330-012-2725-6]
- 17 **Burnett AS**, Calvert TJ, Chokshi RJ. Sensitivity of endoscopic retrograde cholangiopancreatography standard cytology: 10-y review of the literature. *J Surg Res* 2013; **184**: 304-311 [PMID: 23866788 DOI: 10.1016/j.jss.2013.06.028]
- 18 **Salomao M**, Gonda TA, Margolskee E, Eguia V, Remotti H, Poneros JM, Sethi A, Saqi A. Strategies for improving diagnostic accuracy of biliary strictures. *Cancer Cytopathol* 2015; **123**: 244-252 [PMID: 25564796 DOI: 10.1002/cncy.21509]
- 19 **DeWitt J**, Misra VL, Leblanc JK, McHenry L, Sherman S. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. *Gastrointest Endosc* 2006; **64**: 325-333 [PMID: 16923477 DOI: 10.1016/j.gie.2005.11.064]
- 20 **Rösch T**, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, Allescher HD, Classen M, Barbur M, Schenck U, Werner M. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. *Gastrointest Endosc* 2004; **60**: 390-396 [PMID: 15332029 DOI: 10.1016/S0016-5107(04)01732-8]
- 21 **Eloubeidi MA**, Chen VK, Jhala NC, Eltoun IE, Jhala D, Chhieng DC, Syed SA, Vickers SM, Mel Wilcox C. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2004; **2**: 209-213 [PMID: 15017604 DOI: 10.1016/S1542-3565(04)00005-9]
- 22 **Topazian M**. Endoscopic ultrasonography in the evaluation of indeterminate biliary strictures. *Clin Endosc* 2012; **45**: 328-330 [PMID: 22977829 DOI: 10.5946/ce.2012.45.3.328]
- 23 **Heimbach JK**, Sanchez W, Rosen CB, Gores GJ. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *HPB (Oxford)* 2011; **13**: 356-360 [PMID: 21492336 DOI: 10.1111/j.1477-2574.2011.00298.x]
- 24 **Meister T**, Heinzow HS, Woestmeyer C, Lenz P, Menzel J, Kucharzik T, Domschke W, Domagk D. Intraductal ultrasound substantiates diagnostics of bile duct strictures of uncertain etiology. *World J Gastroenterol* 2013; **19**: 874-881 [PMID: 23430958 DOI: 10.3748/wjg.v19.i6.874]
- 25 **Navaneethan U**, Parsi MA, Gutierrez NG, Bhatt A, Venkatesh PG, Lourdasamy D, Grove D, Hammel JP, Jang S, Sanaka MR, Stevens T, Vargo JJ, Dweik RA. Volatile organic compounds in bile can diagnose malignant biliary strictures in the setting of pancreatic cancer: a preliminary observation. *Gastrointest Endosc* 2014; **80**: 1038-1045 [PMID: 24929484 DOI: 10.1016/j.gie.2014.04.016]
- 26 **Kipp BR**, Stadheim LM, Halling SA, Pochron NL, Harmsen S, Nagorney DM, Sebo TJ, Therneau TM, Gores GJ, de Groen PC, Baron TH, Levy MJ, Halling KC, Roberts LR. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. *Am J Gastroenterol* 2004; **99**: 1675-1681 [PMID: 15330900 DOI: 10.1111/j.1572-0241.2004.30281.x]
- 27 **Moreno Luna LE**, Kipp B, Halling KC, Sebo TJ, Kremers WK, Roberts LR, Barr Fritcher EG, Levy MJ, Gores GJ. Advanced cytologic techniques for the detection of malignant pancreaticobiliary strictures. *Gastroenterology* 2006; **131**: 1064-1072 [PMID: 17030177 DOI: 10.1053/j.gastro.2006.08.021]
- 28 **Harewood GC**. Endoscopic tissue diagnosis of cholangiocarcinoma. *Curr Opin Gastroenterol* 2008; **24**: 627-630 [PMID: 19122506 DOI: 10.1097/MOG.0b013e32830bf7e1]
- 29 **Levy MJ**, Baron TH, Clayton AC, Enders FB, Gostout CJ, Halling KC, Kipp BR, Petersen BT, Roberts LR, Rumalla A, Sebo TJ, Topazian MD, Wiersma MJ, Gores GJ. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. *Am J Gastroenterol* 2008; **103**: 1263-1273 [PMID: 18477350 DOI: 10.1111/j.1572-0241.2007.01776.x]
- 30 **Chen YK**, Parsi MA, Binmoeller KF, Hawes RH, Pleskow DK, Slivka A, Haluszka O, Petersen BT, Sherman S, Devière J, Meisner S, Stevens PD, Costamagna G, Ponchon T, Peetermans JA, Neuhaus H. Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos). *Gastrointest Endosc* 2011; **74**: 805-814 [PMID: 21762903 DOI: 10.1016/j.gie.2011.04.016]
- 31 **Giovannini M**, Bories E, Monges G, Pesenti C, Caillol F, Delpero JR. Results of a phase I-II study on intraductal confocal microscopy (IDCM) in patients with common bile duct (CBD) stenosis. *Surg Endosc* 2011; **25**: 2247-2253 [PMID: 21424206 DOI: 10.1007/s00464-010-1542-8d]
- 32 **Meining A**, Chen YK, Pleskow D, Stevens P, Shah RJ, Chuttani R, Michalek J, Slivka A. Direct visualization of indeterminate pancreaticobiliary strictures with probe-based confocal laser endomicroscopy: a multicenter experience. *Gastrointest Endosc* 2011; **74**: 961-968 [PMID: 21802675 DOI: 10.1016/j.gie.2011.05.009]
- 33 **Meining A**, Frimberger E, Becker V, Von Delius S, Von Weyhern CH, Schmid RM, Prinz C. Detection of cholangiocarcinoma in vivo using miniprobe-based confocal fluorescence microscopy. *Clin Gastroenterol Hepatol* 2008; **6**: 1057-1060 [PMID: 18639496 DOI: 10.1016/j.cgh.2008.04.014]
- 34 **Lim LG**, von Delius S, Meining A. Cholangioscopy and probe-based confocal laser endomicroscopy in the diagnosis of an unusual liver cyst. Diagnosis: Biliary intraductal papillary mucinous neoplasia. *Gastroenterology* 2011; **141**: e5-e6 [PMID: 21878331 DOI: 10.1053/j.gastro.2010.06.081]
- 35 **Chennat J**, Konda VJ, Madrigal-Hoyos E, Fernandez-Sordo J, Xiao SY, Hart J, Waxman I. Biliary confocal laser endomicroscopy real-time detection of cholangiocarcinoma. *Dig Dis Sci* 2011; **56**: 3701-3706 [PMID: 21695400 DOI: 10.1007/s10620-011-1795-7]
- 36 **Caillol F**, Bories E, Poizat F, Pesenti C, Esterni B, Monges G, Giovannini M. Endomicroscopy in bile duct: Inflammation interferes with pCLE applied in the bile duct: A prospective study of 54 patients. *United European Gastroenterol J* 2013; **1**: 120-127 [PMID: 24917949 DOI: 10.1177/2050640613483462]
- 37 **Somogyi L**, Chuttani R, Croffie J, Disario J, Liu J, Mishkin D, Shah R, Tierney W, Wong Kee Song LM, Petersen BT. Guidewires for use in GI endoscopy. *Gastrointest Endosc* 2007; **65**: 571-576 [PMID: 17383455 DOI: 10.1016/j.gie.2006.10.003]
- 38 **Albert JG**, Lucas K, Filmann N, Herrmann E, Schröder O, Sarrazin C, Trojan J, Kronenberger B, Bojunga J, Zeuzem S, Friedrich-Rust M. A novel, stiff-shaft, flexible-tip guidewire for cannulation of biliary stricture during endoscopic retrograde cholangiopancreatography: a randomized trial. *Endoscopy* 2014; **46**: 857-861 [PMID: 25208030 DOI: 10.1055/s-0034-1377628]
- 39 **Baron TH**, Morgan DE. Dilation of a difficult benign pancreatic duct stricture using the Soehendra stent extractor. *Gastrointest Endosc* 1997; **46**: 178-180 [PMID: 9283873 DOI: 10.1016/S0016-5107(97)70071-3]
- 40 **Baron TH**, Poterucha JJ. Use of a small-caliber angioplasty balloon for the management of an impassable choledochcholedochal anastomotic biliary stricture. *Liver Transpl* 2008; **14**: 1683-1684 [PMID: 18975279 DOI: 10.1002/lt.21521]
- 41 **Kawakami H**, Abo D, Kawakubo K, Kuwatani M, Yoshino Y, Kubota Y, Abe Y, Kawahata S, Kubo K, Sakuhara Y, Shirato H, Sakamoto N. Rendezvous biliary recanalization combining percutaneous and endoscopic techniques using a diathermic dilator for bile duct obstruction. *Endoscopy* 2014; **46** Suppl 1 UCTN: E460-E461 [PMID: 25314194 DOI: 10.1055/s-0034-1377553]

- 42 **Kawakami H**, Kuwatani M, Kawakubo K, Eto K, Haba S, Kudo T, Abe Y, Kawahata S, Sakamoto N. Transpapillary dilation of refractory severe biliary stricture or main pancreatic duct by using a wire-guided diathermic dilator (with video). *Gastrointest Endosc* 2014; **79**: 338-343 [PMID: 24021490 DOI: 10.1016/j.gie.2013.07.055]
- 43 **Smith MT**, Sherman S, Lehman GA. Endoscopic management of benign strictures of the biliary tree. *Endoscopy* 1995; **27**: 253-266 [PMID: 7664705 DOI: 10.1055/s-2007-1005681]
- 44 **Draganov P**, Hoffman B, Marsh W, Cotton P, Cunningham J. Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. *Gastrointest Endosc* 2002; **55**: 680-686 [PMID: 11979250 DOI: 10.1067/mge.2002.122955]
- 45 **Foutch PG**, Sivak MV. Therapeutic endoscopic balloon dilatation of the extrahepatic biliary ducts. *Am J Gastroenterol* 1985; **80**: 575-580 [PMID: 4014111]
- 46 **van Milligen de Wit AW**, van Bracht J, Rauws EA, Jones EA, Tytgat GN, Huibregtse K. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. *Gastrointest Endosc* 1996; **44**: 293-299 [PMID: 8885349 DOI: 10.1016/S0016-5107(96)70167-0]
- 47 **May GR**, Bender CE, LaRusso NF, Wiesner RH. Nonoperative dilatation of dominant strictures in primary sclerosing cholangitis. *AJR Am J Roentgenol* 1985; **145**: 1061-1064 [PMID: 3876737 DOI: 10.2214/ajr.145.5.1061]
- 48 **Dickson ER**, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, LaRusso NF, Malinchoc M, Chapman RW, Kaplan MM. Primary sclerosing cholangitis: refinement and validation of survival models. *Gastroenterology* 1992; **103**: 1893-1901 [PMID: 1451982]
- 49 **Baluyut AR**, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2001; **53**: 308-312 [PMID: 11231388]
- 50 **Costamagna G**, Pandolfi M, Mutignani M, Spada C, Perri V. Long-term results of endoscopic management of postoperative bile duct strictures with increasing numbers of stents. *Gastrointest Endosc* 2001; **54**: 162-168 [PMID: 11474384 DOI: 10.1067/mge.2001.116876]
- 51 **Costamagna G**, Tringali A, Mutignani M, Perri V, Spada C, Pandolfi M, Galasso D. Endotherapy of postoperative biliary strictures with multiple stents: results after more than 10 years of follow-up. *Gastrointest Endosc* 2010; **72**: 551-557 [PMID: 20630514 DOI: 10.1016/j.gie.2010.04.052]
- 52 **Perri V**, Familiari P, Tringali A, Boskoski I, Costamagna G. Plastic biliary stents for benign biliary diseases. *Gastrointest Endosc Clin N Am* 2011; **21**: 405-33, viii [PMID: 21684462 DOI: 10.1016/j.giec.2011.04.012]
- 53 **Baron TH**. Covered self-expandable metal stents for benign biliary tract diseases. *Curr Opin Gastroenterol* 2011; **27**: 262-267 [PMID: 21248636 DOI: 10.1097/MOG.0b013e3283438a26]
- 54 **Gotthardt D**, Stiehl A. Endoscopic retrograde cholangio-pancreatography in diagnosis and treatment of primary sclerosing cholangitis. *Clin Liver Dis* 2010; **14**: 349-358 [PMID: 20682240 DOI: 10.1016/j.cld.2010.03.010]
- 55 **Gotthardt DN**, Rudolph G, Klöters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. *Gastrointest Endosc* 2010; **71**: 527-534 [PMID: 20189511 DOI: 10.1016/j.gie.2009.10.041]
- 56 **Stiehl A**, Rudolph G, Klöters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol* 2002; **36**: 151-156 [PMID: 11830325 DOI: 10.1016/S0168-8278(01)00251-3]
- 57 **Berstad AE**, Aabakken L, Smith HJ, Aasen S, Boberg KM, Schrumpf E. Diagnostic accuracy of magnetic resonance and endoscopic retrograde cholangiography in primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2006; **4**: 514-520 [PMID: 16616358 DOI: 10.1016/j.cgh.2005.10.007]
- 58 **Kaya M**, Petersen BT, Angulo P, Baron TH, Andrews JC, Gostout CJ, Lindor KD. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. *Am J Gastroenterol* 2001; **96**: 1059-1066 [PMID: 11316147 DOI: 10.1111/j.1572-0241.2001.03690.x]
- 59 **Katanuma A**, Maguchi H, Takahashi K, Osanai M, Yane K, Kin T, Matsumoto K, Matsumori T, Takaki R, Gon K, Tomonari A. Endoscopic management of benign biliary stricture: should we treat more aggressively? *Dig Endosc* 2014; **26**: 536-537 [PMID: 25040210 DOI: 10.1111/den.12287]
- 60 **Bergman JJ**, Burgemeister L, Bruno MJ, Rauws EA, Gouma DJ, Tytgat GN, Huibregtse K. Long-term follow-up after biliary stent placement for postoperative bile duct stenosis. *Gastrointest Endosc* 2001; **54**: 154-161 [PMID: 11474383 DOI: 10.1067/mge.2001.116455]
- 61 **Dumonceau JM**, Tringali A, Blero D, Devière J, Laugier R, Heresbach D, Costamagna G. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 2012; **44**: 277-298 [PMID: 22297801 DOI: 10.1055/s-0031-1291633]
- 62 **Rustagi T**, Jamidar PA. Endoscopic management of benign biliary strictures. *Curr Gastroenterol Rep* 2015; **17**: 422 [PMID: 25613176 DOI: 10.1007/s11894-014-0422-0]
- 63 **Draganov P**, Patel A, Fazel A, Toskes P, Forsmark C. Prospective evaluation of the accuracy of the intraductal secretin stimulation test in the diagnosis of chronic pancreatitis. *Clin Gastroenterol Hepatol* 2005; **3**: 695-699 [PMID: 16206503 DOI: 10.1016/S1542-3565(05)00364-2]
- 64 **Baron TH**, Davee T. Endoscopic management of benign bile duct strictures. *Gastrointest Endosc Clin N Am* 2013; **23**: 295-311 [PMID: 23540962 DOI: 10.1016/j.giec.2013.01.001]
- 65 **Kaffes A**, Griffin S, Vaughan R, James M, Chua T, Tee H, Dinesen L, Corte C, Gill R. A randomized trial of a fully covered self-expandable metallic stent versus plastic stents in anastomotic biliary strictures after liver transplantation. *Therap Adv Gastroenterol* 2014; **7**: 64-71 [PMID: 24587819 DOI: 10.1177/1756283X13503614]
- 66 **Dumonceau JM**, Delhaye M, Tringali A, Dominguez-Munoz JE, Poley JW, Arvanitaki M, Costamagna G, Costea F, Devière J, Eisendrath P, Lakhtakia S, Reddy N, Fockens P, Ponchon T, Bruno M. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2012; **44**: 784-800 [PMID: 22752888 DOI: 10.1055/s-0032-1309840]
- 67 **Kahl S**, Zimmermann S, Genz I, Glasbrenner B, Pross M, Schulz HU, Mc Namara D, Schmidt U, Malferteiner P. Risk factors for failure of endoscopic stenting of biliary strictures in chronic pancreatitis: a prospective follow-up study. *Am J Gastroenterol* 2003; **98**: 2448-2453 [PMID: 14638347 DOI: 10.1111/j.1572-0241.2003.08667.x]
- 68 **Catalano MF**, Linder JD, George S, Alcocer E, Geenen JE. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs. multiple simultaneous stents. *Gastrointest Endosc* 2004; **60**: 945-952 [PMID: 15605010 DOI: 10.1016/S0016-5107(04)02275-8]
- 69 **Pozsár J**, Sahin P, László F, Forró G, Topa L. Medium-term results of endoscopic treatment of common bile duct strictures in chronic calcifying pancreatitis with increasing numbers of stents. *J Clin Gastroenterol* 2004; **38**: 118-123 [PMID: 14745285 DOI: 10.1097/00004836-200402000-00007]
- 70 **Haapamäki C**, Kylänpää L, Udd M, Lindström O, Grönroos J, Saarela A, Mustonen H, Halttunen J. Randomized multicenter study of multiple plastic stents vs. covered self-expandable metallic stent in the treatment of biliary stricture in chronic pancreatitis. *Endoscopy* 2015; **47**: 605-610 [PMID: 25590182 DOI: 10.1055/s-0034-1391331]
- 71 **Lawrence C**, Romagnuolo J, Payne KM, Hawes RH, Cotton PB. Low symptomatic premature stent occlusion of multiple plastic stents for benign biliary strictures: comparing standard and prolonged stent change intervals. *Gastrointest Endosc* 2010; **72**: 558-563 [PMID: 20638060 DOI: 10.1016/j.gie.2010.05.029]

- 72 **Kahaleh M**, Brijbassie A, Sethi A, Degaetani M, Poneros JM, Loren DE, Kowalski TE, Sejjal DV, Patel S, Rosenkranz L, McNamara KN, Raijman I, Talreja JP, Gaidhane M, Sauer BG, Stevens PD. Multicenter trial evaluating the use of covered self-expanding metal stents in benign biliary strictures: time to revisit our therapeutic options? *J Clin Gastroenterol* 2013; **47**: 695-699 [PMID: 23442836 DOI: 10.1097/MCG.0b013e31827fd311]
- 73 **Cantù P**, Hookey LC, Morales A, Le Moine O, Devière J. The treatment of patients with symptomatic common bile duct stenosis secondary to chronic pancreatitis using partially covered metal stents: a pilot study. *Endoscopy* 2005; **37**: 735-739 [PMID: 16032492 DOI: 10.1055/s-2005-870130]
- 74 **Tringali A**, Mutignani M, Perri V, Zuccalà G, Cipolletta L, Bianco MA, Rotondano G, Philipper M, Schumacher B, Neuhaus H, Schmit A, Devière J, Costamagna G. A prospective, randomized multicenter trial comparing DoubleLayer and polyethylene stents for malignant distal common bile duct strictures. *Endoscopy* 2003; **35**: 992-997 [PMID: 14648409 DOI: 10.1055/s-2003-44601]
- 75 **Kahaleh M**, Behm B, Clarke BW, Brock A, Shami VM, De La Rue SA, Sundaram V, Tokar J, Adams RB, Yeaton P. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). *Gastrointest Endosc* 2008; **67**: 446-454 [PMID: 18294506 DOI: 10.1016/j.gie.2007.06.057]
- 76 **Sauer B**, Talreja J, Ellen K, Ku J, Shami VM, Kahaleh M. Temporary placement of a fully covered self-expandable metal stent in the pancreatic duct for management of symptomatic refractory chronic pancreatitis: preliminary data (with videos). *Gastrointest Endosc* 2008; **68**: 1173-1178 [PMID: 19028226 DOI: 10.1016/j.gie.2008.06.011]
- 77 **Chaput U**, Scatton O, Richard P, Ponchon T, Chrysostalis A, Gaudric M, Mangialavori L, Duchmann JC, Massault PP, Conti F, Calmus Y, Chaussade S, Soubrane O, Prat F. Temporary placement of partially covered self-expandable metal stents for anastomotic biliary strictures after liver transplantation: a prospective, multicenter study. *Gastrointest Endosc* 2010; **72**: 1167-1174 [PMID: 20970790 DOI: 10.1016/j.gie.2010.08.016]
- 78 **Waldthaler A**, Schütte K, Weigt J, Kropf S, Malfertheiner P, Kahl S. Long-term outcome of self expandable metal stents for biliary obstruction in chronic pancreatitis. *JOP* 2013; **14**: 57-62 [PMID: 23306336 DOI: 10.6092/1590-8577/870]
- 79 **Irani S**, Baron TH, Akbar A, Lin OS, Gluck M, Gan I, Ross AS, Petersen BT, Topazian M, Kozarek RA. Endoscopic treatment of benign biliary strictures using covered self-expandable metal stents (CSEMS). *Dig Dis Sci* 2014; **59**: 152-160 [PMID: 24061590 DOI: 10.1007/s10620-013-2859-7]
- 80 **Artifon EL**, Coelho F, Frazao M, Marques S, Paione JB, Takada J, Boaventura P, Rebello C, Pinhata Otoch J. A prospective randomized study comparing partially covered metal stent versus plastic multistent in the endoscopic management of patients with postoperative benign bile duct strictures: a follow-up above 5 years. *Rev Gastroenterol Peru* 2012; **32**: 26-31 [PMID: 22476175]
- 81 **van Boeckel PG**, Vleggaar FP, Siersema PD. Plastic or metal stents for benign extrahepatic biliary strictures: a systematic review. *BMC Gastroenterol* 2009; **9**: 96 [PMID: 20017920 DOI: 10.1186/1471-230X-9-96]
- 82 **Wagh MS**, Chavalitthamrong D, Moezardalan K, Chauhan SS, Gupte AR, Nosler MJ, Forsmark CE, Draganov PV. Effectiveness and safety of endoscopic treatment of benign biliary strictures using a new fully covered self expandable metal stent. *Diagn Ther Endosc* 2013; **2013**: 183513 [PMID: 23956613 DOI: 10.1155/2013/183513]
- 83 **Cahen DL**, Rauws EA, Gouma DJ, Fockens P, Bruno MJ. Removable fully covered self-expandable metal stents in the treatment of common bile duct strictures due to chronic pancreatitis: a case series. *Endoscopy* 2008; **40**: 697-700 [PMID: 18704837 DOI: 10.1055/s-2008-1077353]
- 84 **Mahajan A**, Ho H, Sauer B, Phillips MS, Shami VM, Ellen K, Rehan M, Schmitt TM, Kahaleh M. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). *Gastrointest Endosc* 2009; **70**: 303-309 [PMID: 19523620 DOI: 10.1016/j.gie.2008.11.029]
- 85 **Moon JH**, Choi HJ, Koo HC, Han SH, Lee TH, Cho YD, Park SH, Kim SJ. Feasibility of placing a modified fully covered self-expandable metal stent above the papilla to minimize stent-induced bile duct injury in patients with refractory benign biliary strictures (with videos). *Gastrointest Endosc* 2012; **75**: 1080-1085 [PMID: 22401821 DOI: 10.1016/j.gie.2012.01.016]
- 86 **García-Cano J**. Endoscopic management of benign biliary strictures. *Curr Gastroenterol Rep* 2013; **15**: 336 [PMID: 23857116 DOI: 10.1007/s11894-013-0336-2]
- 87 **Devière J**, Nageshwar Reddy D, Püspök A, Ponchon T, Bruno MJ, Bourke MJ, Neuhaus H, Roy A, González-Huix Lladó F, Barkun AN, Kortan PP, Navarrete C, Peetermans J, Blero D, Lakhtakia S, Dolak W, Lepilliez V, Poley JW, Tringali A, Costamagna G. Successful management of benign biliary strictures with fully covered self-expanding metal stents. *Gastroenterology* 2014; **147**: 385-395; quiz e15 [PMID: 24801350 DOI: 10.1053/j.gastro.2014.04.043]
- 88 **Siiki A**, Helminen M, Sand J, Laukkanen J. Covered self-expanding metal stents may be preferable to plastic stents in the treatment of chronic pancreatitis-related biliary strictures: a systematic review comparing 2 methods of stent therapy in benign biliary strictures. *J Clin Gastroenterol* 2014; **48**: 635-643 [PMID: 24275713 DOI: 10.1097/MCG.000000000000020]
- 89 **Kaffes AJ**, Liu K. Fully covered self-expandable metal stents for treatment of benign biliary strictures. *Gastrointest Endosc* 2013; **78**: 13-21 [PMID: 23548962 DOI: 10.1016/j.gie.2013.02.019]
- 90 **Park do H**, Lee SS, Lee TH, Ryu CH, Kim HJ, Seo DW, Park SH, Lee SK, Kim MH, Kim SJ. Anchoring flap versus flared end, fully covered self-expandable metal stents to prevent migration in patients with benign biliary strictures: a multicenter, prospective, comparative pilot study (with videos). *Gastrointest Endosc* 2011; **73**: 64-70 [PMID: 21184871 DOI: 10.1016/j.gie.2010.09.039]
- 91 **Walter D**, Laleman W, Jansen JM, van Milligen de Wit AW, Weusten BL, van Boeckel PG, Hirdes MM, Vleggaar FP, Siersema PD. A fully covered self-expandable metal stent with antimigration features for benign biliary strictures: a prospective, multicenter cohort study. *Gastrointest Endosc* 2015; **81**: 1197-1203 [PMID: 25660982 DOI: 10.1016/j.gie.2014.10.026]
- 92 **Hu B**, Wang TT, Shi ZM, Wang SZ, Lu R, Pan YM, Huang H, Wang SP. A novel antireflux metal stent for the palliation of biliary malignancies: a pilot feasibility study (with video). *Gastrointest Endosc* 2011; **73**: 143-148 [PMID: 20970788 DOI: 10.1016/j.gie.2010.08.048]
- 93 **Kim DU**, Kwon CI, Kang DH, Ko KH, Hong SP. New antireflux self-expandable metal stent for malignant lower biliary obstruction: in vitro and in vivo preliminary study. *Dig Endosc* 2013; **25**: 60-66 [PMID: 23286258 DOI: 10.1111/j.1443-1661.2012.01324.x]
- 94 **Hwang JC**, Kim JH, Yoo BM, Lim SG, Kim JH, Kim WH, Kim MW. Temporary placement of a newly designed, fully covered, self-expandable metal stent for refractory bile leaks. *Gut Liver* 2011; **5**: 96-99 [PMID: 21461081 DOI: 10.5009/gnl.2011.5.1.96]
- 95 **Meng B**, Wang J, Zhu N, Meng QY, Cui FZ, Xu YX. Study of biodegradable and self-expandable PLLA helical biliary stent in vivo and in vitro. *J Mater Sci Mater Med* 2006; **17**: 611-617 [PMID: 16770545 DOI: 10.1007/s10856-006-9223-9]
- 96 **Itoi T**, Kasuya K, Abe Y, Isayama H. Endoscopic placement of a new short-term biodegradable pancreatic and biliary stent in an animal model: a preliminary feasibility study (with videos). *J Hepatobiliary Pancreat Sci* 2011; **18**: 463-467 [PMID: 21170555 DOI: 10.1007/s00534-010-0364-3]
- 97 **Yamamoto K**, Yoshioka T, Furuichi K, Sakaguchi H, Anai H, Tanaka T, Morimoto K, Uchida H, Kichikawa K. Experimental study of poly-L-lactic acid biodegradable stents in normal canine bile ducts. *Cardiovasc Intervent Radiol* 2011; **34**: 601-608 [PMID: 21153415 DOI: 10.1007/s00270-010-0045-2]
- 98 **Hu B**, Gao DJ, Wu J, Wang TT, Yang XM, Ye X. Intraductal radiofrequency ablation for refractory benign biliary stricture: pilot feasibility study. *Dig Endosc* 2014; **26**: 581-585 [PMID: 24405166 DOI: 10.1111/den.12225]

- 99 **Bourke MJ**, Elfant AB, Alhalel R, Scheider D, Kortan P, Haber GB. Sphincterotomy-associated biliary strictures: features and endoscopic management. *Gastrointest Endosc* 2000; **52**: 494-499 [PMID: 11023566]
- 100 **Kuzela L**, Oltman M, Sutka J, Hrecka R, Novotna T, Vavrecka A. Prospective follow-up of patients with bile duct strictures secondary to laparoscopic cholecystectomy, treated endoscopically with multiple stents. *Hepatogastroenterology* 2005; **52**: 1357-1361 [PMID: 16201073]
- 101 **Morelli G**, Fazel A, Judah J, Pan JJ, Forsmark C, Draganov P. Rapid-sequence endoscopic management of posttransplant anastomotic biliary strictures. *Gastrointest Endosc* 2008; **67**: 879-885 [PMID: 18178206 DOI: 10.1016/j.gie.2007.08.046]
- 102 **Tabibian JH**, Asham EH, Han S, Saab S, Tong MJ, Goldstein L, Busuttil RW, Durazo FA. Endoscopic treatment of postorthotopic liver transplantation anastomotic biliary strictures with maximal stent therapy (with video). *Gastrointest Endosc* 2010; **71**: 505-512 [PMID: 20189508 DOI: 10.1016/j.gie.2009.10.023]

P- Reviewer: Lee KT **S- Editor:** Qiu S
L- Editor: A **E- Editor:** Li D



Prospective Study

Efficiency and patient experience with propofol vs conventional sedation: A prospective study

Patrick Thornley, Mohammad Al Beshir, James Gregor, Andreas Antoniou, Nitin Khanna

Patrick Thornley, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario L8S 4L8, Canada

Mohammad Al Beshir, Division of Gastroenterology, King Fahad Specialist Hospital - Dammam, Dammam 31444, Saudi Arabia

James Gregor, Nitin Khanna, Division of Gastroenterology, Western University, London, Ontario N6A 3K7, Canada

Andreas Antoniou, Department of Anesthesia and Perioperative Medicine, Western University, London, Ontario N6A 3K7, Canada

Author contributions: Thornley P, Al Beshir M, Gregor J, Antoniou A and Khanna N contributed to study conception and design; Thornley P, Al Beshir M and Khanna N contributed to data acquisition, data analysis and interpretation, and writing of the article; Gregor J, Antoniou A and Khanna N contributed to editing, reviewing and final approval of the article.

Supported by Division of Gastroenterology at Western University (in part), Canada.

Institutional review board statement: The study was reviewed and approved by the Western University Institutional Review Board.

Informed consent statement: All study participants provided informed verbal and written consent prior to study enrolment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Nitin Khanna, MD, Division of Gastroenterology, Western University, 529 McGarrell Place, London, Ontario N6A 3K7, Canada. nitin.khanna@sjhc.london.on.ca
Telephone: +1-519-6466125
Fax: +1-519-6466130

Received: October 2, 2015

Peer-review started: October 2, 2015

First decision: November 5, 2015

Revised: December 7, 2015

Accepted: December 19, 2015

Article in press: December 23, 2015

Published online: February 25, 2016

Abstract

AIM: To determine whether anaesthesiologist-administered sedation with propofol (AAP) or endoscopist-administered conscious sedation (EAC) with fentanyl/midazolam shortens colonoscopy duration/total room time.

METHODS: This is a prospective, non-randomized, comparative study that enrolled patients greater than 18 years of age undergoing colonoscopy in a single Canadian academic outpatient endoscopy unit over a three-month consecutive period. Colonoscopies in this unit are performed both with AAP and EAC. Patient demographics, procedure-related data and adverse events were documented. Additionally, the level of procedure difficulty, and whether a staff endoscopist, trainee with assistance, or independent trainee, performed the procedure were documented. A validated modified 4-question, 5-point Likert scale telephone survey was used to assess patient satisfaction with colonoscopy. The telephone patient satisfaction survey was conducted 24-72 h following the procedure.

RESULTS: Two hundred and thirty patients were

enrolled during the study period with 126 patients in the AAP group and 104 patients in the EAC group. Mean procedure time was 18.3 ± 10.1 min in the AAP group and 14.7 ± 7.1 min in the EAC group ($P = 0.002$). Mean total room time was 36.8 ± 13.7 with AAP and 30.1 ± 11 min with EAC ($P < 0.001$). Multivariate analysis revealed the use of AAP ($P = 0.002$), resident participation ($P < 0.001$), diagnostic interventions ($P = 0.033$), therapeutic interventions ($P < 0.001$), lower body mass index ($P = 0.008$) and American Society of Anaesthesiologist class ($P = 0.016$), to be predictors of longer total room time. Patient age and gender were not significant predictors. After excluding cases in which trainees were involved, there was no significant difference in procedure time between the two groups ($P = 0.941$), however total room time was still prolonged in the AAP group ($P = 0.019$). The amount of pain experienced was lower with AAP ($P = 0.02$), with a trend toward overall higher patient satisfaction ($P = 0.074$). There were 2 sedation-related adverse events, both in the AAP group involving a patient with aspiration requiring hospitalization and a patient with hypoxia managed with bronchodilators.

CONCLUSION: EAC results in reduced total room time compared to AAP. Resident participation doubles procedure time regardless of sedation type.

Key words: Patient satisfaction; Fentanyl; Colonoscopy; Midazolam; Propofol

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There is little research examining sedation type in light of patient satisfaction and overall efficiency of colonoscopy. Our novel prospective study evaluated the total procedure room time and patient satisfaction in a high-volume endoscopy center, which performs colonoscopy using conventional sedation and propofol sedation. A statistically significant reduction in total room time with conventional sedation (midazolam/fentanyl) when compared to anaesthetist-administered propofol was demonstrated. Patients reported less procedure pain when receiving propofol sedation compared to conventional sedation. Special discussion emphasizes the need to further examine strategies to maximize endoscopy unit efficiency to respond to increasing patient demand, while maximizing patient satisfaction.

Thornley P, Al Beshir M, Gregor J, Antoniou A, Khanna N. Efficiency and patient experience with propofol vs conventional sedation: A prospective study. *World J Gastrointest Endosc* 2016; 8(4): 232-238 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/232.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.232>

INTRODUCTION

Colorectal cancer is the leading cause of cancer related death among non-smokers in Canada and is the fourth leading cause of cancer death worldwide^[1]. Patients presenting with a high suspicion of colorectal cancer based on physical examination and imaging studies should receive a colonoscopy within two weeks of diagnostic suspicion^[2]. Furthermore, any patient referred for a screening colonoscopy should receive a colonoscopy within six months of referral^[2]. However, with an ever-increasing average population age, demand for colonoscopies is expected to increase by 5%-10% per annum over the coming decades^[3]. Presently, hospital endoscopy units are experiencing overwhelming demand for their service and as such it is imperative to examine methods to improve overall endoscopy unit efficiency^[4,5].

There has been growing interest in finding the ideal sedation for colonoscopy that is safe, easy to administer, provides adequate sedation and allows for rapid recovery. A combination of benzodiazepines and opiates (midazolam and fentanyl), the medications used most commonly by gastroenterologists for procedural sedation, provides adequate analgesia and sedation during colonoscopy^[6]. Propofol is an intravenously administered hypnotic drug used for induction and maintenance of general anaesthesia and is also used in procedural sedation. The perceived benefits of propofol sedation during colonoscopy include rapid post-procedure drug clearance, improved patient comfort and rapid recovery/discharge^[2]. Propofol administered by an anaesthesiologist has been extensively investigated and multiple randomized controlled trials have shown that using propofol sedation for colonoscopy in generally healthy individuals can lead to faster recovery and discharge times and increase patient satisfaction without an increase in side-effects^[7]. Furthermore, propofol sedation is preferred by some endoscopists for colonoscopy procedures compared to conventional sedation^[6].

The Canadian Association of Gastroenterology released a position statement on the use of propofol for sedation during endoscopic procedures indicating "propofol has advantages over standard agents used for conscious sedation"^[2]. The rate of cecal intubation (a marker of colonoscopy completion) is increased in procedures in which propofol-induced sedation has been used^[6]. However, the literature regarding the experience, overall efficacy and efficiency of using propofol in endoscopy units is limited.

The aim of this study was to determine whether anaesthesiologist-administered propofol sedation (AAP) results in a shorter duration of colonoscopy procedure time and total procedure room time in comparison to endoscopist-administered conventional sedation (EAC) with midazolam and fentanyl for colonoscopy. Secondary outcomes include a comparison of procedure times with

or without resident involvement, patient satisfaction and procedure related complications.

MATERIALS AND METHODS

Overview and patient selection

We performed a prospective, non-randomized, comparative study recruiting patients during a three-month (12 wk) consecutive period at a single high-volume Canadian academic outpatient endoscopy unit where both AAP and EAC are utilized. Bowel preparation protocols, colonoscopy indication, therapeutics performed and American Society of Anaesthesiologists (ASA) class are identical for patients receiving both AAP and EAC and patients do not select the type of sedation they receive. The Western University Ethics Review Board approved this study for patient recruitment. All patients 18 years of age and over undergoing colonoscopy either for symptomatic or screening purposes were approached for possible involvement in the study. Study enrolment involved an informed consenting process prior to the potential participant entering the procedure room. Verbal consent as well as written consent was obtained prior to enrolment in the study. Patients were provided a contact telephone number and electronic mail address of the study research assistant who was available to answer study questions and remove participants from the trial at their request at any point during the study period. A total of five patients declined participation in the study and no participants requested to be removed from the study after enrolment. Exclusion criteria included age less than 18 years, inability to read or write English and patients with major psychiatric or cognitive impairment. Six gastroenterologists participated in the study. All participating endoscopists in the study were experienced gastroenterologists with more than 200 colonoscopies performed per year.

Measurement tools and data collection

Following patient consent, a detailed list of parameters was documented for each patient during their colonoscopy. Patient demographics including age, sex, body mass index (BMI) and ASA class, and procedure related data including indication, pre-procedure time, procedure duration, the presence or absence of any intervention, procedure completion time and total procedure room time were all recorded. Additionally, the level of procedure difficulty, and whether a staff endoscopist, trainee with assistance, or independent trainee, performed the procedure were documented. The trainee included either a gastroenterology resident or second year general surgery resident. We also collected anaesthesia related data, including type of sedation used and total sedative dose/administration method.

A validated modified 4-question, 5-point Likert scale telephone survey was used to assess patient satisfaction with colonoscopy^[8]. Forty-eight hours post-procedure, enrolled patients were contacted regarding our post-

procedure patient satisfaction survey. If unable to reach the patient at this time, one additional follow-up call was made the following day (72 h post-procedure). To avoid recall biases and maximize group standardization, no participants were contacted prior to 48-h post-procedure, nor were participants contacted beyond the 72-h post-procedure time interval. Participant satisfaction data was combined according to the group represented by each participant (AAP or EAC). Patient satisfaction data was analyzed as a whole. Thus, stratification for difference between participants reached at the 48 h vs 72-h post-procedure time point was not performed.

Throughout the study, a research assistant (PT) was available to answer participants' questions. The study research assistant was not involved in any direct care of study participants and was responsible for collecting patient written consent, recording study measurable and contacting patients post-procedure for the patient satisfaction survey.

Statistical analysis

For the purposes of statistical analysis, statistical significance was understood to be achieved when *P*-value was less than 0.05. χ^2 analysis and unpaired *t*-test were used to compare differences between the two patient groups (AAP vs EAC). χ^2 analysis and Wilcoxon 2 sample test were used to analyze the patient satisfaction survey responses. Study endpoints were analyzed with unpaired *t*-tests, Fischer exact tests and analysis of covariance were adjusted for gender where appropriate. Height discrepancies were correlated to gender differences. This approach was justified by performing a logistic regression of height and gender as independent variables with respective group as an endpoint and it was noted that only gender was a significant variable, height was not. Multivariate analysis was utilized to normalize the collected data set. Adjustments were made for a non-normally distributed total room and total procedure time and between-group statistical tests are based on the log-transformed data. All database management and statistical analysis was conducted and reviewed by the department's staff biomedical statistician, Larry Stitt, from Western University Department of Epidemiology and Biostatistics.

RESULTS

A total of 230 patients were enrolled in our study. A total of 126 (55%) patients received AAP, while 104 (45%) patients received EAC. The cecum was intubated in all patients and confirmed by standard cecal landmarks and in most instances by intubation of the ileum and direct visualization of intestinal villi. Patient demographics are outlined in Table 1.

Mean procedure time (time measured from scope insertion to scope removal) was 18.3 ± 10.1 min in the AAP group and 14.7 ± 7.1 min in the EAC group (*P* = 0.002). Mean total procedure room time (time measured

Table 1 Participants' demographics for endoscopist-administered sedation and anaesthesiologist-administered sedation with propofol groups *n* (%)

	EAC (<i>n</i> = 104)	AAP (<i>n</i> = 126)	<i>P</i> -value
Male sex - frequency	60 (57.7)	46 (36.5)	0.001
Age	59.8 (11.6)	57.1 (13.3)	0.101
Weight	183.3 (49.1)	174.6 (46.5)	0.169
Height	67.6 (4.2)	66.3 (4.0)	0.016
BMI	28.0 (6.5)	27.7 (6.2)	0.750
Indication - symptomatic	33 (31.7)	55 (43.7)	0.064
Intervention			0.936
None	31 (29.8)	37 (29.4)	
Diagnostic	25 (24.0)	34 (27.0)	
Therapeutic	36 (34.6)	43 (34.1)	
Diagnostic and therapeutic	12 (11.5)	12 (9.5)	
ASA class			0.089
1	42 (40.4)	52 (41.3)	
2	54 (51.9)	53 (42.1)	
3	8 (7.7)	21 (16.7)	

EAC: Endoscopist-administered conscious sedation; AAP: Anaesthesiologist-administered sedation with propofol; BMI: Body mass index; ASA: American Society of Anaesthesiologists.

Table 2 Multivariate analysis of procedure measurables

	Coefficient	<i>P</i> -value
BMI	-0.008	0.008
ASA class	0.066	0.016
Intervention - diagnostic	0.084	0.033
Intervention - therapeutic	0.246	< 0.001
Propofol sedation (AAP)	0.091	0.002
Resident involved	0.391	< 0.001

AAP: Anaesthesiologist-administered sedation with propofol; BMI: Body mass index; ASA: American Society of Anaesthesiologists.

from the moment the patient entered the room until the moment the patient was wheeled to recovery) was 36.8 ± 13.7 min with AAP and 30.1 ± 11 min with EAC ($P < 0.001$). Trainee involvement was 51/126 (40%) in the AAP group and 15/104 (14%) in the EAC group ($P < 0.001$). Multivariate analysis revealed the use of AAP ($P = 0.002$), resident participation ($P < 0.001$), diagnostic interventions ($P = 0.033$), therapeutic interventions ($P < 0.001$), lower BMI ($P = 0.008$) and ASA class ($P = 0.016$), to be predictors of longer total procedure room time, as detailed in Table 2. There were two sedation related adverse events in the AAP group. One case involved a patient who aspirated during procedure, which subsequently required hospitalization. The second adverse event involved a post-procedure, recovery room incidence of hypoxia, which was resolved by bronchodilators.

Log transformation of procedure time and total procedure room time was performed to normalize data for height and gender. With removal of trainee presence, there was no significant difference in procedure time between the two groups ($P = 0.941$) (Table 3). However, the total procedure room time was still prolonged in the AAP group ($P = 0.019$) relative to the EAC group

Table 3 Procedure time and total procedure room time with removal of trainee presence (staff endoscopist data only) for endoscopist-administered sedation and anaesthesiologist-administered sedation with propofol groups

	EAC (<i>n</i> = 89)	AAP (<i>n</i> = 75)	<i>P</i> -value
Total procedure time			
Mean \pm SD	13.0 \pm 4.9 min	12.9 \pm 4.8 min	0.941
Total room time			
Mean \pm SD	28.1 \pm 9.3 min	31.1 \pm 10.1 min	0.019

EAC: Endoscopist-administered conscious sedation; AAP: Anaesthesiologist-administered sedation with propofol.

(Table 3). With respect to the post-procedure patient satisfaction surveys, 74/104 (71%) of participants from the EAC and 80/126 (64%) of participants from the AAP group completed the telephone survey (Table 4). There was a trend toward overall higher patient satisfaction with AAP 72/80 (90%) in comparison to EAC 59/74 (80%) ($P = 0.074$). However there were no differences between the two groups with regard to statement 2, "I would strongly recommend this procedure to friends who qualify for it" ["strongly agree": EAC 55/74 (74%) and AAP 61/80 (76%)] and statement 3, "I would be willing to repeat this examination in the future if necessary" ["strongly agree": EAC 64/74 (87%) and AAP 67/80 (84%)] ($P = 0.882$ and 0.667 respectively). When examining pain experienced during procedures and patient satisfaction, the amount of pain experienced was lower with AAP 78/80 (98%) than EAC 64/74 (87%) ($P = 0.02$).

When examining the effect of resident participation on the efficiency of colonoscopy, we found that the mean procedure time was 12.9 ± 4.8 min in the staff endoscopist alone group (SE) and 26 ± 10.2 min in the resident participation (RP) group ($P < 0.001$). Mean total room time was 29.5 ± 9.8 min in the SE group and 44.4 ± 13.7 in the RP group ($P < 0.001$) (Table 5). Using multivariate analysis, the use of AAP was still a predictor of longer total procedure room time ($P = 0.002$).

DISCUSSION

As endoscopy units continue to receive increasing pressures to maximize efficiency, mechanisms to reduce cost of colonoscopy, while increasing overall number of colonoscopies performed annually must be examined. Propofol vs conventional sedation in colonoscopy has been extensively investigated and compared in multiple previous studies^[9]. Common outcomes studied include procedure time, recovery time, discharge time, cecal intubation rate, patient satisfaction, endoscopist satisfaction, level of sedation, pain control and complications. There is little literature comparing AAP to EAC with regard to total procedure room time and overall endoscopy unit efficiency.

This investigation has demonstrated that at a single-centre high-volume endoscopy unit, and after

Table 4 Results of the telephone patient satisfaction survey for endoscopist-administered sedation and anaesthesiologist-administered sedation with propofol groups *n* (%)

	EAC (<i>n</i> = 104)	AAP (<i>n</i> = 126)	<i>P</i> -value
Response rate	74 (71)	80 (64)	0.219
Question 1: I was very satisfied with the care I received			0.074
Agree	15 (20)	8 (10)	
Strongly agree	59 (80)	72 (90)	
Question 2: I would strongly recommend this procedure to friends who qualify for it			0.882
Disagree	1 (1.4)	0 (0.0)	
Not sure	2 (2.7)	6 (7.5)	
Agree	16 (22)	13 (16)	
Strongly agree	55 (74)	61 (76)	
Question 3: I would be willing to repeat this examination again in the future if necessary			0.667
Disagree	0 (0.0)	1 (1.3)	
Not sure	2 (2.7)	0 (0.0)	
Agree	8 (11)	12 (15)	
Strongly agree	64 (87)	67 (84)	
Question 4: I did not experience too much pain/discomfort during the procedure			0.021
Strongly disagree	4 (5.4)	0 (0.0)	
Disagree	5 (6.8)	2 (2.5)	
Not sure	1 (1.4)	0 (0.0)	
Agree	7 (9.5)	6 (7.5)	
Strongly agree	57 (77)	72 (90)	

EAC: Endoscopist-administered conscious sedation; AAP: Anaesthesiologist-administered sedation with propofol.

Table 5 Study endpoints - comparing staff endoscopists only with cases involving resident participation

	Resident involved (<i>n</i> = 66)	Staff endoscopist only (<i>n</i> = 164)	<i>P</i> -value
Total procedure time			< 0.001
Mean ± SD	26.0 ± 10.2	12.9 ± 4.8	< 0.001
Total room time			< 0.001
Mean ± SD	44.4 ± 13.7	29.5 ± 9.8	< 0.001

removal of trainee presence, there was no difference in procedure time with AAP or EAC but there was a significant difference in total procedure room time. There was however a trend toward overall greater patient satisfaction with AAP sedation. This raises important questions requiring further elucidation of how best to maximize patient satisfaction and efficiency in delivery of colonoscopy to the masses.

A previously reported model indicated that practice efficiency gains from rapid recovery agents (*i.e.*, propofol) could offset higher operating costs^[10]. There are multiple steps in the flow of a patient through the endoscopy unit affecting efficiency. Our findings suggest that the time saved in the recovery room with the use of propofol may be offset by increased time within the procedure room, thus not improving overall unit efficiency. Our study between EAC and AAP with respect to total procedure room time demonstrates a difference of 3 min per colonoscopy on average. This has implications when cumulatively added over the course of a full endoscopy day, with the potential for 1 full additional colonoscopy performed per day with EAC compared to AAP sedation (assuming a standard eight hour endoscopy procedure day).

Previous concerns regarding the cost prohibitive

nature of AAP have been raised and addressed in the literature^[11]. The cost of anaesthesia consultation and anaesthesiologist reimbursement for colonoscopy may represent limiting factors in AAP use over EAC. In a questionnaire conducted in the United States addressing 451 gastroenterologist and 460 endoscopy nurses it was demonstrated that 53% of gastroenterologists and 70% of endoscopy nurses preferred AAP to EAC if they were to have screening colonoscopy. When they were asked how much extra they were willing to pay out of pocket to have AAP, 60% and 63% (respectively) were unwilling to pay more than \$200, significantly less than is currently charged to patients in the United States^[12]. The administration of propofol by non-anaesthesiologists has been endorsed by several gastroenterology societies and there is growing evidence to suggest that propofol can be safely administered by a trained gastroenterologist or registered nurse particularly in low-risk patients in a screening setting^[13,14]. However, this is controversial and likely would not suit all endoscopists or endoscopy units. Similarly, the impact of endoscopist-directed propofol sedation on unit efficiency is unknown.

Our study was too small to demonstrate significant differences in safety between AAP and EAC. Korman *et al*^[15] previously outlined some of the implications of propofol sedation for colonoscopy. One such implication indicated that endoscopists are more likely to apply more forces during colonoscope insertion and push through loops and angulated segments as a result of deep sedation^[15]. Whether this can be linked to significant adverse event is unknown. In a retrospective study by Adeyemo *et al*^[16] among patients having a therapeutic colonoscopy, propofol use was independently and significantly associated with an increased perforation

risk, with adjusted odds ratios of 1.32. Additionally, there are implications to trainees learning colonoscopy techniques on patients under propofol sedation given that patient feedback is greatly reduced and thus reduction techniques are different and potentially dangerous^[15]. The significant difference between trainees involved in AAP vs EAC cases in our study is cause for reflection and evaluation of the number of AAP and EAC cases to which our trainees are exposed.

Our study has shown a significant difference in the pain/discomfort experienced during colonoscopy favouring AAP when compared with EAC ($P = 0.021$). However, 86.5% of patients in the EAC group either "agreed" or "strongly agreed" with the telephone survey statement: "I did not experience too much pain/discomfort during the procedure" which correlate with the result of the recent meta-analysis that showed little to no difference in pain scores for patients receiving propofol vs conventional sedation^[7]. Patients were also equally likely to have the procedure repeated which is important for surveillance. One important limitation of the current investigation.

Consistent with previous studies, trainee involvement in colonoscopy (either EAC or AAP) doubles procedure time and significantly increased total procedure room time^[17]. Colonoscopy training is the corner stone of any accredited gastroenterology fellowship program and adequate training is essential to ensure all future endoscopists are competent in conducting colonoscopy independently and delivering the best standard of care to their patients. Given the fixed costs associated with endoscopy units, it will be important to consider the impact of resident training in academic centers if colonoscopy funding changes to a cost per case model. Standard guidelines on teaching techniques may also improve efficiency.

Its worth mentioning that some other factors that could potentially improve overall colonoscopy performance and patient experience - particularly for inexperienced endoscopists - such as cap-assisted colonoscopy, magnetic endoscopic imaging system and anti-spasmodic medication were not investigated in our study^[18,19].

In conclusion, the principal results of this study suggest that AAP sedation is associated with increased total procedure room time relative to EAC. However, no significant difference in procedure time between EAC and AAP groups was observed. Given that the difference in total room time is not manifested in a difference in procedure time itself, it is likely that the additional time comes from either pre-procedure consultation required by the anaesthesiology team or post-procedure management prior to transfer out of the room to the recovery area. Strategies to reduce the need for in-room anaesthesiologist assessment may help improve overall unit efficiency. Future investigations should include overall cost-effectiveness analysis for EAC vs AAP and

direct comparison between AAP and EAC in terms of safety and efficiency.

ACKNOWLEDGMENTS

We would like to thank Larry Stitt (Western University, Department of Epidemiology) for his help with statistical analysis.

COMMENTS

Background

Colorectal cancer is the leading cause of cancer-related death among non-smokers in Canada and the fourth leading cause of cancer-related death worldwide. As the gold standard procedure for treatment and diagnosis of conditions of the colon, colonoscopies are an important screening measure. Additionally, with increased emphasis on colon cancer screening programs among the aging population of many nations, the number of colonoscopies performed globally will continue to increase drastically in the near future.

Research frontiers

A main factor known to increase patient satisfaction and willingness to return for a repeat colonoscopy is the organization of the clinic and its efficiency (*i.e.*, reduced patient anxiety and increased patient satisfaction with colonoscopy is associated with a reduced wait time before procedure). The research hotspot is to pursue a novel measurement of colonoscopy unit efficiency (total procedure room time), which has direct implications for overall unit efficiency, with emphasis on assessing patient satisfaction with different sedation types for colonoscopy, a highly controversial topic in current colonoscopy literature.

Innovations and breakthroughs

Much emphasis in currently focuses on decreasing the length of the colonoscopy procedure as a means to increase unit efficiency. In this study, the authors analyze the differences in total procedure room time between two differing sedation types for colonoscopy. The results demonstrate that currently administration of propofol-based sedation is better tolerated by patients and efforts to improve efficiency must be pursued as this modality is currently significantly slower in terms of total procedure room time than conventional sedation techniques for colonoscopy, which carries implications for responding to the rising demand for colonoscopy globally.

Applications

The results of this study suggest that anaesthesiologist-administered sedation with propofol leads to increased patient satisfaction with colonoscopy. However, this sedation type was found to lead to a significantly increased total procedure room time, without a difference in procedure time, which has important implications for efficiency of colonoscopy units.

Terminology

Throughout this article, the following terms are used frequently: Anaesthesiologist-administered propofol sedation (AAP) and endoscopist-administered conscious sedation (EAC). AAP refers to anaesthesiologist-administered sedation with propofol, whereby deeper sedation occurs with propofol during the colonoscopy procedure under the guidance of a trained anaesthesiologist. EAC refers to endoscopist-administered conscious sedation, a conventional sedation type commonly used for colonoscopies throughout Canada, whereby sedation is administered by the endoscopist (a trained gastroenterologist in the case of this study) in the form of a combination of midazolam and fentanyl, titrated to maximize patient comfort and ensure procedural safety.

Peer-review

Available papers concerning total procedure room time for colonoscopy are highly limited. This study includes important results on a controversial issue about colonoscopy sedation procedures and contributes to the ongoing discussion on the mode and delivery of sedation for colonoscopy.

REFERENCES

- 1 **Olsen AH**, Parkin DM, Sasieni P. Cancer mortality in the United Kingdom: projections to the year 2025. *Br J Cancer* 2008; **99**: 1549-1554 [PMID: 18854832 DOI: 10.1038/sj.bjc.6604710]
- 2 **Paterson WG**, Depew WT, Paré P, Petrunia D, Switzer C, Veldhuyzen van Zanten SJ, Daniels S. Canadian consensus on medically acceptable wait times for digestive health care. *Can J Gastroenterol* 2006; **20**: 411-423 [PMID: 16779459]
- 3 **Shah TU**, Voils CI, McNeil R, Wu R, Fisher DA. Understanding gastroenterologist adherence to polyp surveillance guidelines. *Am J Gastroenterol* 2012; **107**: 1283-1287 [PMID: 22951869 DOI: 10.1038/ajg.2012.59]
- 4 **Gellad ZF**, Thompson CP, Taheri J. Endoscopy unit efficiency: quality redefined. *Clin Gastroenterol Hepatol* 2013; **11**: 1046-1049. e1 [PMID: 23978500 DOI: 10.1016/j.cgh.2013.06.005]
- 5 **Ho WM**, Yen CM, Lan CH, Lin CY, Yong SB, Hwang KL, Chou MC. Comparison between the recovery time of alfentanil and fentanyl in balanced propofol sedation for gastrointestinal and colonoscopy: a prospective, randomized study. *BMC Gastroenterol* 2012; **12**: 164 [PMID: 23170921 DOI: 10.1186/1471-230X-12-164]
- 6 **Cohen LB**, Weesler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, Aisenberg J. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006; **101**: 967-974 [PMID: 16573781]
- 7 **Singh H**, Poluha W, Cheung M, Choptain N, Baron KI, Taback SP. Propofol for sedation during colonoscopy. *Cochrane Database Syst Rev* 2008; (4): CD006268 [PMID: 18843709 DOI: 10.1002/14651858.CD006268.pub2]
- 8 **Sint Nicolaas J**, de Jonge V, Korfage IJ, Ter Borg F, Brouwer JT, Cahen DL, Lesterhuis W, Ouwendijk RJ, Kuipers EJ, van Leerdam ME. Benchmarking patient experiences in colonoscopy using the Global Rating Scale. *Endoscopy* 2012; **44**: 462-472 [PMID: 22389231 DOI: 10.1055/s-0031-1291663]
- 9 **Heuss LT**, Peter S. Propofol use by gastroenterologists-the European experience. *Gastrointest Endosc Clin N Am* 2008; **18**: 727-738, ix [PMID: 18922411 DOI: 10.1016/j.giec.2008.06.007]
- 10 **Vargo JJ**, Bramley T, Meyer K, Nightengale B. Practice efficiency and economics: the case for rapid recovery sedation agents for colonoscopy in a screening population. *J Clin Gastroenterol* 2007; **41**: 591-598 [PMID: 17577116]
- 11 **Aisenberg J**, Brill JV, Ladabaum U, Cohen LB. Sedation for gastrointestinal endoscopy: new practices, new economics. *Am J Gastroenterol* 2005; **100**: 996-1000 [PMID: 15842568]
- 12 **Agrawal D**, Rockey DC. Propofol for screening colonoscopy in low-risk patients: are we paying too much? *JAMA Intern Med* 2013; **173**: 1836-1838 [PMID: 23857456 DOI: 10.1001/jamainternmed.2013.8417]
- 13 **Rex DK**, Deenadayalu VP, Eid E, Imperiale TF, Walker JA, Sandhu K, Clarke AC, Hillman LC, Horiuchi A, Cohen LB, Heuss LT, Peter S, Beglinger C, Sinnott JA, Welton T, Rofail M, Subei I, Sleven R, Jordan P, Goff J, Gerstenberger PD, Munnings H, Tagle M, Sipe BW, Wehrmann T, Di Palma JA, Occhipinti KE, Barbi E, Riphaut A, Amann ST, Tohda G, McClellan T, Thueson C, Morse J, Meah N. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology* 2009; **137**: 1229-1237; quiz 1518-1519 [PMID: 19549528 DOI: 10.1053/j.gastro.2009.06.042]
- 14 **Rex DK**, Heuss LT, Walker JA, Qi R. Trained registered nurses/endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology* 2005; **129**: 1384-1391 [PMID: 16285939]
- 15 **Korman LY**, Haddad NG, Metz DC, Brandt LJ, Benjamin SB, Lazerow SK, Miller HL, Mete M, Patel M, Egorov V. Effect of propofol anesthesia on force application during colonoscopy. *Gastrointest Endosc* 2014; **79**: 657-662 [PMID: 24472761 DOI: 10.1016/j.gie.2013.12.002]
- 16 **Adeyemo A**, Bannazadeh M, Riggs T, Shellnut J, Barkel D, Wasvary H. Does sedation type affect colonoscopy perforation rates? *Dis Colon Rectum* 2014; **57**: 110-114 [PMID: 24316954 DOI: 10.1097/DCR.0000000000000002]
- 17 **Depew WT**, Hookey LC, Vanner SJ, Louw JA, Lowe CE, Ropeleski MJ, Beyak MJ, Lazarescu A, Paterson WG. Opportunity costs of gastrointestinal endoscopic training in Canada. *Can J Gastroenterol* 2010; **24**: 733-738 [PMID: 21165381]
- 18 **Mark-Christensen A**, Brandsborg S, Iversen LH. Magnetic endoscopic imaging as an adjuvant to elective colonoscopy: a systematic review and meta-analysis of randomized controlled trials. *Endoscopy* 2015; **47**: 251-261 [PMID: 25521574 DOI: 10.1055/s-0034-1390767]
- 19 **Marshall JB**, Patel M, Mahajan RJ, Early DS, King PD, Banerjee B. Benefit of intravenous antispasmodic (hyoscyamine sulfate) as premedication for colonoscopy. *Gastrointest Endosc* 1999; **49**: 720-726 [PMID: 10343216]

P- Reviewer: Koc S, Mark-Christensen A

S- Editor: Ma YJ L- Editor: A E- Editor: Li D



Peroral endoscopic reduction of dilated gastrojejunal anastomosis after bariatric surgery: Techniques and efficacy

Kinesh Changela, Emmanuel Ofori, Sushil Duddempudi, Sury Anand, Shashideep Singhal

Kinesh Changela, Emmanuel Ofori, Sushil Duddempudi, Sury Anand, Division of Gastroenterology, the Brooklyn Hospital Center - Clinical Affiliate of Mount Sinai Hospital, Brooklyn, NY 11201, United States

Shashideep Singhal, Division of Gastroenterology, Hepatology and Nutrition, University of Texas Health Science Center at Houston, Houston, TX 77030, United States

Author contributions: Changela K and Ofori E wrote the paper; Duddempudi S, Anand S and Singhal S supervised the writing of paper; all authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at kinooo2002@gmail.com.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Kinesh Changela, MD, Division of Gastroenterology, the Brooklyn Hospital Center - Clinical Affiliate of Mount Sinai Hospital, 121 DeKalb Avenue, Brooklyn, NY 11201, United States. kinooo2002@gmail.com
Telephone: +1-516-5828772

Received: September 8, 2015

Peer-review started: September 17, 2015

First decision: October 13, 2015

Revised: December 16, 2015

Accepted: December 29, 2015

Article in press: January 4, 2016

Published online: February 25, 2016

Abstract

AIM: To investigate the techniques and efficacy of peroral endoscopic reduction of dilated gastrojejunal anastomosis after bariatric surgery.

METHODS: An extensive English language literature search was conducted using PubMed, MEDLINE, Medscape and Google to identify peer-reviewed original and review articles using the keywords "bariatric endoscopic suturing", "overstitch bariatric surgery", "endoscopic anastomotic reduction", "bariatric surgery", "gastric bypass", "obesity", "weight loss". We identified articles describing technical feasibility, safety, efficacy, and adverse outcomes of overstitch endoscopic suturing system for transoral outlet reduction in patients with weight regain following Roux-en-Y gastric bypass (RYGB). All studies that contained material applicable to the topic were considered. Retrieved peer-reviewed original and review articles were reviewed by the authors and the data extracted using a standardized collection tool. Data were analyzed using statistical analysis as percentages of the event.

RESULTS: Four original published articles which met our search criteria were pooled. The total number cases were fifty-nine with a mean age of 46.75 years (34-63 years). Eight of the patients included in those studies were males (13.6%) and fifty-one were females (86.4%). The mean time elapsed since the primary bypass surgery was 5.75 years. The average pre-endoscopic procedure body mass index (BMI) was 38.68 (27.5-48.5). Mean body weight regained post-RYGB surgery was 13.4 kg from their post-RYGB nadir. The average pouch length at the initial upper endoscopy was 5.75 cm (2-14 cm). The pre-intervention anastomotic diameter was averaged at 24.85 mm (8-40 mm). Average procedure time was 74 min (50-164 min). Mean post endoscopic intervention anastomotic diameter was 8 mm (3-15 mm). Weight reduction at 3 to 4 mo post revision noted to be an

average of 10.1 kg. Average overall post revision BMI was recorded at 37.7. The combined technical and clinical success rate was 94.9% (56/59) among studied participants.

CONCLUSION: Endoscopic suturing can be technically feasible, effective and safe for transoral outlet reduction in patients with weight regain following RYGB.

Key words: Endoscopic anastomosis reduction; Bariatric surgery; Endoscopic suturing; EndoCinch; Overstitch bariatric surgery

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Roux-en-Y gastric bypass is one of the most effective bariatric surgical procedures, but is associated with 5% weight regain during 1 to 3 years post procedure. Such weight regain has been attributed to a dilated gastrojejunal anastomosis (GJA). However given the increased perioperative risk of mortality, surgical revision is not generally considered. Endoscopic suturing system has shown potential in reducing the dilated GJA.

Changela K, Ofori E, Duddempudi S, Anand S, Singhal S. Peroral endoscopic reduction of dilated gastrojejunal anastomosis after bariatric surgery: Techniques and efficacy. *World J Gastrointest Endosc* 2016; 8(4): 239-243 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/239.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.239>

INTRODUCTION

Obesity is an epidemic and persists as one of the world's leading chronic diseases with increasing prevalence, morbidity and mortality. According to the National Health and Nutrition Examination surveys conducted in 2009-2010, 35.7% of American adults were obese [body mass index (BMI) > 30] with 6.3% considered to have severe obesity (BMI > 40 kg/m²)^[1]. Obesity is associated with increased mortality and risk of developing comorbid conditions such as type 2 diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, obstructive sleep apnea and obesity hypoventilation syndrome^[2,3]. Treatment options available for obesity include lifestyle and behavioral modifications, pharmacological, and surgical interventions.

Surgery has proven to be the best option for significant weight reduction with low rates of weight regain^[4]. Bariatric procedures work mainly to achieve and maintain weight loss *via* two main modalities; they function to restrict food accommodation in the stomach thereby causing early satiety and reducing caloric intake and or cause intestinal malabsorption^[5]. Four main types of bariatric procedures exist, namely laparoscopic adjustable gastric banding, sleeve gastrectomy,

biliopancreatic diversion with duodenal switch, and Roux-en-Y gastric bypass (RYGB).

RYGB as a bariatric procedure is considered the best and as a result the most popularly performed in the United States^[6]. RYGB is achieved by creating a small gastric pouch which is connected to a Roux limb of the jejunum^[7]. Its mechanism of weight loss reduction is mainly three folds: Food intake restriction by the small gastric pouch, dumping syndrome caused by the gastrojejunal anastomosis causing diarrhea and abdominal pain which act as negative reinforcement against high sugar diets, and the selective malabsorption due to the decreased length of Roux limb^[8]. Additionally, the reduction of Ghrelin levels due to the bypass of the stomach and duodenum in RYGB is reported to cause decreased stimulation of appetite leading to decreased food intake^[9].

Many studies on RYGB have reported weight reduction averages of 65% and more than 85% of patients losing and maintaining 50% of initial excess weight loss. However, studies have noted significant weight regain in patients beyond 18-24 mo after the initial weight loss surgery. Sugerman *et al*^[10] reported a 5% weight regain noted in bariatric surgical patients during a follow-up evaluation at 1 to 3 years. Powers *et al*^[11] also noted an average of 40 lb excess weight regain in bariatric surgery patients during a 2-year follow-up duration. Many factors have been suggested to contribute to such weight regain in patients who undergo weight loss surgery. Mechanical dehiscence of staple lines has been cited by many studies as a major contributing factor to weight regain^[12-14]. Additionally, dilation of the gastrojejunal anastomosis has been suggested as another possible mechanism of weight regain resulting in decreased distension of the gastric pouch and hence a reduction in satiety stimulation.

Fixation of such gastrojejunal dilation is however controversial as it carries significant surgical risks and often times the degree of weight regain does not justify surgical revision. Linner *et al*^[15] in their study of revision procedures noted a doubling of perioperative morbidity (15%) and mortality (0.7%) rates when compared to morbidity (8%) and mortality (0.3%) associated with the primary bariatric surgeries. Many different open revision surgeries have been suggested to restrict the dilated gastrojejunal anastomosis; however most of the patients did not achieve significant weight reduction, and suffered major procedural complications^[14,16].

Technological advancement in endoscopy has led to a novel approach of endoscopic fixation of gastrojejunal dilation in bariatric patients with weight regain after RYGB. This article discussed the endoscopic devices and their success in transoral gastric pouch outlet reduction to treat weight gain after RYGB.

MATERIALS AND METHODS

An extensive English language literature search was conducted using PubMed, MEDLINE, Medscape and Google to identify peer-reviewed original and review

articles using the keywords “bariatric endoscopic suturing”, “overstitch bariatric surgery”, “endoscopic anastomotic reduction”, “bariatric surgery”, “gastric bypass”, “obesity”, “weight loss”. Studies involving human models were selected. The references of pertinent studies were manually searched to identify additional relevant studies. The technical feasibility, safety, efficacy, and adverse outcomes of overstitch endoscopic suturing system for transoral outlet reduction in patients with weight regain following RYGB were considered as inclusion criteria for evaluation. Search results yielded mostly small sample sized studies including case reports and case series.

RESULTS

Four original published articles were considered suitable for inclusion in this review article. All studies were performed in Boston, Massachusetts, United States. All the four articles were case series on human subjects. The total number cases were fifty-nine with a mean age of 46.75 years (range, 34-63 years). Eight of the patients included in those studies were males (13.6%) and fifty-one were females (86.4%). All cases are summarized in Table 1.

Time since primary bypass surgery

The mean time elapsed since the primary bypass surgery in the studied population was 5.75 years with a range from 2 to 10 years^[17-19]. Fernández-Esparrach *et al*^[20] did not report the number of years after the primary bariatric surgery for their study patients.

Average pre-procedure BMI

The average pre-endoscopic procedure BMI among the study participants was 38.68 with range between 27.5-48.5^[17-20].

Average weight regain post RYGB nadir

The mean body weight regained post RYGB surgery was 13.4 kg from their post-RYGB nadir with a range between 0.9-53.6 kg^[17-20]. Fernández-Esparrach *et al*^[20] did not report the average weight gained post RYGB for their study patients.

Average pre-intervention pouch length and anastomotic diameter

The average pouch length at the initial upper endoscopy was 5.75 cm; ranging between 2-14 cm. The pre-intervention anastomotic diameter was also averaged at 24.85 mm; ranging from 8-40 mm^[17-20].

Endoscopic equipment used

Studies have described use of EndoCinch suturing system (CR Bard, Murray Hill, NJ), EndoSurgical Operating System (EOS) (USGI Medical San Clemente, Calif) and Overstitch Endoscopic Suturing System (Apollo Endosurgery) without any differences in outcome.

The Overstitch Endoscopic Suturing System (Apollo

Endosurgery) was connected to a two channel endoscope (GIF-2T160; Olympus America, Central Valley, Pennsylvania, United States). With a curved suture arm on one channel, and the anchor exchange on the other channel, stitches were placed through the tissue when the handle was closed. The tissue was released upon opening of the handle and a new stitch placed when the suture arm was returned to the anchor^[19]. Mullady *et al*^[18] used the EOS (USGI Medical San Clemente, Calif), which has a main component of the TransPort, The TransPort has 4 large channels accepting a 4.9-mm endoscope (GIF-N180; Olympus America, Inc, Center Valley Pa) and flexible equipments. With a 4 way tip, the TransPort uses a shapelock system in suturing, where a tissue approximator (g-Prox; USGI Medical), a tissue grasper and a needle catheter were advanced through the TransPort channels. The tissue grasper grasps the tissue and pulls into the approximator, which then closes onto the tissue. The needle catheter is then passed through the tissue and a self-expanding tissue anchor passed through the catheter is deployed. The approximator is opened and then the tissue anchor released. A stitch connecting the 2 anchors was then tightened, bringing together the 2 anchors^[18].

EndoCinch suturing system (CR Bard, Murray Hill, NJ) by Thompson *et al*^[17] was passed through the gastrojejunostomy site where tissue at the anastomosis site was pulled into the device and the stitch placed by activation of the handle. The Bard device was then removed and reloaded for a second bite and stitch placement. The process was repeated to attain one to three interrupted sutures around that anastomosis rim. Suture were tightened to plicate the tissue^[17,20].

Average number of interrupted stitches applied and procedure time

The average procedure time was charted at 74 min, ranging from 50-164 min^[17-20]. The number of interrupted stitches applied at the gastrojejunal anastomosis and the gastric pouch is averaged at 3.8 (range, 0-7)^[17-20].

Average post intervention anastomotic diameter

The mean post endoscopic intervention anastomotic diameter was 8 mm with a range between 3-15 mm^[17-20]. Overall the average anastomotic diameter reduction was 16.85 mm; a 67.8% reduction.

Average weight loss at 3-4 mo after revision

Weight reduction at 3-4 mo post revision was observed at an average of 10.1 kg (range, 1.4-19.5 kg)^[17-20].

Overall post procedure BMI

The average overall post revision BMI was recorded at 37.7^[9]. The remaining three articles did not report the post revision BMI^[18-20].

Major complications and limitations

The use of EndoCinch as an overstitch endoscopic suturing system for transoral outlet reduction in patients

Table 1 Summary of reports describing use of endoscopic suturing systems for transoral outlet reduction in patients with weight regain following Roux-en-Y gastric bypass

Ref.	Gender	Mean age (yr)	Time since bypass (yr)	Avg. pre-procedure BMI	Avg. weight gain (kg) post RYGB nadir	Avg. preintervention pouch length (cm)	Avg. preintervention anastomotic diameter (mm)	Type of equipment	Avg. number of interrupted stitches	Avg. post intervention anastomotic diameter (mm)	Avg. procedure time (min)	Avg. weight loss (kg) at 3-4 mo post procedure	Overall post procedure BMI	Major complications	Technical success (%)
Thompson <i>et al</i> ^[17] 2006, Boston, United States	F × 8	46 (41-54)	6	40.5	24 (8.6 - 53.6)	5.7 (3-8)	25 (17-25)	EndoCinch suturing system (CR Bard, Murray Hill, NJ)	2 (1-3)	10 (5-15)	98 (50-164)	10 (1.4-19.5)	37.7	None	100 (8/8)
Mullady <i>et al</i> ^[18] 2009, Boston, United States	F × 19 M × 1	48 (36-62)	5.25 (2-9.75)	36.7 (28.4-48.8)	13.3 (0.9-34.6)	7 (4-14)	25 (8-35)	EOS (USGI Medical, San Clemente, Calif)	Pouch: 1.7 (0-6) GJA: 3.4 (0-7)	16 (0-26)	103 (50-154)	8.8	Not reported	None	85 (17/20)
Fernández-Esparrach <i>et al</i> ^[19] 2010, Boston, United States	F × 6	45 (33-63)	Not reported	34.5 (27.5-41.5)	Not reported	5 (4-6)	23 (18.5-27.5)	EndoCinch suturing system (CR Bard, Murray Hill, NJ)	3	8 (7.6-8.4)	Not reported	Not reported	33	None	100 (6/6)
Jirapinyo <i>et al</i> ^[19] 2013, Boston, United States	F × 18 M × 7	48 (34-69)	6 (2-10)	43	24 (14-59)	5.3 (2-9)	26.4 (18-40)	Overstitch Endoscopic Suturing System (Apollo Endosurgery)	GJA: 3 (1-7) Pouch: 2 (1-5)	6 (3-10)	Anastomosis: 27 (7-80) Pouch: 15 (4-30)	11.5	Not reported	3/25	100 (25/25)

GJA: Gastrojejunal anastomosis; EOS: EndoSurgical Operating System; F: Female; M: Male; BMI: Body mass index; RYGB: Roux-en-Y gastric bypass.

with weight regain following RYGB has been associated with no reported significant procedure-related complications. Minor complications reported have included postprocedural nausea and vomiting, sore throat, mild transient abdominal pain, diarrhea and constipation^[17,20]. Jirapinyo *et al*^[19] reported three intra-procedural complications including a small esophageal abrasion which was remedied with fibrin glue and two patients who had arterial bleeding after the stitch placement, resolved with tissue plication.

Technical and clinical success rates

The combined technical and clinical success rate of EndoCinch as an endoscopic suturing system for outlet reduction in post RYGB patients with weight regain was 94.9% (56/59) among studied participants.

DISCUSSION

The reported findings on the use of endoscopic suturing devices are promising and appear to be safe in practice. Outlet reduction appears to be effective in decreasing the gastrojejunal anastomosis diameter and the gastric pouch length, ultimately leading to significant weight reduction and addressing the problem of weight regain in RYGB patients. The cases discussed above have some limitations however. The main limitation is the small number of subjects studied. Also the number of male participants in these studies was disproportionately low (8/59; 13.6%). More studies with larger sample size, are needed to study the long-term efficacy of endoscopic suturing systems in treatment of weight regain in post RYGB.

COMMENTS

Background

Obesity is an epidemic and persists as one of the world's leading chronic diseases. Many treatment options for obesity exist, but surgery has proven to be the best for significant weight reduction with low rates of weight regain. Roux-en-Y gastric bypass (RYGB) is one of the most effective bariatric surgical procedures, but is associated with 5% weight regain during 1 to 3 years post procedure. Such weight regain has been attributed to a dilated gastrojejunal anastomosis (GJA). However given the increased perioperative risk of mortality, surgical revision is not generally considered. Endoscopic suturing system has shown potential in reducing the dilated GJA. The aim of this review is to verify the techniques and efficacy of peroral endoscopic reduction of dilated gastrojejunal anastomosis after RYGB.

Research frontiers

The endoscopic suturing system was first used in 1996, in the treatment of gastroesophageal reflux disease. Sutures were placed at the gastric cardia to plicate and ultimately tighten the gastroesophageal junction. In its application for the treatment of dilated GJA, the endoscopic suturing system is attached to the endoscope via channels and advanced to the gastrojejunal anastomosis. By opening and closing of the handle of endoscopic suturing system, endoscopic stitches are applied to plicate the tissues resulting in a tightening of the GJA.

Innovations and breakthroughs

Peroral endoscopic reduction of dilated gastrojejunal anastomosis post RYGB has been successfully performed in various clinical studies. The retrieved manuscripts were reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that peroral endoscopic reduction *via* the endoscopic suturing system is an efficacious method in reducing dilated gastrojejunal anastomosis, thereby curbing the problem of weight regain post RYGB.

Terminology

The peroral endoscopic reduction technique is a novel modality employed in addressing the problem of dilated gastrojejunal anastomosis in RYGB as the cause of weight regain. The endoscopic suturing system is attached to the endoscope *via* its channels and advanced to the gastrojejunal anastomosis. Stitches are then applied through the tissue with opening and closing of the handle of endoscopic suturing system.

Peer-review

Overall, this is an interesting review of transoral endoscopic fixation of gastrojejunal dilation.

REFERENCES

- 1 Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012; **307**: 491-497 [PMID: 22253363 DOI: 10.1001/jama.2012.39]
- 2 Bray GA. Is new hope on the horizon for obesity? *Lancet* 2008; **372**: 1859-1860 [PMID: 19041787 DOI: 10.1016/S0140-6736(08)61792-4]
- 3 Tice JA, Karliner L, Walsh J, Petersen AJ, Feldman MD. Gastric banding or bypass? A systematic review comparing the two most popular bariatric procedures. *Am J Med* 2008; **121**: 885-893 [PMID: 18823860 DOI: 10.1016/j.amjmed.2008.05.036]
- 4 Boza C, Gamboa C, Perez G, Crovari F, Escalona A, Pimentel F, Raddatz A, Guzman S, Ibáñez L. Laparoscopic adjustable gastric banding (LAGB): surgical results and 5-year follow-up. *Surg Endosc* 2011; **25**: 292-297 [PMID: 20652325 DOI: 10.1007/s00464-010-1176-x]
- 5 Lee WJ, Ser KH, Lee YC, Tsou JJ, Chen SC, Chen JC. Laparoscopic Roux-en-Y vs. mini-gastric bypass for the treatment of morbid obesity: a 10-year experience. *Obes Surg* 2012; **22**: 1827-1834 [PMID: 23011462 DOI: 10.1007/s11695-012-0726-9]
- 6 Madura JA, Dibaise JK. Quick fix or long-term cure? Pros and cons of bariatric surgery. *F1000 Med Rep* 2012; **4**: 19 [PMID: 23091563 DOI: 10.3410/M4-19]
- 7 Elder KA, Wolfe BM. Bariatric surgery: a review of procedures and outcomes. *Gastroenterology* 2007; **132**: 2253-2271 [PMID: 17498516]
- 8 Kellum JM, Kuemmerle JF, O'Dorisio TM, Rayford P, Martin D, Engle K, Wolf L, Sugerman HJ. Gastrointestinal hormone responses to meals before and after gastric bypass and vertical banded gastroplasty. *Ann Surg* 1990; **211**: 763-770; discussion 770-771 [PMID: 2192696]
- 9 Tritos NA, Mun E, Bertkau A, Grayson R, Maratos-Flier E, Goldfine A. Serum ghrelin levels in response to glucose load in obese subjects post-gastric bypass surgery. *Obes Res* 2003; **11**: 919-924 [PMID: 12917494]
- 10 Sugerman HJ, Starkey JV, Birkenhauer R. A randomized prospective trial of gastric bypass versus vertical banded gastroplasty for morbid obesity and their effects on sweets versus non-sweets eaters. *Ann Surg* 1987; **205**: 613-624 [PMID: 3296971]
- 11 Powers PS, Rosemurgy A, Boyd F, Perez A. Outcome of gastric restriction procedures: weight, psychiatric diagnoses, and satisfaction. *Obes Surg* 1997; **7**: 471-477 [PMID: 9730503]
- 12 Macgregor AM, Rand CS. Revision of Staple Line Failure Following Roux-en-Y Gastric Bypass for Obesity: a follow-up of weight loss. *Obes Surg* 1991; **1**: 151-154 [PMID: 10775908]
- 13 McCormick JT, Papasavas PK, Caushaj PF, Gagné DJ. Laparoscopic revision of failed open bariatric procedures. *Surg Endosc* 2003; **17**: 413-415 [PMID: 12457212]
- 14 Schwartz RW, Strodel WE, Simpson WS, Griffen WO. Gastric bypass revision: lessons learned from 920 cases. *Surgery* 1988; **104**: 806-812 [PMID: 3051478]
- 15 Linner JH, Drew RL. Reoperative surgery--indications, efficacy, and long-term follow-up. *Am J Clin Nutr* 1992; **55**: 606S-610S [PMID: 1733138]
- 16 Spaulding L. Treatment of dilated gastrojejunostomy with sclerotherapy. *Obes Surg* 2003; **13**: 254-257 [PMID: 12740134]
- 17 Thompson CC, Slattery J, Bundga ME, Lautz DB. Peroral endoscopic reduction of dilated gastrojejunal anastomosis after Roux-en-Y gastric bypass: a possible new option for patients with weight regain. *Surg Endosc* 2006; **20**: 1744-1748 [PMID: 17024527]
- 18 Mullady DK, Lautz DB, Thompson CC. Treatment of weight regain after gastric bypass surgery when using a new endoscopic platform: initial experience and early outcomes (with video). *Gastrointest Endosc* 2009; **70**: 440-444 [PMID: 19555944 DOI: 10.1016/j.gie.2009.01.042]
- 19 Jirapinyo P, Slattery J, Ryan MB, Abu Dayyeh BK, Lautz DB, Thompson CC. Evaluation of an endoscopic suturing device for transoral outlet reduction in patients with weight regain following Roux-en-Y gastric bypass. *Endoscopy* 2013; **45**: 532-536 [PMID: 23801313 DOI: 10.1055/s-0032-1326638]
- 20 Fernández-Esparrach G, Lautz DB, Thompson CC. Peroral endoscopic anastomotic reduction improves intractable dumping syndrome in Roux-en-Y gastric bypass patients. *Surg Obes Relat Dis* 2010; **6**: 36-40 [PMID: 19560979 DOI: 10.1016/j.soard.2009.04.002]

P- Reviewer: Aquina CT, Cottam DR, Li JF
S- Editor: Ji FF L- Editor: A E- Editor: Li D



Gastric adenocarcinoma of fundic gland type: Endoscopic and clinicopathological features

Gen Tohda, Takeshi Osawa, Yasuyuki Asada, Masaki Dochin, Shintarou Terahata

Gen Tohda, Masaki Dochin, Department of Gastroenterology, Fukui Kosei Hospital, Fukui 918-8537, Japan

Takeshi Osawa, Yasuyuki Asada, Department of Surgery, Fukui Kosei Hospital, Fukui 918-8537, Japan

Shintarou Terahata, Department of Diagnostic Pathology, Tonami General Hospital, Tonami 939-1395, Japan

Author contributions: Tohda G wrote the manuscript; Osawa T and Asada Y contributed to the manuscript discussion; Dochin M and Terahata S reviewed the manuscript.

Institutional review board statement: This case report was reviewed and approved by the Fukui Kosei Hospital Institutional Review Board.

Informed consent statement: All involved persons gave their informed consent.

Conflict-of-interest statement: Authors have no conflict of interest relevant to this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Gen Tohda, MD, PhD, Department of Gastroenterology, Fukui Kosei Hospital, Shimo-rokujyo 201, Fukui 918-8537, Japan. genkipapa178@yahoo.co.jp
Telephone: +81-776-413377
Fax: +81-776-413372

Received: July 28, 2015

Peer-review started: August 6, 2015

First decision: September 23, 2015

Revised: December 20, 2015

Accepted: January 5, 2016

Article in press: January 7, 2016

Published online: February 25, 2016

Abstract

Gastric adenocarcinoma of fundic gland type (GA-FG) with chief cell differentiation was recently proposed as an extremely rare type of gastric adenocarcinoma. Here, we report 4 cases of GA-FG with chief cell differentiation. Endoscopic features included a submucosal tumor shape or a flat shape, whitish discoloration and dilated vessels on the surface. The tumors were located in the upper or middle third of the stomach. All cases were preoperatively diagnosed as GA-FG by biopsy, and endoscopic submucosal dissection was performed. Resected specimens revealed well-differentiated adenocarcinomas resembling chief cells. Tumor cells were diffusely positive for pepsinogen- I , but partially positive for H⁺/K⁺-ATPase in scattered locations around the tumor margin. Despite the presence of minimal invasion of the carcinoma into the submucosal layer, which was observed in two cases, neither lymphatic nor venous invasion was detected in any of the cases. Finally, all cases showed less aggressive clinical behavior with low grade malignancy.

Key words: Early gastric cancer; Low grade malignancy; Fundic gland type; Chief cells; Endoscopic submucosal dissection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Gastric adenocarcinoma of fundic gland type (GA-FG) with chief cell differentiation is a new and extremely rare type of gastric adenocarcinoma, and the clinicopathological features of GA-FG have thus not yet been elucidated. In the present study, we discuss 4 cases of GA-FG that displayed low grade malignancy, slow-growth and less aggressive clinical behavior. Endoscopic submucosal dissection was performed and

complete tumor resection was confirmed pathologically. None of the patients showed any signs of recurrence during the follow-up periods. We decided to report these rare cases because of their distinct endoscopic and clinicopathological features and unique biological behaviors.

Tohda G, Osawa T, Asada Y, Dochin M, Terahata S. Gastric adenocarcinoma of fundic gland type: Endoscopic and clinicopathological features. *World J Gastrointest Endosc* 2016; 8(4): 244-251 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i4/244.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i4.244>

INTRODUCTION

Gastric carcinoma has been histologically classified into differentiated and undifferentiated types^[1]. Following the advent of recent advanced techniques such as mucin histochemistry and immunohistochemistry, gastric adenocarcinomas can be classified as having either a gastric or an intestinal phenotype^[2,3], irrespective of their histological features. Among the types of differentiated adenocarcinomas with gastric phenotypes, tumors of both the foveolar type and the pyloric gland type have been reported. However, gastric adenocarcinomas of fundic gland type (GA-FG) have been considered extremely rare. After several cases of GA-FG with a parietal cell phenotype were reported^[4-9], a GA-FG with a chief cell differentiation was reported^[10] and was proposed as a new entity of gastric adenocarcinoma^[11]. Since this proposal, several cases of GA-FG have been reported^[12-20], but it is still considered an extremely rare type of gastric cancer. In the present study, we describe 4 cases of GA-FG with a chief cell differentiation, and evaluate their endoscopic findings, clinicopathological features and biological behaviors.

CASE REPORT

Between October 2010 and September 2014, among the 30182 patients who underwent upper gastrointestinal endoscopy as part of a yearly check-up, 4 patients were diagnosed with GA-FG. The clinicopathological findings are summarized in Table 1. The two male and two female patients were between 42 and 62 years of age. Concerning the gastric mucosa, atrophic changes with *Helicobacter pylori* (*H. pylori*) infection were observed in two of the 4 cases. The tumors were located in the upper or middle third of the stomach, and some appeared as either submucosal tumor (SMT)-like elevated lesions, whereas others had a flat shape. Faded or whitish discoloration and dilated vessels on the surface were also observed by conventional endoscopy (Figure 1). Neither irregular microvascular architecture nor an irregular microsurface pattern was detected by magnifying endoscopy with narrow band imaging. All

of the tumors were smaller than 5 mm in diameter. Histological examination of the biopsy specimens showed well-differentiated adenocarcinomas composed of chief cell-like cells. No evidence of metastasis was observed on computed tomography. After a preoperative diagnosis of GA-FG, endoscopic submucosal dissection (ESD) was performed.

According to the hematoxylin and eosin staining, the tumors were primarily composed of well-differentiated adenocarcinoma with columnar cells that mimicked fundic gland cells (Figure 2). Irregularly anastomosing glands with mildly enlarged and hyperchromatic nuclei were also observed. Histologically, in all cases, the tumors arose within the deeper zone of the gastric mucosa and were covered with a non-neoplastic epithelium. Despite the small sizes of the tumors, minimal invasion of the submucosal layer by tumor cells was observed in 2 cases. However, none of the cases demonstrated lymphatic or venous invasion. Moreover, none of the endoscopically resected specimens showed atrophic changes or intestinal metaplasia in the surrounding mucosa.

Cell differentiation according to the expression of Mucin 2 (MUC2) (a marker of goblet cells), MUC5AC (a marker of gastric foveolar epithelium), MUC6 (a marker of mucous neck cells and pyloric glands), CD10 (a marker of the brush border), pepsinogen-I (a marker of chief cells), H⁺/K⁺-ATPase (a marker of parietal cells) was evaluated immunohistochemically (Table 2). The tumor cells were classified as the gastric mucin phenotype based on diffuse positive staining for MUC6 and negativity for MUC2 and CD10. Immunohistochemical staining showed diffuse positive staining for pepsinogen-I and limited positivity for H⁺/K⁺-ATPase in scattered locations around the tumor margin (Figures 3 and 4). Finally, all 4 cases were diagnosed as GA-FG with chief cell differentiation. Cell proliferation, which was based on the Ki-67 (MIB-1) labeling index, was lower than 5% in all cases. Complete tumor resection was confirmed pathologically without further treatment. No complications associated with ESD were observed. None of the patients showed any signs of recurrence during the follow-up periods.

DISCUSSION

Histologically, GA-FG is typically classified into a chief cell-predominant type, a parietal cell-predominant type, or a mixed type. GA-FG with chief cell differentiation has been considered extremely rare and has been proposed as a new entity and pathologic subtype of gastric adenocarcinoma^[11]. GA-FG is associated with distinct clinicopathological characteristics, tumor location (they arise within a deeper zone of the gastric mucosa), and histological features (high-frequency of submucosal invasion independent of tumor size) as well as mucin expression (stomach type), and low-grade malignancy (mild atypism, lack of lymphovascular invasion and low proliferative activity). Moreover, GA-FG is not associated with *H. pylori* infection^[11]. In the present study, we describe 4 cases of GA-FG with chief cell differentiation.

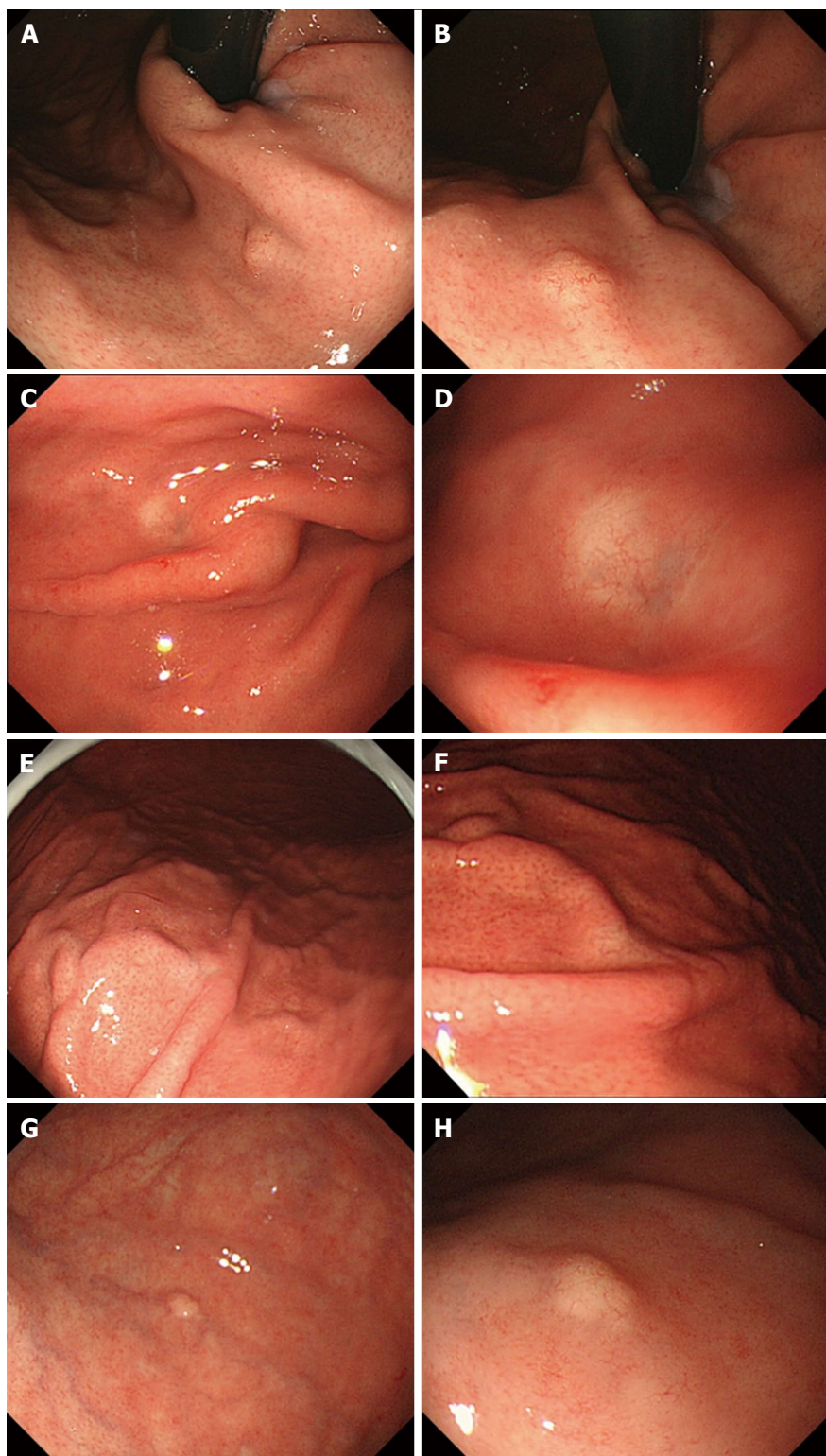


Figure 1 Endoscopic findings: Case 1 (A, B), case 2 (C, D), case 3 (E, F) and case 4 (G, H). Conventional endoscopy on white-light imaging showed flat lesions with whitish discoloration (C-F) or yellowish submucosal tumor shapes (A, B, G, H). Dilated vessels were shown on the surface of tumors (B, D, F, H).

During the diagnostic process of GA-FG, endoscopic features should be taken into consideration. According to previous reports^[11,18], GA-FG has distinct endoscopic features, such as an SMT shape or a flat/depressed shape, a faded/whitish color and dilated vessels on the surface, which can provide valuable information in

the diagnostic process. In the present study, 2 cases revealed an SMT-like morphology on endoscopy. For these cases, we would have to consider the possibility of sporadic carcinoid tumors that may also have been centered in the deeper zone of the gastric mucosa. The other 2 cases featured a flat mucosa with faded/

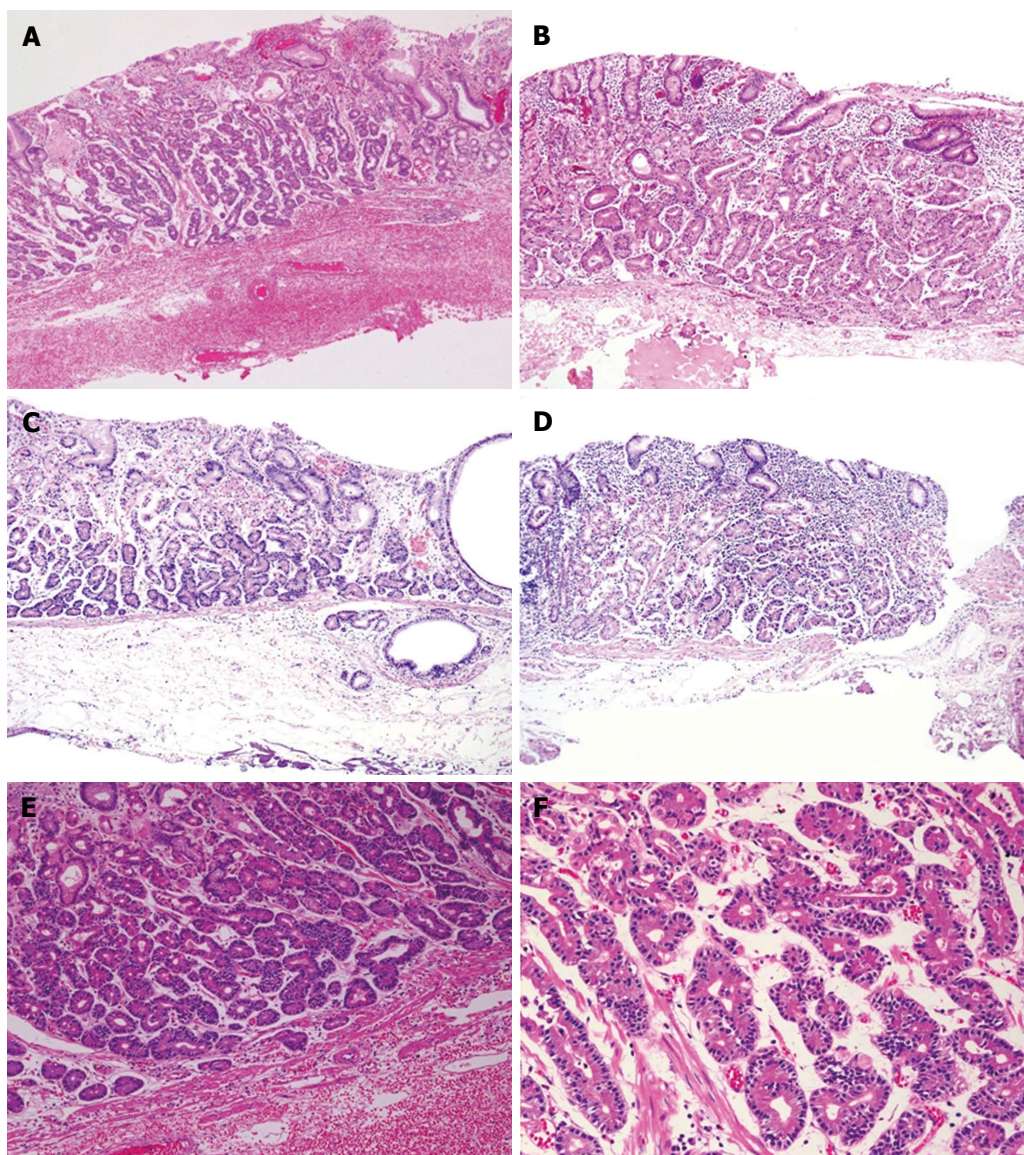


Figure 2 Histological findings (hematoxylin and eosin staining): Case 1 (A, E, F), case 2 (B), case 3 (C) and case 4 (D). Well-differentiated adenocarcinomas with columnar cells that mimicked fundic gland cells were observed. Tumors histologically arose in the deeper zone of gastric mucosa (A-D). Irregularly anastomosing glandular structures with mildly enlarged and hyperchromatic nuclei were observed (E, F). Minimum carcinoma invasion of the submucosal layer was detected (C, D). Neither lymphatic nor vascular invasion was observed. Magnification: A-D (low-power view $\times 100$), E (high-power view $\times 200$), F (high-power view $\times 400$).

whitish discoloration. For these cases, undifferentiated adenocarcinoma, mucosa-associated lymphoid tissue lymphoma, and normal gastric mucosa with focal atrophy would have to be considered as the differential diagnoses. Although distinct endoscopic features might be helpful in the diagnosis of GA-FG, it may still be difficult to discriminate among the differential diagnoses by endoscopic findings.

In the process of a histological diagnosis of GA-FG, dysplasia and adenocarcinoma in the fundic gland polyps (FGPs) have to be considered as the differential diagnoses. According to previous reports^[21,22], dysplasia and adenocarcinoma in the FGPs usually arise from the foveolar epithelium, which is different from the epithelium of the fundic glands. Therefore, these diseases can be distinguished from GA-FG. Cases of FGPs with chief cell hyperplasia and morphologic atypia have also been

reported^[23,24]. In these reports, structural and nuclear atypia in chief cell hyperplastic lesions were detected, but they were not diagnosed as adenocarcinoma due to a low Ki-67 labeling index. However, it is possible that such cases may become carcinomas because they are similar to the tumors of GA-FG chief cell-predominant type.

In the present study, all cases of GA-FG were discovered in the early stages. Neither lymphatic nor venous invasion was observed despite the presence of minimal tumor invasion into the submucosal layer. A high Ki-67 labeling index is considered to be related to a poor prognosis of gastric adenocarcinoma^[25,26]. In our study, all cases show a low proliferative index in regards to Ki-67 expression. No signs of recurrence or metastasis were observed during the follow-up periods. Patients with GA-FG are considered to have a favorable prognosis^[11,16-18]. In the current report, long-term follow-up of patients with

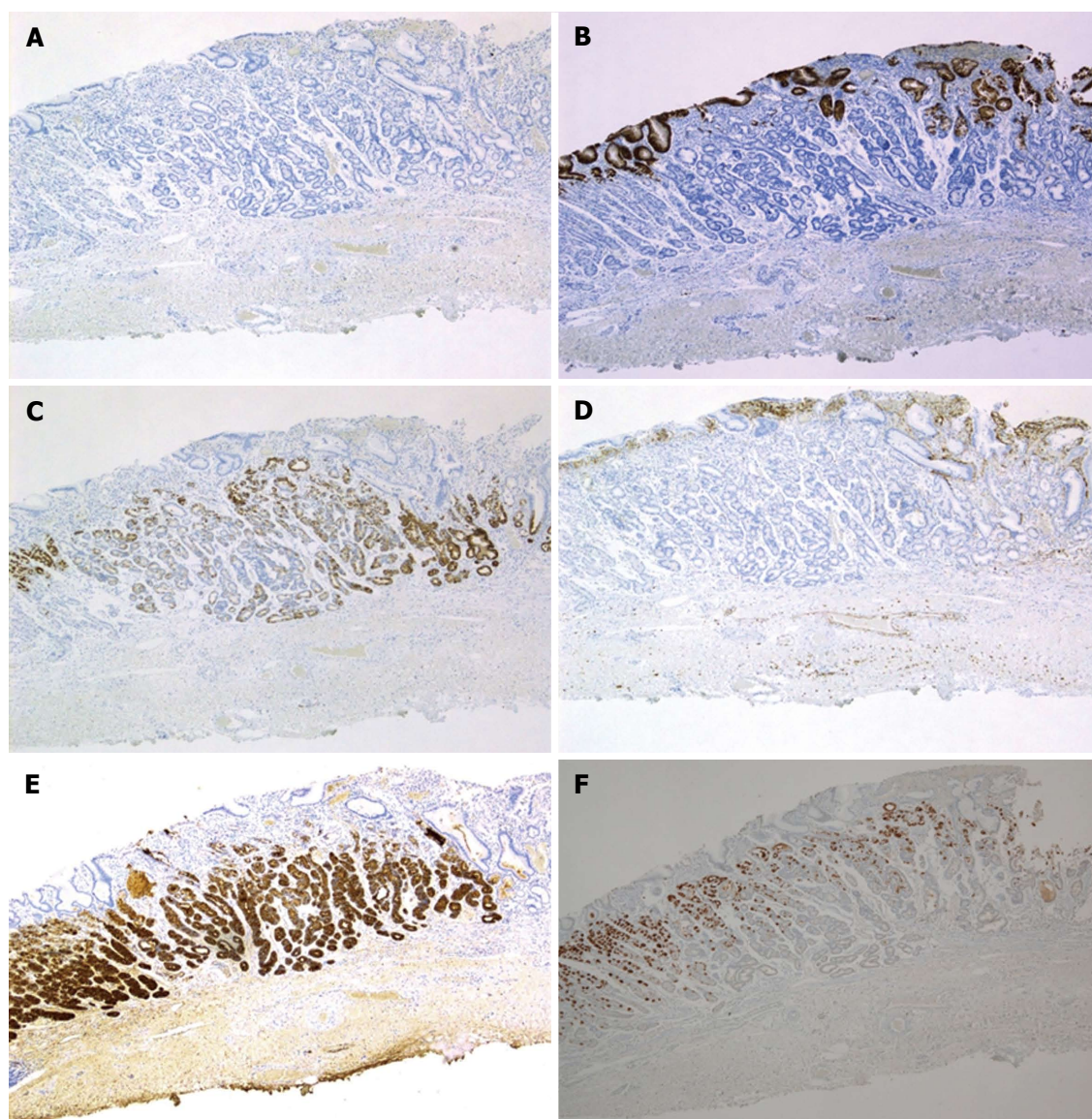


Figure 3 Immunohistochemical staining: Case 1. Tumor cells were diffusely positive for MUC6 (C) and pepsinogen-I (E), partially positive for H⁺/K⁺-ATPase in scattered locations around the tumor margin (F), negative staining for MUC2 (A), MUC5AC (B) and CD10 (D). Magnification: A-F (low-power view × 40). MUC: Mucin.

Table 1 Clinicopathological findings

	Case 1	Case 2	Case 3	Case 4
Age (yr)	42	60	62	50
Sex	Male	Female	Male	Female
Location	Upper third	Upper third	Middle third	Upper third
<i>H. pylori</i>	Negative	Positive	Negative	Positive
Morphological type	SMT-like	0 II b	0 II b	SMT-like
Size (mm)	4 × 3	5 × 4	5 × 5	2 × 2
Depth of invasion	M	M	SM	SM
Lymphatic invasion	-	-	-	-
Venous invasion	-	-	-	-
Observation time	10 mo	16 mo	28 mo	57 mo
Recurrence	-	-	-	-
Outcome	Alive	Alive	Alive	Alive

SMT: Submucosal tumor; SM: Submucosa; M: Mucosa; *H. pylori*: *Helicobacter pylori*.

GA-FG using upper gastrointestinal endoscopy showed

Table 2 Immunohistochemical expression of cell differentiation markers

	Case 1	Case 2	Case 3	Case 4
MUC 2	Negative	Negative	Negative	Negative
MUC 5AC	Negative	Negative	Negative	Negative
MUC 6	Positive	Positive	Positive	Positive
CD 10	Negative	Negative	Negative	Negative
Pepsinogen-I	Positive	Positive	Positive	Positive
H ⁺ /K ⁺ -ATPase	NS	NS	NS	NS

MUC: Mucin; NS: Non-specific.

changes that were barely detectable^[17]. In our study, a 50-year-old woman who was diagnosed with GA-FG underwent follow-up endoscopy every 8 mo. However, no detectable changes in the tumor were observed, and ESD was performed after three years of observation. Minimal invasion by the cancer cells into the submucosa

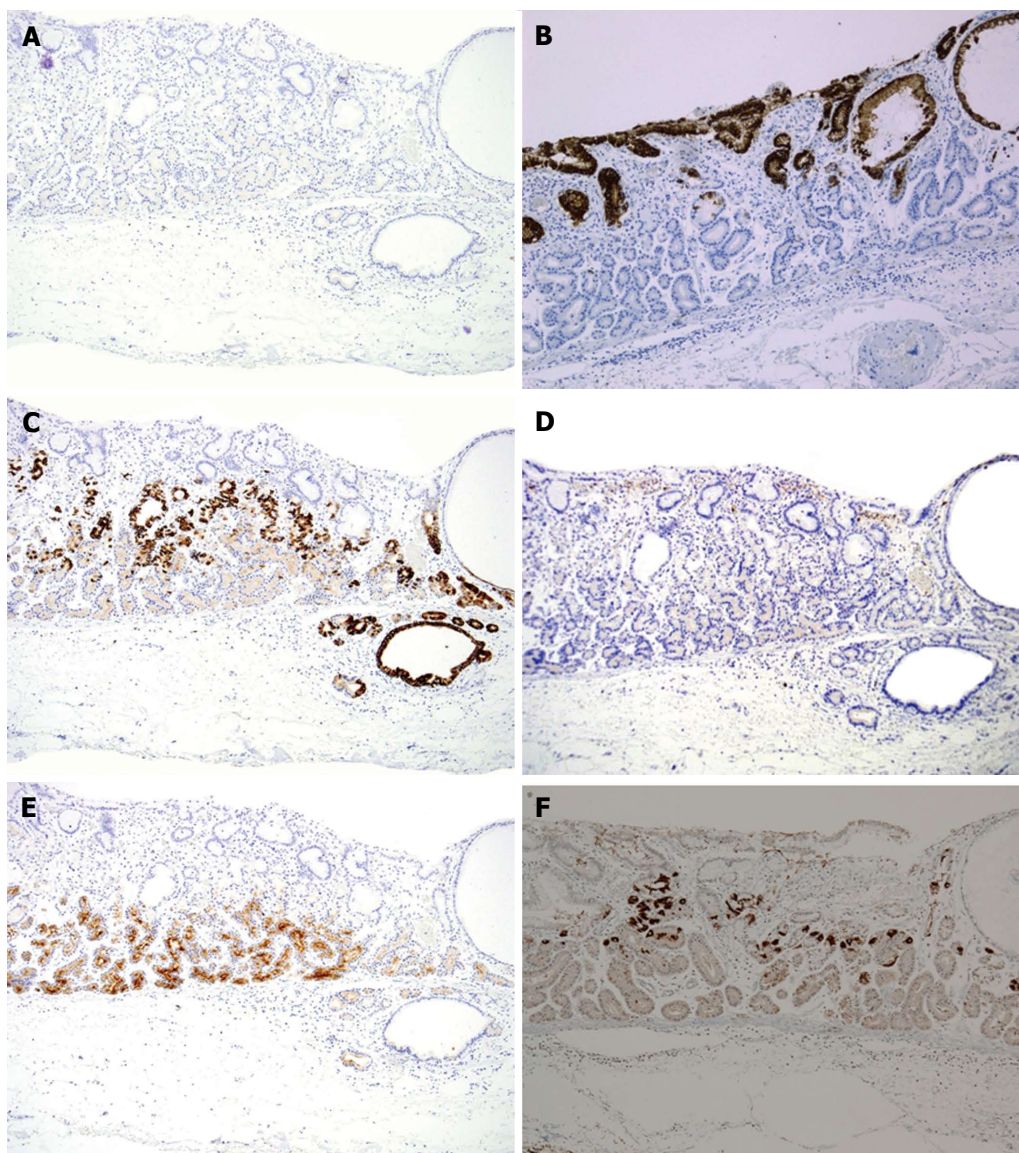


Figure 4 Immunohistochemical staining: **Case 3.** Tumor cells were diffusely positive for MUC6 (C) and pepsinogen-I (E), partially positive for H⁺/K⁺-ATPase in scattered locations around the tumor margin (F), negative staining for MUC2 (A), MUC5AC (B) and CD10 (D). Magnification: A-F (low-power view × 100). MUC: Mucin.

was observed, but no lymphovascular invasion was noted. Our cases also suggest that GA-FG displays slow-growth and less aggressive clinical behavior compared with typical gastric adenocarcinomas.

Base on the less aggressive biological behavior of GA-FG, a reclassification of GA-FG as a benign, oxyntic gland polyp/adenoma was proposed^[16]. However, advanced stage GA-FG with unusual clinicopathological features has since been reported^[19]. It has also been reported that GA-FG shows a favorable prognosis with less aggressive clinical behavior but that some cases of GA-FG might transform into high-grade malignancies during tumor progression^[11,19]. A recent study clarified that the molecular pathway of GA-FG is different from that of conventional type gastric adenocarcinomas^[27-29]. Because only a few case reports of early stage GA-FG have been published, the pathogenesis of GA-FG has not yet been elucidated. Further research is needed to analyze the

molecular mechanism of GA-FG and to evaluate the clinicopathological features including those of tumor development.

In conclusion, we reported 4 cases of well-differentiated adenocarcinoma of GA-FG with chief cell differentiation. GA-FG is extremely rare and has distinct characteristics that distinguish it from the more common types of gastric adenocarcinoma. Future studies will be expected to analyze the clinical behavior of GA-FG.

COMMENTS

Case characteristics

Four middle-aged patients without symptom underwent upper gastrointestinal endoscopy as a yearly check-up, and diagnosed as gastric adenocarcinoma of fundic gland type (GA-FG) with chief cell differentiation.

Clinical diagnosis

Upon physical examination, no significant physical findings were observed.

Differential diagnosis

Carcinoid tumors, undifferentiated adenocarcinoma, mucosa-associated lymphoid tissue lymphoma, normal gastric mucosa with focal atrophy, and adenocarcinoma in the fundic gland polyps were considered as differential diagnoses.

Laboratory diagnosis

All laboratory data were within normal limits.

Imaging diagnosis

In the upper or middle third of the stomach, a submucosal tumor-like elevated lesions or a flat shape with faded/whitish discoloration and dilated vessels on the surface were observed by upper gastrointestinal endoscopy.

Pathological diagnosis

The tumors were primarily composed of well-differentiated adenocarcinoma resembling fundic gland cells, and diagnosed as GA-FG with chief cell differentiation by immunohistochemical staining.

Treatment

In all cases, endoscopic submucosal dissection was performed and complete tumor resection was confirmed pathologically.

Related reports

GA-FG is a novel diagnostic entity with getting more reported cases worldwide. GA-FG usually shows low grade malignancy and less aggressive clinical behavior. Future studies will be expected to analyze the long-term prognosis of GA-FG.

Term explanation

GA-FG is a new diagnostic entity of gastric adenocarcinoma. Endoscopic treatment is often performed because of its low grade malignancy and less aggressive clinical behavior.

Experiences and lessons

GA-FG has been reported as a new entity and pathologic subtype of gastric adenocarcinoma. Recognizing the endoscopic and clinicopathological features of GA-FG can prevent misdiagnosis and provide adequate treatment.

Peer-review

GA-FG has been recently reported as a novel diagnostic entity of gastric adenocarcinoma. There is little information about GA-FG. In this study, the clinicopathologic findings of GA-FG are summarized. It is worthwhile for the readers because of its rarity or being less noticed.

REFERENCES

- 1 Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. *Gan* 1968; **59**: 251-258 [PMID: 5726267]
- 2 Kabashima A, Yao T, Sugimachi K, Tsuneyoshi M. Gastric or intestinal phenotypic expression in the carcinomas and background mucosa of multiple early gastric carcinomas. *Histopathology* 2000; **37**: 513-522 [PMID: 11122433]
- 3 Matsui N, Yao T, Akazawa K, Nawata H, Tsuneyoshi M. Different characteristics of carcinoma in the gastric remnant: histochemical and immunohistochemical studies. *Oncol Rep* 2001; **8**: 17-26 [PMID: 11115563]
- 4 Capella C, Frigerio B, Cornaggia M, Solcia E, Pinzon-Trujillo Y, Chejfec G. Gastric parietal cell carcinoma--a newly recognized entity: light microscopic and ultrastructural features. *Histopathology* 1984; **8**: 813-824 [PMID: 6083970]
- 5 Byrne D, Holley MP, Cuschieri A. Parietal cell carcinoma of the stomach: association with long-term survival after curative resection. *Br J Cancer* 1988; **58**: 85-87 [PMID: 3166896]
- 6 Hedenbro JL, Hägerstrand I, Rychterova V. Parietal cell carcinoma. A new differential diagnosis for submucosal gastric tumors.

- Endoscopy* 1990; **22**: 47-48 [PMID: 2307130]
- 7 Rychterova V, Hägerstrand I. Parietal cell carcinoma of the stomach. *APMIS* 1991; **99**: 1008-1012 [PMID: 1958345]
- 8 Takubo K, Honma N, Sawabe M, Arai T, Izumiya-Shimomura N, Kammori M, Sasajima K, Esaki Y. Oncocytic adenocarcinoma of the stomach: parietal cell carcinoma. *Am J Surg Pathol* 2002; **26**: 458-465 [PMID: 11914623]
- 9 Yang GY, Liao J, Cassai ND, Smolka AJ, Sidhu GS. Parietal cell carcinoma of gastric cardia: immunophenotype and ultrastructure. *Ultrastruct Pathol* 2003; **27**: 87-94 [PMID: 12746199]
- 10 Tsukamoto T, Yokoi T, Maruta S, Kitamura M, Yamamoto T, Ban H, Tatematsu M. Gastric adenocarcinoma with chief cell differentiation. *Pathol Int* 2007; **57**: 517-522 [PMID: 17610477]
- 11 Ueyama H, Yao T, Nakashima Y, Hirakawa K, Oshiro Y, Hirahashi M, Iwashita A, Watanabe S. Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. *Am J Surg Pathol* 2010; **34**: 609-619 [PMID: 20410811 DOI: 10.1097/PAS.0b013e3181d94d53]
- 12 Fukatsu H, Miyoshi H, Ishiki K, Tamura M, Yao T. Gastric adenocarcinoma of fundic gland type (chief cell predominant type) treated with endoscopic aspiration mucosectomy. *Dig Endosc* 2011; **23**: 244-246 [PMID: 21699569 DOI: 10.1111/j.1443-1661.2011.01125.x]
- 13 Terada T. Well differentiated adenocarcinoma of the stomach composed of chief cell-like cells and parietal cells (Gastric adenocarcinoma of fundic gland type). *Int J Clin Exp Pathol* 2011; **4**: 797-798 [PMID: 22135729]
- 14 Park ES, Kim YE, Park CK, Yao T, Kushima R, Kim KM. Gastric adenocarcinoma of fundic gland type: report of three cases. *Korean J Pathol* 2012; **46**: 287-291 [PMID: 23110017 DOI: 10.4132/KoreanJPathol.2012.46.3.287]
- 15 Chen WC, Rodriguez-Waitkus PM, Barroso A, Balsaver A, McKechnie JC. A Rare Case of Gastric Fundic Gland Adenocarcinoma (Chief Cell Predominant Type). *J Gastrointest Cancer* 2012; **43** Suppl 1: S262-S265 [PMID: 22791069]
- 16 Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. *Am J Surg Pathol* 2012; **36**: 1030-1035 [PMID: 22472957 DOI: 10.1097/PAS.0b013e31825033e7]
- 17 Abe T, Nagai T, Fukunaga J, Okawara H, Nakashima H, Syutou M, Kajimoto N, Wake R, Oyama T, Yao T. Long-term follow-up of gastric adenocarcinoma with chief cell differentiation using upper gastrointestinal tract endoscopy. *Intern Med* 2013; **52**: 1585-1588 [PMID: 23857090]
- 18 Ueyama H, Matsumoto K, Nagahara A, Hayashi T, Yao T, Watanabe S. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). *Endoscopy* 2014; **46**: 153-157 [PMID: 24338239 DOI: 10.1055/s-0033-1359042]
- 19 Ueo T, Yonemasu H, Ishida T. Gastric adenocarcinoma of fundic gland type with unusual behavior. *Dig Endosc* 2014; **26**: 293-294 [PMID: 24321002 DOI: 10.1111/den.12212]
- 20 Hori K, Ide YH, Hirota S, Toyoshima F, Takagawa T, Nakamura S. Early gastric adenocarcinoma of the fundic gland type. *Endoscopy* 2015; **47** Suppl 1 UCTN: E177-E178 [PMID: 25928827 DOI: 10.1055/s-0034-1391500]
- 21 Jalving M, Koornstra JJ, Boersma-van Ek W, de Jong S, Karrenbeld A, Hollema H, de Vries EG, Kleibeuker JH. Dysplasia in fundic gland polyps is associated with nuclear beta-catenin expression and relatively high cell turnover rates. *Scand J Gastroenterol* 2003; **38**: 916-922 [PMID: 14531526]
- 22 Stolte M, Vieth M, Ebert MP. High-grade dysplasia in sporadic fundic gland polyps: clinically relevant or not? *Eur J Gastroenterol Hepatol* 2003; **15**: 1153-1156 [PMID: 14560146]
- 23 Müller-Höcker J, Rellecke P. Chief cell proliferation of the gastric mucosa mimicking early gastric cancer: an unusual variant of fundic gland polyp. *Virchows Arch* 2003; **442**: 496-500 [PMID: 12698365]
- 24 Matsukawa A, Kurano R, Takemoto T, Kagayama M, Ito T. Chief cell hyperplasia with structural and nuclear atypia: a variant of fundic gland polyp. *Pathol Res Pract* 2005; **200**: 817-821 [PMID: 15792126]

- 25 **Kikuyama S**, Kubota T, Shimizu K, Miyakita M. Ki-67 antigen expression in relation to clinicopathological variables and prognosis in gastric cancer. *Oncol Rep* 1998; **5**: 867-870 [PMID: 9625834]
- 26 **Goishi H**, Tanaka S, Haruma K, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F. Predictive value of cathepsin D and Ki-67 expression at the deepest penetration site for lymph node metastases in gastric cancer. *Oncol Rep* 2000; **7**: 713-718 [PMID: 10854531]
- 27 **Nomura R**, Saito T, Mitomi H, Hidaka Y, Lee SY, Watanabe S, Yao T. GNAS mutation as an alternative mechanism of activation of the Wnt/ β -catenin signaling pathway in gastric adenocarcinoma of the fundic gland type. *Hum Pathol* 2014; **45**: 2488-2496 [PMID: 25288233 DOI: 10.1016/j.humpath.2014.08.016]
- 28 **Kushima R**, Sekine S, Matsubara A, Taniguchi H, Ikegami M, Tsuda H. Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. *Pathol Int* 2013; **63**: 318-325 [PMID: 23782334 DOI: 10.1111/pin.12070]
- 29 **Hidaka Y**, Mitomi H, Saito T, Takahashi M, Lee SY, Matsumoto K, Yao T, Watanabe S. Alteration in the Wnt/ β -catenin signaling pathway in gastric neoplasias of fundic gland (chief cell predominant) type. *Hum Pathol* 2013; **44**: 2438-2448 [PMID: 24011952 DOI: 10.1016/j.humpath.2013.06.002]

P- Reviewer: Lee CL, Ozkan OV **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

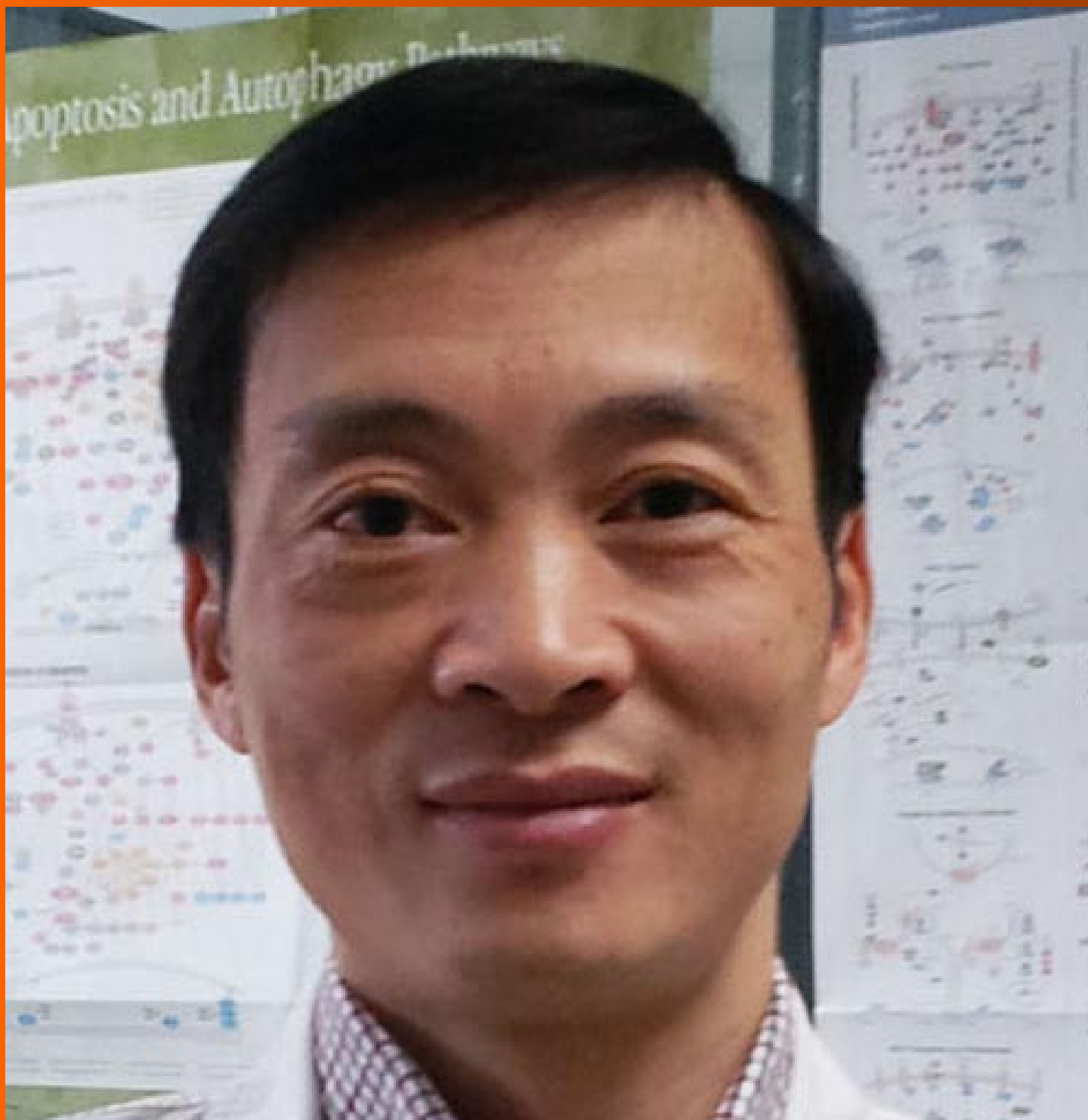
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 March 10; 8(5): 252-281





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Rajiman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



TOPIC HIGHLIGHT

- 252 New era of colorectal cancer screening
El Zoghbi M, Cummings LC

MINIREVIEWS

- 259 Endoscopic imaging of Barrett's esophagus
Naveed M, Dunbar KB
- 267 Efforts to increase image quality during endoscopy: The role of pronase
Kim GH, Cho YK, Cha JM, Lee SY, Chung IK
- 273 Raman spectroscopy for early real-time endoscopic optical diagnosis based on biochemical changes during the carcinogenesis of Barrett's esophagus
Shi H, Chen SY, Lin K

ORIGINAL ARTICLE

Retrospective Study

- 276 Endoscopic mucosal resection of colorectal adenomas > 20 mm: Risk factors for recurrence
Briedigkeit A, Sultanie O, Sido B, Dumoulin FL

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 5 March 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Yong-Liang Zhu, PhD, Assistant Professor, Second Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, China

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
March 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

2016 Colorectal Cancer: Global view

New era of colorectal cancer screening

Maysaa El Zoghbi, Linda C Cummings

Maysaa El Zoghbi, Linda C Cummings, Division of Gastroenterology and Liver Disease, University Hospitals Case Medical Center, Cleveland, OH 44106-5066, United States

Author contributions: El Zoghbi M and Cummings LC contributed equally to this paper.

Supported by An American College of Gastroenterology Junior Faculty Development Award to Linda C Cummings.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Maysaa El Zoghbi, MD, Gastroenterology Fellow, Division of Gastroenterology and Liver Disease, University Hospitals Case Medical Center, 11000 Euclid Avenue, Cleveland, OH 44106-5066, United States. maysaa.elzoghbi@uhhospitals.org
Telephone: +1-216-8445386
Fax: +1-216-9830347

Received: April 30, 2015

Peer-review started: May 7, 2015

First decision: July 17, 2015

Revised: October 24, 2015

Accepted: December 29, 2015

Article in press: January 1, 2016

Published online: March 10, 2016

Abstract

Colorectal cancer (CRC) is the 2nd most common cancer in women and 3rd most common cancer in men worldwide. Most CRCs develop from adenomatous polyps arising from glandular epithelium. Tumor growth is

initiated by mutation of the tumor suppressor gene *APC* and involves other genetic mutations in a stepwise process over years. Both hereditary and environmental factors contribute to the development of CRC. Screening has been proven to reduce the incidence of CRC. Screening has also contributed to the decrease in CRC mortality in the United States. However, CRC incidence and/or mortality remain on the rise in some parts of the world (Eastern Europe, Asia, and South America), likely due to factors including westernized diet, lifestyle, and lack of healthcare infrastructure. Multiple screening options are available, ranging from direct radiologic or endoscopic visualization tests that primarily detect premalignant or malignant lesions such as flexible sigmoidoscopy, optical colonoscopy, colon capsule endoscopy, computed tomographic colonography, and double contrast barium enema - to stool based tests which primarily detect cancers, including fecal DNA, fecal immunochemical test, and fecal occult blood test. The availability of some of these tests is limited to areas with high economic resources. This article will discuss CRC epidemiology, pathogenesis, risk factors, and screening modalities with a particular focus on new technologies.

Key words: Colorectal neoplasm; Prevention and control; Guidelines; Epidemiology; Colonoscopy; Capsule endoscopy; Computed tomographic colonography; Occult blood

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Multiple societies have issued screening guidelines for colorectal cancer (CRC). However, global CRC screening implementation can be challenging due to wide variability in healthcare infrastructure and resources in different countries. The practical implementation of CRC screening in a given area depends mainly upon availability of endoscopic resources. In areas with the greatest healthcare resources, colonoscopy remains the gold standard, although technological advances have provided alternative screening methods including

computed tomographic colonography, fecal DNA testing, and colon capsule endoscopy. In areas with fewer healthcare resources, guaiac-based fecal occult blood testing is the predominant screening modality.

El Zoghbi M, Cummings LC. New era of colorectal cancer screening. *World J Gastrointest Endosc* 2016; 8(5): 252-258 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i5/252.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i5.252>

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in women and third most common cancer in men worldwide^[1]. Globally, there is marked variation in CRC incidence and mortality^[1,2]. Some countries in Eastern Europe and Asia have demonstrated increasing incidence rates (Slovakia, Czech Republic, Singapore, and Japan) which have been attributed to behavioral risk factors related to westernization of diet and lifestyle^[3]. In addition, some countries (Brazil, Mexico, and Romania) have experienced increasing CRC mortality rates from CRC purportedly due to limited healthcare resources^[4]. In the United States, CRC is the third leading cause of cancer death and accounts for approximately 7% and 9% of overall cancer deaths in females and males, respectively^[5]. CRC incidence and mortality rates have been declining in the United States secondary to increased screening mainly *via* colonoscopy, which enables primary prevention and early detection^[6,7]. In recent years, technological advances have led to the development of new, less invasive screening modalities including fecal immunochemical testing, computed tomographic colonography (CTC), stool DNA testing, and colon capsule endoscopy. This article will discuss CRC pathogenesis, risk factors, and screening with a particular focus on new screening methods.

PATHOGENESIS

Most colorectal carcinomas develop from adenomatous polyp arising from the glandular epithelium of the intestine^[8]. Adenomas are initiated by somatic mutation of the tumor suppressor gene *APC*^[9]. Additional genetic alterations of oncogenes and tumor suppressor genes are involved in a stepwise growth process that occurs over years^[10-12]. The accumulation of genetic mutations in accordance with chromosomal instability, shifts the normal intestinal lining to an adenomatous polyp, then high-grade adenoma and finally to a carcinoma^[13,14]. CRC can also arise from nonpolypoid and depressed lesions. Although these lesions are less common than that of the polypoid adenoma, they manifest more aggressive behavior and more rapid growth, and they are more difficult to diagnose^[15,16].

SCREENING TESTS

Available tests for CRC screening are divided into 2 major types, stool-based tests or endoscopic and radiologic tests. The stool-based tests include the guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and fecal DNA testing. These tests detect cell debris and blood shed by vascularized polyps, adenomas and cancers^[17]. The endoscopic and radiologic examinations include optical colonoscopy, flexible sigmoidoscopy (FS or FSIG), double-contrast barium enema (DCBE), capsule endoscopy, and CTC and are based on direct or radiographic visualization of the polyp or cancer.

STOOL-BASED TESTS

gFOBT

gFOBT detects the presence of blood in feces through a chemical reaction dependent upon the peroxidase activity of heme. It is an inexpensive test that can be mailed to patients. Annual or biennial gFOBT have shown to decrease CRC mortality rates by 15%-33%^[18-20]. In the Minnesota Colon Cancer Control Study, a 30-year follow-up of patients randomly assigned to annual/or biennial gFOBT vs usual care showed a 32% decrease in CRC mortality. Furthermore, mortality reduction was more pronounced in men compared to women^[21].

A disadvantage of gFOBT is the requirement for 3 different stool samples^[22]. This makes collection more cumbersome to the patient, which results in lowered adherence and thus decreases its effectiveness as a screening test^[23,24]. gFOBT endorses a risk of false-positive results if patients ingest animal products or vegetables prior to testing, or if the patient is on anticoagulants or antiplatelet agents^[25]. On the other hand, a risk of false negative test arises if patient is on ascorbic acid or any other form of antioxidants^[26].

FIT

FIT is an antibody-based test that detects and binds to the globin component of hemoglobin. The FIT sampling technique is simpler and easier to collect compared to that of gFOBT. Only one or two fecal samples are required and no dietary or medication restrictions are needed prior to the test. The overall accuracy of FIT for detection of CRC was 95% with 79% sensitivity and 94% specificity as been shown in systematic review and meta-analysis including 19 qualified studies performed by Lee *et al*^[27]. FIT has been shown to have a greater sensitivity in detecting advanced adenomas and CRC than gFOBT^[28-31].

A disadvantage of FIT is its more expensive cost compared to FOBT. Although FIT is easier to collect, its sensitivity decreases with any delay in mailing or processing of the sample. Furthermore, similar to other non-invasive tests, if the test is positive, a follow-up colonoscopy would be needed.

Fecal DNA testing

Fecal DNA testing, or Cologuard (Exact Sciences), is a non-invasive, easy to perform test based on a single stool sample, and does not require dietary or medication restriction. It is a composite test that includes an immunochemical assay similar to the one used in FIT, methylated markers and molecular mutations markers associated with CRC. In 2014, this test was approved by the United States Food and Drug Administration as a screening test for CRC.

One multicenter study on 9989 patients comparing fecal DNA test to FIT using colonoscopy as the gold standard showed that the fecal DNA test had a higher sensitivity than FIT for detecting CRC, (92% vs 74%), adenomas with high-grade dysplasia (69% vs 46%), and serrated sessile polyps (42% vs 5%). However, specificity was lower with fecal DNA test at 87%-90% compared to FIT at 95%-96%^[32].

In a large multicenter case-control study, automated fecal DNA testing accurately detected CRC regardless of the site or the stage of the lesion with an overall sensitivity of more than 98%. Sensitivity for precancerous lesions increased in proportion to lesion size from 57% for lesions > 1 cm to 83% for those > 3 cm^[33].

Disadvantages of fecal DNA testing include its expensive cost; the inconvenience stool sampling and shipment to the lab; and the need for colonoscopy if the test is positive.

ENDOSCOPIC AND RADIOLOGIC TESTS**DCBE**

DCBE is a non-invasive radiological test, which provides a complete evaluation of the large intestine. The sensitivity and specificity of barium enema for polyps of any size is 38% and 86%, respectively^[34]. One study comparing barium enema to CT colonography and colonoscopy showed that DCBE has the lowest sensitivity and specificity with sensitivity of 41% for lesions ≥ 6 mm and sensitivity and specificity of 48% and 90% respectively for lesions ≥ 10 mm^[35]. These results are consistent with a meta-analysis comparing the performance of barium enema to that of CTC showing CTC is more sensitive and more specific than barium enema for large polyps (≥ 10 mm) and small polyps (6-9 mm) in average-risk and high-risk populations^[36]. In the United States, CT colonography has largely replaced DCBE as a radiographic option for CRC screening. A disadvantage of DCBE is that the test must be followed by colonoscopy if abnormalities are found.

Colonoscopy

Optical colonoscopy entails direct visualization of the colonic mucosa from the cecum to the rectum with a flexible endoscope. Insufflation, irrigation, and suction facilitate careful inspection of the mucosa. Colonoscopy allows both detection and removal of polyps, which can be submitted for histopathological examination.

Colonoscopy is routinely performed in some countries with sedation, whereas in others sedation is rarely used. Colonoscopy requires a bowel preparation with a laxative and clear liquid diet prior to the procedure. Split-dose protocols, in which patients ingest half the bowel preparation the day of the procedure, may encourage compliance and are now recommended for optimal bowel cleansing^[37]. Procedural risks include cardiopulmonary complications due to sedation, the possibility of missed lesions, bleeding, and a 0.08% rate of perforation, which is typically related to polypectomy^[38]. Although traditionally colonoscopy has been considered to be the gold standard for CRC screening, the miss rate for adenomas ≥ 1 cm was 6% in a tandem colonoscopy study^[39]. Moreover, colonoscopy is less effective at reducing proximal compared with distal CRCs^[40-43]. This finding may result from a combination of factors including inadequate bowel preparation, which is more likely to affect the right colon; incomplete colonoscopy; and a higher prevalence in the proximal colon of non-polypoid colorectal neoplasms, which are often more difficult to detect than traditional polypoid neoplasms^[44]. Based on pooled data from several large North American studies, 0.6% of patients with adenomas developed CRC within an average of 4 years after clearing colonoscopy^[45]. Fifty-two percent of these cancers were felt to be missed lesions, 19% were thought to be potentially incompletely resected lesions, and 24% were thought to be new lesions. These statistics reflect the fact that colonoscopy is operator dependent. Indeed, the development of interval cancers within 3 years after colonoscopy has been associated with performance of colonoscopy by non-gastroenterologists^[46].

FS

FS is used to visualize the left-sided or descending colon and the rectum where approximately 60% of all CRCs develop. Compared to colonoscopy, FS is safer, faster, and more easily tolerated procedure. Sedation is not required, and self-administered enemas are usually used in bowel preparation^[47,48].

Screening with FS decreases the incidence and overall mortality of CRC^[48,49]. A large randomized control trial involving 34272 participants between the ages of 55 and 64 years with a median follow-up of around 11 years showed a 31% decrease in the incidence of CRC and a 38% decrease in CRC mortality after one-time screening with FS, compared with no screening^[49].

A disadvantage of FS is that follow-up colonoscopy is required given that about 3%-5% of patients with CRC in the distal colon will have lesions in the proximal colon^[50]. In the United States, colonoscopy has largely replaced FS for CRC screening.

Colon capsule endoscopy

With capsule endoscopy (Pillcam COLON, Given Imaging Ltd, Yoqneam, Israel) the patient swallows a capsule which records digital images on 2 camera heads at a rate ranging from 4 to 35 frames per second for appro-

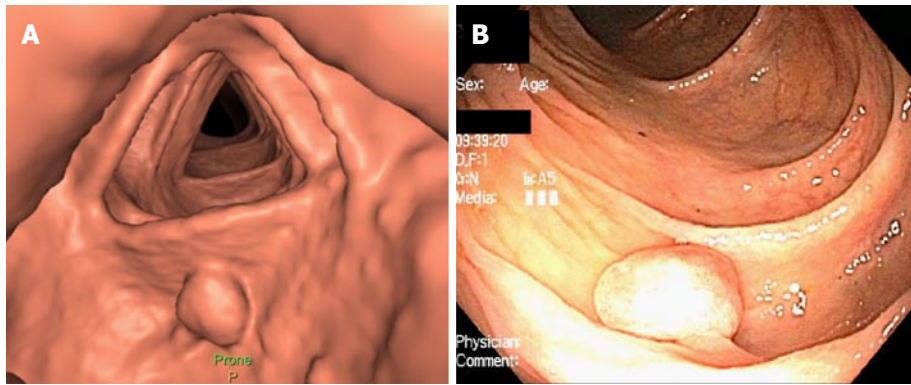


Figure 1 Visualization of a colonic polyp by computed tomographic colonography and optical colonoscopy. A: Three dimensional view of a splenic flexure colonic polyp on computed tomographic colonography; B: View of the same polyp on optical colonoscopy.

ximately 10 h. These images are then transmitted wirelessly to a recording device carried by the patient. The data are transferred from the device to a computer that uses a software (RAPID) to compile the video to be analyzed then by an experienced gastroenterologist^[51]. Indications for colon capsule endoscopy have not been standardized; the use of CE is recommended in cases of colonoscopy contraindication, colonoscopy failure, or in patients unwilling to perform colonoscopy. In the United States, the Food and Drug Administration has approved Pillcam COLON 2 (second generation) for patients who have had an incomplete colonoscopy.

A recent prospective study conducted by Doug Rex on 884 patients comparing accuracy of PillCam COLON 2 to that of optical colonoscopy demonstrated 88% sensitivity and 82% specificity in detecting adenoma \geq 6 mm in average risk screening population^[52].

An advantage of capsule endoscopy compared to other non-invasive methods is the lack of radiation exposure. Disadvantages of capsule endoscopy include the need for a complex bowel preparation regimen and the risk, albeit low, of capsule retention, which may necessitate surgical removal.

CTC

CTC, or virtual colonoscopy, is a radiographic imaging test in which two-dimensional or three-dimensional images of the colon and rectum are generated using specialized computer software and abdominal computed tomography scanning. It is offered to the patient if colonoscopy is incomplete or in the event of patients' refusal or has additional risk factors. CT colonography every 5 years is a screening option according to some CRC screening guidelines (see below). Multiple steps are involved in completing CTC. The first step is the bowel preparation, which includes a fiber-free diet and ingestion of a laxative and contrast medium prior to the test. The second step is colonic insufflation, which is done by insufflation of CO₂ *via* a rectal catheter and bulb in a gradual manner with a controlled pressure to prevent perforation. The third step is acquisition of the

radiographic images. An adjusted scout-view is obtained so that the entire colon is covered. Images are obtained in 2 positions, supine and prone; decubitus lateral positions are performed if patient is overweight.

The final step is interpretation of images; two dimensional interpretation identifies any lesion that is larger than a centimeter. The infracentimetric lesions are identified *via* three dimensional interpretation. After identification of a polyp-like lesion, its density should be determined. The lipoma or an inverted tumor is fatty, fecal residue is dense, and tumor tissue's density is similar to that of the colonic wall. Each lesion is then classified by C-RAD, which specifies the site, the shape, type of density, and the largest diameter of the head of the polyp. A colonoscopy is indicated for lesions that are \geq 10 mm or more than 3 lesions $>$ 5 mm^[53]. Figure 1 displays a polyp visualized on CT colonography and subsequent colonoscopy.

A multicenter trial enrolling 845 patients who underwent screening with CTC followed by colonoscopy showed 69% sensitivity and 91% specificity in detecting polyps $>$ 6 mm^[54]. CTC was found to accurately detect 90% of lesions $>$ 10 mm in diameter^[55]. The detection rate for advanced neoplasm was found to be similar for patients undergoing CTC compared to colonoscopy, while the rate of polypectomies and complications was considerably smaller in the CTC group compared to that of colonoscopy^[56]. Radiation exposure is one of disadvantage of CTC^[57]. In addition, perforation is still a risk, although it is less than that with colonoscopy^[36].

SCREENING GUIDELINES

In the United States, the two major guidelines for CRC screening are: (1) joint guidelines from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology; and (2) the US Preventive Services Task Force (USPSTF) guidelines. Other organizations have issued their own guidelines as well, such as the American College of Gastroenterology and the American College of Physicians. Table 1 summarizes the varying

Table 1 Summary of colorectal cancer screening guidelines from various organizations in the United States

	Joint guidelines	USPSTF	ACG	ACP
Flexible sigmoidoscopy	Every 5 yr	Every 5 yr, with high sensitivity FOBT every 3 yr	Every 5-10 yr	Every 5 yr
Colonoscopy	Every 10 yr	Every 10 yr	Every 10 yr	Every 10 yr
Barium enema	Every 5 yr	Not recommended	Not recommended	Every 5 yr
CT colonography	Every 5 yr	Insufficient evidence to recommend	Every 5 yr	Every 5 yr
gFOBT	Annual	Annual	Annual	Annual
FIT	Annual	Every year	Annual	Annual
sDNA	Uncertain	Insufficient evidence to recommend	Every 3 yr	Uncertain

USPSTF: United States Preventive Services Task Force; ACG: American College of Gastroenterology; ACP: American College of Physicians; FOBT: Fecal occult blood testing; CT: Computed tomographic; gFOBT: Guaiac-based fecal occult blood testing; FIT: Fecal immunochemical test; sDNA: Stool deoxyribonucleic acid.

recommendations from these different sets of guidelines for average risk individuals. USPSTF guidelines were issued in 2008 and are in the process of being updated. On a global level, CRC screening can be challenging to implement due to wide variability in healthcare infrastructure and resources in different countries. The World Gastroenterology Organization practice guidelines on CRC screening provide differing recommendations for average risk screening depending upon the availability of endoscopic resources^[58]. In areas with the lowest access to FS and colonoscopy, for example, biennial gFOBT or FIT is recommended, while colonoscopy every 10 years is recommended in areas with greater healthcare and endoscopic resources.

CONCLUSION

CRC screening is associated with decreased CRC incidence and mortality. CRC screening modalities include radiographic or endoscopic methods (colonoscopy, FS, CT colonography, double contrast barium enema, colon capsule endoscopy) and stool-based tests (fecal DNA test, gFOBT, and FIT). Options for screening also depend upon the healthcare infrastructure of the country including the availability of endoscopic resources. In offering CRC screening, the physician should discuss with the patient the advantages and disadvantages of each test and ascertain the patient's preferences for better adherence.

ACKNOWLEDGMENTS

We thank Luis Landeras, MD, for providing the CT

colonographic image.

REFERENCES

- 1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
- 2 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 3 Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009; **59**: 366-378 [PMID: 19897840 DOI: 10.3322/caac.20038]
- 4 Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1893-1907 [PMID: 20647400 DOI: 10.1158/1055-9965.EPI-10-0437]
- 5 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]
- 6 Siegel RL, Ward EM, Jemal A. Trends in colorectal cancer incidence rates in the United States by tumor location and stage, 1992-2008. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 411-416 [PMID: 22219318 DOI: 10.1158/1055-9965.EPI-11-1020]
- 7 Edwards BK, Ward E, Kohler BA, Ehemann C, Zaubner AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 2010; **116**: 544-573 [PMID: 19998273 DOI: 10.1002/cncr.24760]
- 8 Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007; **50**: 113-130 [PMID: 17204026 DOI: 10.1111/j.1365-2559.2006.02549.x]
- 9 Lamlum H, Papadopoulos A, Ilyas M, Rowan A, Gillet C, Hanby A, Talbot I, Bodmer W, Tomlinson I. APC mutations are sufficient for the growth of early colorectal adenomas. *Proc Natl Acad Sci USA* 2000; **97**: 2225-2228 [PMID: 10681434 DOI: 10.1073/pnas.040564697]
- 10 Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988; **319**: 525-532 [PMID: 2841597 DOI: 10.1056/NEJM198809013190901]
- 11 Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**: 2251-2270 [PMID: 1203876]
- 12 Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735]
- 13 Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. *Nature* 1997; **386**: 623-627 [PMID: 9121588 DOI: 10.1038/386623a0]
- 14 Markowitz SD, Bertagnolli MM. Molecular origins of cancer: Molecular basis of colorectal cancer. *N Engl J Med* 2009; **361**: 2449-2460 [PMID: 20018966 DOI: 10.1056/NEJMra0804588]
- 15 Hurlstone DP, Cross SS, Adam I, Shorthouse AJ, Brown S, Sanders DS, Lobo AJ. A prospective clinicopathological and endoscopic evaluation of flat and depressed colorectal lesions in the United Kingdom. *Am J Gastroenterol* 2003; **98**: 2543-2549 [PMID: 14638361 DOI: 10.1111/j.1572-0241.2003.07679.x]
- 16 Kudo Se, Lambert R, Allen JJ, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Triadafilopoulos G, Zaubner A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Vieth M, Jass JR, Hurlstone PD. Nonpolypoid neoplastic lesions of the colorectal mucosa. *Gastrointest Endosc* 2008; **68**: S3-47 [PMID: 18805238 DOI: 10.1016/j.gie.2008.07.052]
- 17 Carroll MR, Seaman HE, Halloran SP. Tests and investigations for colorectal cancer screening. *Clin Biochem* 2014; **47**: 921-939

- [PMID: 24769265 DOI: 10.1016/j.clinbiochem.2014.04.019]
- 18 **Hardcastle JD**, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; **348**: 1472-1477 [PMID: 8942775 DOI: 10.1016/S0140-6736(96)03386-7]
 - 19 **Kronborg O**, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; **348**: 1467-1471 [PMID: 8942774 DOI: 10.1016/S0140-6736(96)03430-7]
 - 20 **Mandel JS**, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365-1371 [PMID: 8474513 DOI: 10.1056/NEJM199305133281901]
 - 21 **Shaukat A**, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, Church TR. Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013; **369**: 1106-1114 [PMID: 24047060 DOI: 10.1056/NEJMoa1300720]
 - 22 **Deutekom M**, van Rossum LG, van Rijn AF, Laheij RJ, Fockens P, Bossuyt PM, Dekker E, Jansen JB. Comparison of guaiac and immunological fecal occult blood tests in colorectal cancer screening: the patient perspective. *Scand J Gastroenterol* 2010; **45**: 1345-1349 [PMID: 20560814 DOI: 10.3109/00365521.2010.497937]
 - 23 **Gellad ZF**, Stechuchak KM, Fisher DA, Olsen MK, McDuffie JR, Ostbye T, Yancy WS. Longitudinal adherence to fecal occult blood testing impacts colorectal cancer screening quality. *Am J Gastroenterol* 2011; **106**: 1125-1134 [PMID: 21304501 DOI: 10.1038/ajg.2011.11]
 - 24 **Fenton JJ**, Elmore JG, Buist DS, Reid RJ, Tancredi DJ, Baldwin LM. Longitudinal adherence with fecal occult blood test screening in community practice. *Ann Fam Med* 2010; **8**: 397-401 [PMID: 20843880 DOI: 10.1370/afm.1133]
 - 25 **Clarke P**, Jack F, Carey FA, Steele RJ. Medications with anticoagulant properties increase the likelihood of a negative colonoscopy in faecal occult blood test population screening. *Colorectal Dis* 2006; **8**: 389-392 [PMID: 16684082 DOI: 10.1111/j.1463-1318.2005.00919.x]
 - 26 **Jaffe RM**, Kasten B, Young DS, MacLowry JD. False-negative stool occult blood tests caused by ingestion of ascorbic acid (vitamin C). *Ann Intern Med* 1975; **83**: 824-826 [PMID: 1200528]
 - 27 **Lee JK**, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014; **160**: 171 [PMID: 24658694 DOI: 10.7326/M13-1484]
 - 28 **Allison JE**, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). *Gut Liver* 2014; **8**: 117-130 [PMID: 24672652 DOI: 10.5009/gnl.2014.8.2.117]
 - 29 **Allison JE**, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, Pauly MP, Shlager L, Palitz AM, Zhao WK, Schwartz JS, Ransohoff DF, Selby JV. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst* 2007; **99**: 1462-1470 [PMID: 17895475 DOI: 10.1093/jnci/djm150]
 - 30 **Allison JE**, Lawson M. Screening tests for colorectal cancer: a menu of options remains relevant. *Curr Oncol Rep* 2006; **8**: 492-498 [PMID: 17040627]
 - 31 **Whitlock EP**, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2008; **149**: 638-658 [PMID: 18838718]
 - 32 **Imperiale TF**, Ransohoff DF, Itzkowitz SH. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014; **371**: 187-188 [PMID: 25006736 DOI: 10.1056/NEJMc1405215]
 - 33 **Lidgard GP**, Domanico MJ, Bruinsma JJ, Light J, Gagrath ZD, Oldham-Haltom RL, Fourrier KD, Allawi H, Yab TC, Taylor WR, Simonson JA, Devens M, Heigh RI, Ahlquist DA, Berger BM. Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia. *Clin Gastroenterol Hepatol* 2013; **11**: 1313-1318 [PMID: 23639600 DOI: 10.1016/j.cgh.2013.04.023]
 - 34 **Winawer SJ**, Stewart ET, Zauber AG, Bond JH, Ansel H, Wayne JD, Hall D, Hamlin JA, Schapiro M, O'Brien MJ, Sternberg SS, Gottlieb LS. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med* 2000; **342**: 1766-1772 [PMID: 10852998 DOI: 10.1056/NEJM200006153422401]
 - 35 **Rockey DC**, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L, Yee J, Henderson J, Hatten P, Burdick S, Sanyal A, Rubin DT, Sterling M, Akerkar G, Bhutani MS, Binmoeller K, Garvie J, Bini EJ, McQuaid K, Foster WL, Thompson WM, Dachman A, Halvorsen R. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet* 2005; **365**: 305-311 [PMID: 15664225 DOI: 10.1016/S0140-6736(05)17784-8]
 - 36 **Burling D**, Halligan S, Slater A, Noakes MJ, Taylor SA. Potentially Serious Adverse Events at CT Colonography in Symptomatic Patients: National Survey of the United Kingdom 1. *Radiology* 2006; **239**: 464-471
 - 37 **Johnson DA**, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, Robertson DJ, Boland CR, Giardello FM, Lieberman DA, Levin TR, Rex DK. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US multi-society task force on colorectal cancer. *Gastroenterology* 2014; **147**: 903-924 [PMID: 25239068 DOI: 10.1053/j.gastro.2014.07.002]
 - 38 **Arora G**, Mannalithara A, Singh G, Gerson LB, Triadafilopoulos G. Risk of perforation from a colonoscopy in adults: a large population-based study. *Gastrointest Endosc* 2009; **69**: 654-664 [PMID: 19251006 DOI: 10.1016/j.gie.2008.09.008]
 - 39 **Rex DK**, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 1997; **112**: 24-28 [PMID: 8978338]
 - 40 **Lakoff J**, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. *Clin Gastroenterol Hepatol* 2008; **6**: 1117-1121; quiz 1064 [PMID: 18691942 DOI: 10.1016/j.cgh.2008.05.016]
 - 41 **Raginel T**, Puvinel J, Ferrand O, Bouvier V, Levillain R, Ruiz A, Lantieri O, Launoy G, Guittet L. A population-based comparison of immunochemical fecal occult blood tests for colorectal cancer screening. *Gastroenterology* 2013; **144**: 918-925 [PMID: 23376426 DOI: 10.1053/j.gastro.2013.01.042]
 - 42 **Nishihara R**, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013; **369**: 1095-1105 [PMID: 24047059 DOI: 10.1056/NEJMoa1301969]
 - 43 **Brenner H**, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst* 2010; **102**: 89-95 [PMID: 20042716 DOI: 10.1093/jnci/djp436]
 - 44 **Rondagh EJ**, Bouwens MW, Riedl RG, Winkens B, de Ridder R, Kaltenbach T, Soetikno RM, Masclee AA, Sanduleanu S. Endoscopic appearance of proximal colorectal neoplasms and potential implications for colonoscopy in cancer prevention. *Gastrointest Endosc* 2012; **75**: 1218-1225 [PMID: 22482917 DOI: 10.1016/j.gie.2012.02.010]
 - 45 **Robertson DJ**, Lieberman DA, Winawer SJ, Ahnen DJ, Baron JA, Schatzkin A, Cross AJ, Zauber AG, Church TR, Lance P, Greenberg ER, Martínez ME. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. *Gut* 2014; **63**: 949-956 [PMID: 23793224 DOI: 10.1136/gutjnl-2012-303796]
 - 46 **Cooper GS**, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. *Cancer* 2012; **118**: 3044-3052 [PMID: 21989586 DOI: 10.1002/cncr.26602]
 - 47 **Atkin WS**, Cook CF, Cuzick J, Edwards R, Northover JM, Wardle

- J. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; **359**: 1291-1300 [PMID: 11965274 DOI: 10.1016/S0140-6736(02)08268-5]
- 48 **Atkin WS**, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; **375**: 1624-1633 [PMID: 20430429 DOI: 10.1016/S0140-6736(10)-60551-X]
- 49 **Segnan N**, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, Andreoni B, Arrigoni A, Bisanti L, Casella C, Crosta C, Falcini F, Ferrero F, Giacomini A, Giuliani O, Santarelli A, Visioli CB, Zanetti R, Atkin WS, Senore C. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. *J Natl Cancer Inst* 2011; **103**: 1310-1322 [PMID: 21852264 DOI: 10.1093/jnci/djr284]
- 50 **Cappell MS**. The pathophysiology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps. *Med Clin North Am* 2005; **89**: 1-42, vii [PMID: 15527807 DOI: 10.1016/j.mcna.2004.08.011]
- 51 **Mamonov AV**, Figueiredo IN, Figueiredo PN, Tsai YH. Automated polyp detection in colon capsule endoscopy. *IEEE Trans Med Imaging* 2014; **33**: 1488-1502 [PMID: 24710829 DOI: 10.1109/TMI.2014.2314959]
- 52 **Rex DK**, Adler SN, Aisenberg J, Burch WC, Carretero C, Chowers Y, Fein SA, Fern SE, Fernandez-Urien Sainz I, Fich A, Gal E, Horlander JC, Isaacs KL, Kariv R, Lahat A, Leung WK, Malik PR, Morgan D, Papageorgiou N, Romeo DP, Shah SS, Waterman M. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. *Gastroenterology* 2015; **148**: 948-957.e2 [PMID: 25620668 DOI: 10.1053/j.gastro.2015.01.025]
- 53 **Gandon Y**. Screening for colorectal cancer: the role of CT colonography. *Diagn Interv Imaging* 2014; **95**: 467-474 [PMID: 24794252 DOI: 10.1016/j.diii.2014.03.012]
- 54 **Heresbach D**, Djabbari M, Riou F, Marcus C, Le Sidaner A, Pierredon-Foulogne MA, Ponchon T, Boudiaf M, Seyrig JA, Laumonier H, Luet D, Giraud-Cohen M, Pelletier AL, Charachon A, Ramaholimihaso F, Bouillet P, Veyrac M, Ficarelli S, Vahedi K, Keruhel J, Lamouliatte H, Ridereau-Zins C, Bouhnik Y, Tissier M, Diris B, Zagdanski AM, Josselin JM, Hamonic S, Gandon Y. Accuracy of computed tomographic colonography in a nationwide multicentre trial, and its relation to radiologist expertise. *Gut* 2011; **60**: 658-665 [PMID: 21266723 DOI: 10.1136/gut.2010.225623]
- 55 **Johnson CD**, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, Menias CO, Siewert B, Cheema JI, Obregon RG, Fidler JL, Zimmerman P, Horton KM, Coakley K, Iyer RB, Hara AK, Halvorsen RA, Casola G, Yee J, Herman BA, Burgart LJ, Limburg PJ. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008; **359**: 1207-1217 [PMID: 18799557 DOI: 10.1056/NEJMoa0800996]
- 56 **Kim DH**, Pickhardt PJ, Taylor AJ, Leung WK, Winter TC, Hinshaw JL, Gopal DV, Reichelderfer M, Hsu RH, Pfau PR. CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med* 2007; **357**: 1403-1412 [PMID: 17914041 DOI: 10.1056/NEJMoa070543]
- 57 **Lin OS**. Computed tomographic colonography: hope or hype? *World J Gastroenterol* 2010; **16**: 915-920 [PMID: 20180228]
- 58 **Winawer SJ**, Krabshuis J, Lambert R, O'Brien M, Fried M. Cascade colorectal cancer screening guidelines: a global conceptual model. *J Clin Gastroenterol* 2011; **45**: 297-300 [PMID: 21301355 DOI: 10.1097/MCG.0b013e3182098e07]

P- Reviewer: Tsuji Y S- Editor: Song XX L- Editor: A
E- Editor: Wu HL



Endoscopic imaging of Barrett's esophagus

Mariam Naveed, Kerry B Dunbar

Mariam Naveed, Division of Gastroenterology and Hepatology, University of Iowa Carver College of Medicine, Iowa City, IA 52242, United States

Kerry B Dunbar, Dallas VA Medical Center, Dallas, TX 75216, United States

Kerry B Dunbar, University of Texas Southwestern Medical Center, Dallas, TX 75390, United States

Author contributions: Naveed M and Dunbar KB both and equally contributed to this paper.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Kerry B Dunbar, MD, PhD, Associate Professor of Medicine, Dallas VA Medical Center, GI Lab CA 111-B1, 4500 South Lancaster Road, Dallas, TX 75216, United States. kerry.dunbar@utsouthwestern.edu
Telephone: +1-214-8571603
Fax: +1-214-8571571

Received: June 4, 2015
Peer-review started: June 6, 2015
First decision: August 31, 2015
Revised: December 11, 2015
Accepted: December 16, 2015
Article in press: December 18, 2015
Published online: March 10, 2016

Abstract

The incidence of esophageal adenocarcinoma (EAC) has dramatically increased in the United States as

well as Western European countries. The majority of esophageal adenocarcinomas arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion that can lead to dysplasia and cancer. Because of the increased risk of EAC, GI society guidelines recommend endoscopic surveillance of patients with BE. The emphasis on early detection of dysplasia in BE through surveillance endoscopy has led to the development of advanced endoscopic imaging technologies. These techniques have the potential to both improve mucosal visualization and characterization and to detect small mucosal abnormalities which are difficult to identify with standard endoscopy. This review summarizes the advanced imaging technologies used in evaluation of BE.

Key words: Esophageal adenocarcinoma; Barrett's esophagus; Dysplasia; Intestinal metaplasia; Advanced endoscopic imaging; Narrow band imaging; Confocal laser endomicroscopy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The majority of esophageal adenocarcinomas (EAC) arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion that can lead to dysplasia and cancer. Because of the increased risk of EAC, GI society guidelines recommend endoscopic surveillance of patients with BE. The emphasis on early detection of dysplasia in BE through surveillance endoscopy has led to the development of advanced endoscopic imaging technologies. These techniques have the potential to both improve mucosal visualization and characterization and to detect small abnormalities which are difficult to identify with standard endoscopy. This review summarizes the advanced imaging technologies used in evaluation of BE.

Naveed M, Dunbar KB. Endoscopic imaging of Barrett's esophagus. *World J Gastrointest Endosc* 2016; 8(5): 259-266
Available from: URL: <http://www.wjgnet.com/1948-5190/full/>

INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has been steadily rising over the last three decades, with population-based cohort studies suggestive of a 300%-500% increase during this time^[1]. The majority of esophageal adenocarcinomas arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion which progresses through several stages of dysplasia to cancer. The prevalence and incidence of BE have increased over time, parallel to the increase in frequency of EAC^[2]. There are various estimates (ranging from 0.1%-2.0%) of the annual rate of progression from BE to cancer, with higher rates of progression to cancer reported for patients with low grade dysplasia (0.54% to 1.8% per year) and high grade dysplasia (6.6% per year)^[3-6]. Because of the increased risk of EAC, GI society guidelines recommend that patients with BE undergo endoscopic surveillance^[7-10]. The aim of endoscopic surveillance is to identify areas of dysplasia which can subsequently be treated with endoscopic eradication therapy before progression to cancer. In patients with BE undergoing surveillance, biopsies are collected from areas with visible mucosal abnormalities and at random in four quadrants every 1-2 cm along the BE segment^[11]. This protocol, however, is labor intensive and can still miss neoplasia despite multiple biopsies.

The emphasis on early detection of pre-cancerous lesions has led to the development of advanced imaging technologies to improve care of patients with BE. These techniques have the potential to improve mucosal visualization and detection of abnormal tissue, such as with high-definition white light endoscopy (HD-WLE), while other techniques such as dye-based or electronic chromoendoscopy enhance and adjust the color of the endoscopic images to improve lesion detection and tissue characterization. There are also techniques that allow histological evaluation such as confocal laser endoscopy (CLE). This review summarizes the currently available advanced imaging technologies used in evaluation of BE.

CONVENTIONAL (WHITE LIGHT) ENDOSCOPY

HD-WLE

Over the past decade, high resolution endoscopes using high definition (HD) systems have largely replaced the original low-resolution or standard definition (SD) white light video-endoscopes in most if not all endoscopic units. Capable of producing images with higher magnification and an image resolution of more than 1 million pixels (compared to the 100000-400000 pixels of standard-definition endoscopes), HD-WLE has enhanced

the endoscopists' ability to inspect and visualize subtle mucosal abnormalities^[12,13]. Many research studies using HD-WLE combine it with another advanced endoscopic imaging technique, such as narrow band imaging (NBI) or chromoendoscopy^[14,15]. There are few studies comparing standard endoscopy with HD-WLE, but one study did show improved detection of dysplasia using HD-WLE^[16]. In some studies, addition of additional imaging techniques does not significantly improve detection of BE and neoplasia above HD-WLE alone on a per-patient basis, although additional lesions may be detected and fewer biopsies may be acquired^[17-19]. Though high resolution endoscopes have higher sensitivity for detection of neoplasia than standard endoscopes, targeted biopsies using high resolution endoscopy (HRE) alone may still miss dysplasia that is found using random biopsies^[15].

Magnification endoscopy

Magnifying or zoom endoscopes permit better visualization of mucosal details by enabling the images to be magnified from 1.5 times to 150 times without loss of resolution^[20]. While magnification endoscopy alone allows for visualization of mucosal surface patterns and vessels, this technique has most often been studied in combination with chromoendoscopy. In one study, magnification chromoendoscopy improved the detection of intestinal metaplasia (IM) and HGD in patients BE compared to standard endoscopy^[21]. Magnification endoscopy is not widely used for patients with BE and some studies have shown a high level of inter-observer variability in identifying dysplastic lesions^[22].

ENHANCING COLOR DURING ENDOSCOPY

Chromoendoscopy

Chromoendoscopy involves endoscopic evaluation of gastrointestinal mucosa following the topical application of dyes or contrast agents. The goal of chromoendoscopy is to improve the detection and characterization of abnormalities and facilitate targeted biopsy sampling of suspicious areas. While it can be used with standard endoscopy, chromoendoscopy is most often performed with another advanced imaging modality, such as HD-WLE, magnification endoscopy, or confocal endomicroscopy. There are several types of chromoendoscopy agents, some of which are absorbed by cells, while others highlight the mucosal surface. Absorptive stains, such as methylene blue (MB) and Lugol's iodine, are absorbed across cell membranes while contrast agents such as indigo carmine are not absorbed by the mucosa but highlight the surface topography and mucosal irregularities.

Methylene blue has been used in several studies of patients undergoing chromoendoscopy for evaluation of BE and BE-associated neoplasia. Several studies suggested that MB could discern areas of IM

and dysplasia with high accuracy and with fewer biopsies compared to traditional surveillance techniques^[23-26]. However, other studies have found that chromoendoscopy was not better than conventional four quadrant random biopsies for detection of BE and neoplasia^[27,28]. Further limiting the widespread use of methylene blue chromoendoscopy is the potential risk of DNA damage and carcinogenesis^[29].

Indigo carmine has been used in conjunction with magnification endoscopy to identify the mucosal pit patterns within segments of BE^[21,30]. The presence of villiform pit patterns and irregular mucosal patterns have been shown to correlate with presence of IM and dysplasia^[30].

Acetic acid chromoendoscopy has been used in several recent studies for evaluation of patients with BE. Targeted biopsies following staining with acetic acid has been associated with increased yield for detecting BE as well as dysplasia and early cancer within an area of BE^[31]. One retrospective cohort study evaluated the yield for neoplasia in patients with BE, comparing acetic acid chromoendoscopy and a standard random biopsy protocol. Acetic acid chromoendoscopy detected more neoplasia than conventional protocol-guided mapping biopsies and required significantly fewer biopsies per neoplasia detected^[32]. Another randomized crossover study of acetic acid magnification endoscopy found a higher yield for detection of BE (78%) compared to standard endoscopy with biopsy (57%)^[33].

In comparison to other endoscopic imaging modalities, chromoendoscopy is relatively inexpensive, requiring only a spray catheter and contrast agent, many of which are readily available. On the other hand, chromoendoscopy can be cumbersome requiring a significant increase in endoscopy time and image interpretation is operator dependent, with high inter-observer variability reported in some studies^[22]. These factors and the mixed results of research studies have limited the widespread use of chromoendoscopy in patients with BE.

Electronic chromoendoscopy: Narrow band imaging

First described in 2004 by Gono *et al*^[34], NBI enhances the resolution of the mucosal surface and is the most-investigated image-enhanced endoscopy technique^[34,35]. NBI restricts the wavelengths of light used for endoscopic imaging. Shorter wavelength blue light (440-460 nm) highlights the superficial capillary network, while longer wavelength green light (540 nm) highlights the sub-epithelial vessels, allowing identification of subtle mucosal abnormalities. Furthermore, as blue light is absorbed by hemoglobin, the alterations in vascular patterns associated with neoplasia may be detected.

NBI has shown promise in the detection of BE-associated dysplasia^[36,37]. In a recent meta-analysis of eight studies including 446 patients and 2194 lesions, NBI demonstrated a pooled sensitivity and specificity of 95% and 65%, respectively, for the detection of

BE. The sensitivity and specificity of NBI in detecting HGD was 96% and 94%^[38]. Additional studies have demonstrated NBI's superiority in identifying higher grades of dysplasia in comparison to WLE using significantly fewer biopsies per patient^[14,17,37]. However, not all studies have shown an improvement in detection of neoplasia using NBI. Kara *et al*^[15] found no difference in the detection of HGD and intra-mucosal cancer (IMC) in a tandem study comparing HD-WLE and NBI, although NBI did detect additional lesions in some patients who had neoplasia identified by HD-WLE.

Several studies have focused on the specific mucosal patterns, or pit patterns, associated with BE and BE-associated neoplasia. Hamamoto *et al*^[39] described the use of NBI and a pit pattern classification system in BE and reported superior results when magnifying endoscopy was combined with NBI. Several studies of NBI combined with magnification endoscopy have identified irregular microvascular and microstructural patterns with a high sensitivity, specificity and positive predictive value for identification of HGD and cancer^[36,37,40]. Singh *et al*^[41] demonstrated that presence of a villous or ridged with regular microvasculature was suggestive of IM, while a distorted pit pattern and irregular microvasculature was highly suggestive of dysplasia. A meta-analysis of the various NBI pit pattern classification schemes for BE found a high sensitivity (96%) and specificity (94%) for detection of BE neoplasia when irregular pit patterns and/or microvasculature were identified using NBI with magnification^[38].

The advantages of NBI include the ability to study both mucosal and vascular patterns, the ease of use, and integration into standard endoscopic equipment. Limiting the widespread implementation of NBI-targeted biopsies has been the lack of a universal classification system for the mucosal and vascular patterns observed and some studies have shown only moderate interobserver agreement with interpretation of NBI images^[40,42].

Electronic chromoendoscopy: Flexible intelligent chromoendoscopy and i-scan

Similar to the principle behind NBI, Flexible Intelligent Chromoendoscopy (FICE) and i-scan are electronic chromoendoscopy techniques that manipulate the red, green, and blue components of light to create an image that enhances the superficial mucosal and vascular structures. FICE has been used in several studies, including one that showed FICE was able to clearly demarcate the junction between Barrett's mucosa and gastric mucosa^[43]. In one study comparing FICE and acetic acid chromoendoscopy, FICE was found to have comparable sensitivity to acetic acid chromoendoscopy for detection of BE neoplasia^[44]. I-scan has also been used in patient with BE, most recently in a randomized trial comparing the efficacy of endoscopy with 4-quadrant random biopsies and targeted biopsies using i-scan or acetic acid chromoendoscopy^[45]. Use of i-scan or acetic acid-guided biopsies produced a significantly

higher diagnostic yield for IM compared to endoscopy with random biopsies. Acetic acid and i-scan showed comparable results for diagnosis of BE.

Autofluorescence imaging

Endogenous tissue fluorophores are biological substances in mucosa that emit fluorescent light when exposed to a light of a shorter wavelength. Autofluorescence imaging (AFI) is based on the principle that different tissue types differ in their fluorescence emission, with normal mucosa appearing green under fluorescence excitation, while dysplasia and neoplasia appears magenta or purple^[46]. Differences in fluorescence emission can be examined using a fluorescence-detecting endoscope and these differences in fluorescence can be used for lesion detection and characterization.

AFI is a sensitive but poorly specific tool for the detection HGD and early cancer in BE^[47-49]. Studies comparing AFI to white light endoscopy (WLE) found that AFI increased the detection of HGD and IMC compared with WLE, but was associated with a high false positive rate^[49]. Subsequent studies have attempted to reduce this false positive rate by combining AFI with NBI, with improvement in one study of patients with BE and suspected neoplasia from false positive rate of 40% to 10% using NBI^[48]. The combination of high resolution WLE, AFI and NBI is known as endoscopic trimodal imaging (ETMI), and is not currently available in the United States. An international multicenter study by Curvers *et al*^[50] compared ETMI with standard video endoscopy and demonstrated that addition of AFI to HRE increased detection rate of HGD and IMC compared to WLE alone (90% vs 53%), but did so at the expense of a high false-positive rate of 81%, which was reduced to 26% with the addition of NBI. Two subsequent large randomized studies from the same group comparing ETMI and WLE failed to show superiority of ETMI over endoscopy with a 4 quadrant random biopsy protocol^[19,51]. Furthermore, in these studies random four quadrant biopsies with WLE identified more areas of high grade dysplasia (HGD) and EAC than targeted biopsies after ETMI inspection. The addition of NBI to AFI and HRE reduced the false positive rate in one of the studies, although 17% of dysplastic lesions were re-classified as being normal^[51]. While AFI may be useful as an adjunctive technique to WLE, due to its decreased sensitivity and high false positive rate, AFI as a solo method of detection is not suitable to replace the standard BE surveillance biopsy protocol.

MICROSCOPIC ENDOSCOPY

Several advanced endoscopic imaging techniques are available for *in vivo* histological evaluation of the esophageal mucosa, and are used in conjunction with WLE and other advanced endoscopic imaging techniques to identify suspicious lesions that require

further evaluation.

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) magnifies the mucosa up to 1000-fold and up to 250 μ m below the mucosal surface allowing for real-time histological assessment of the GI mucosa during endoscopy. When evaluating patients with BE, this level of magnification allows for visualization of the specialized IM and goblet cells. Two endomicroscopy platforms have been used for most of the CLE studies of BE, an endoscope based confocal system (eCLE) in which a confocal microscope is integrated into the tip of a standard endoscope and a probe-based system (pCLE), in which a probe is passed through the accessory channel of the endoscope. Both systems use blue laser light and require administration of either topical or intravenous fluorescent contrast agents.

The initial study of eCLE found that BE and BE-associated neoplasia could be identified with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively^[52]. A subsequent prospective randomized controlled crossover trial of eCLE found that CLE with targeted biopsies almost doubled the diagnostic yield for neoplasia compared to a standard biopsy protocol for BE (33% vs 17%), with a significant reduction in the number of mucosal biopsies needed for diagnosis. Two thirds of patients in this study undergoing routine surveillance of BE were able to avoid any mucosal biopsies during their CLE procedures^[53]. In a subsequent multicenter randomized, controlled trial of eCLE, 192 patients with BE were randomized to either HD-WLE with random biopsies or HD-WLE and CLE with targeted biopsies. In this study, CLE with targeted biopsies outperformed HD-WLE with standard biopsies for detection of neoplasia (22% vs 6%) and impacted clinical decision-making (such as the decision to perform endoscopic mucosal resection) in almost 1/3 of patients^[54]. Multiple studies have evaluated use of pCLE in patients with BE with promising results. Bertani *et al*^[55] found the use of pCLE in addition to WLE enhanced the detection of dysplasia compared with WLE alone (28% vs 10%). A multi-center study of 101 patients found the addition of pCLE to HD-WLE improved the diagnostic yield and detection of neoplasia^[56]. This study examined the pCLE for *in vivo* prediction of HGD and EAC and found that the addition of pCLE to WLE and NBI increased sensitivity for neoplasia from 45% to 76% and allowed for a reduction in number of biopsies needed for diagnosis^[56]. The advantages of CLE, such as the potential for real-time histological diagnosis during an endoscopic procedure, may be offset by the increased procedure length, equipment costs, and the training necessary to interpret the images.

Endocytoscopy

Endocytoscopy allows for real time microscopic imaging of the mucosa using white light and special lenses for

magnification. Images are acquired on the surface of the mucosa after application of a contrast agent, most commonly methylene blue. Surface magnification during endocytoscopy is up to 1400-fold, depending on the endocytoscopy system used and has been used in several studies of squamous esophageal cancer and squamous dysplasia^[57]. Studies have reported variable accuracy of endocytoscopy for the detection of neoplasia in a backdrop of BE and the technique has been limited in BE patients by inadequate image quality. In one study evaluating patients undergoing surveillance for BE, image quality was found to be inadequate in 49% of sites imaged at 450-fold magnification and inadequate in 22% of images using 1125-fold magnification^[58]. Another study has examined *ex vivo* EMR specimens with endocytoscopy to develop a classification system which showed good accuracy and interobserver agreement. At this time, endocytoscopy is not widely used in management of patients with BE^[59].

OTHER LIGHT-BASED TECHNIQUES

Optical coherence tomography

Optical coherence tomography (OCT) is similar to ultrasound in acquiring tissue images but uses light waves rather than acoustic waves to generate cross-sectional images of epithelial and sub-epithelial tissues based on differences in optical scattering of the tissue structures. OCT does not require tissue contact and images are obtained *via* a catheter introduced through a standard endoscope. One prospective clinical study assessed the presence of dysplasia in BE in 55 patients using 177 biopsy correlated images and found that OCT could detect HGD and EAC with 83% sensitivity and 75% specificity^[60]. Several other studies have evaluated a variety of OCT systems and found variable sensitivity, specificity, and accuracy for detection of dysplasia in Barrett's esophagus^[61-63].

Optical frequency domain imaging and volumetric laser endomicroscopy

Optical frequency domain imaging (OFDI), also known as volumetric laser endomicroscopy (VLE), allows for high resolution, high-speed acquisition of larger areas of the luminal surface than standard OCT. Preliminary studies with both OFDI/VLE have suggested that differences between normal squamous mucosa, BE, and BE neoplasia can be identified using this technique^[64,65]. Recent studies of VLE have focused on interobserver agreement with image interpretation and correlation of VLE images with histology findings^[66,67].

Spectroscopy

Spectroscopy uses variation in scattered light across a full spectrum to obtain information about nuclear size, crowding, vascularity and tissue structure and organization. Several types of spectroscopy have been used to study BE, including light-scattering, reflectance and Raman spectroscopy. Light-scattering spectroscopy

provides information about cell nuclei characteristics and has demonstrated the ability to detect dysplasia in patients with BE^[68,69]. Reflectance spectroscopy measures the color and intensity of reflected light after tissue illumination to help differentiate normal from neoplastic tissue and has also been used in studies of BE^[70,71]. Raman spectroscopy detects scattered light that has been changed in wavelength (termed inelastic scattering) and results in characteristic peaks and bands that are correspond with normal vs abnormal mucosa. One study reported an accuracy of 96% when using Raman spectroscopy for detecting EAC^[72]. In a large study of 373 BE patients, Raman spectroscopy was used for real-time detection of BE and neoplasia with good success^[73]. At this time, spectroscopy remains an interesting research technique for patients with BE.

CONCLUSION

In the last decade there have been many advances in the field of endoscopic imaging for the detection of early dysplastic changes and neoplasia in patients with BE. While many of these modalities have demonstrated high sensitivity and specificity in detecting dysplasia and EAC, some limitations to widespread adoption exist. The need for training in image interpretation, inter-observer variability in image interpretation, expensive equipment, and potential increases in procedure length have limited use of these technologies. Technological improvements could make several of these novel endoscopic imaging techniques easier to use, and in time endoscopists may become more comfortable with advanced endoscopic imaging options. In the future, advanced endoscopic imaging techniques could improve care for patients with BE and BE-associated neoplasia by providing more accurate detection of dysplasia and providing real-time histology.

REFERENCES

- 1 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97**: 142-146 [PMID: 15657344 DOI: 10.1093/jnci/dji024]
- 2 Spechler SJ, Souza RF. Barrett's esophagus. *N Engl J Med* 2014; **371**: 836-845 [PMID: 25162890 DOI: 10.1056/NEJMr1314704]
- 3 Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011; **365**: 1375-1383 [PMID: 21995385 DOI: 10.1056/NEJMoa1103042]
- 4 Sharma P, Falk GW, Weston AP, Reker D, Johnston M, Sampliner RE. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. *Clin Gastroenterol Hepatol* 2006; **4**: 566-572 [PMID: 16630761 DOI: 10.1016/j.cgh.2006.03.001]
- 5 Singh S, Manickam P, Amin AV, Samala N, Schouten LJ, Iyer PG, Desai TK. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; **79**: 897-909.e4; quiz 983.e1, 983.e3 [PMID: 24556051 DOI: 10.1016/j.gie.2014.01.009]
- 6 Wani S, Falk GW, Post J, Yerian L, Hall M, Wang A, Gupta N, Gaddam S, Singh M, Singh V, Chuang KY, Boolchand V, Gavini H, Kuczyński J, Sud P, Bansal A, Rastogi A, Mathur SC, Young

- P, Cash B, Goldblum J, Lieberman DA, Sampliner RE, Sharma P. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology* 2011; **141**: 1179-1186, 1186. e1 [PMID: 21723218 DOI: 10.1053/j.gastro.2011.06.055]
- 7 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: 1084-1091 [PMID: 21376940 DOI: 10.1053/j.gastro.2011.01.030]
- 8 **Fitzgerald RC**, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, O'Donovan M, Bird-Lieberman E, Bhandari P, Jankowski JA, Attwood S, Parsons SL, Loft D, Lagergren J, Moayyedi P, Lyrazopoulos G, de Caestecker J. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014; **63**: 7-42 [PMID: 24165758 DOI: 10.1136/gutjnl-2013-305372]
- 9 **Wang KK**, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008; **103**: 788-797 [PMID: 18341497 DOI: 10.1111/j.1572-0241.2008.01835.x]
- 10 **Evans JA**, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi KV, Decker GA, Fanelli RD, Fisher DA, Foley KQ, Hwang JH, Jain R, Jue TL, Khan KM, Lightdale J, Malpas PM, Maple JT, Pasha SF, Saltzman JR, Sharaf RN, Shergill A, Dornitz JA, Cash BD. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012; **76**: 1087-1094 [PMID: 23164510 DOI: 10.1016/j.gie.2012.08.004]
- 11 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: e18-52; quiz e13 [PMID: 21376939 DOI: 10.1053/j.gastro.2011.01.031]
- 12 **Kwon RS**, Adler DG, Chand B, Conway JD, Diehl DL, Kantsevoy SV, Mamula P, Rodriguez SA, Shah RJ, Wong Kee Song LM, Tierney WM. High-resolution and high-magnification endoscopes. *Gastrointest Endosc* 2009; **69**: 399-407 [PMID: 19231483 DOI: 10.1016/j.gie.2008.12.049]
- 13 **Mannath J**, Ragunath K. Era of Barrett's surveillance: does equipment matter? *World J Gastroenterol* 2010; **16**: 4640-4645 [PMID: 20872963 DOI: 10.3748/wjg.v16.i37.4640]
- 14 **Wolfsen HC**, Crook JE, Krishna M, Achem SR, Devault KR, Bouras EP, Loeb DS, Stark ME, Woodward TA, Hemminger LL, Cayer FK, Wallace MB. Prospective, controlled tandem endoscopy study of narrow band imaging for dysplasia detection in Barrett's Esophagus. *Gastroenterology* 2008; **135**: 24-31 [PMID: 18442484 DOI: 10.1053/j.gastro.2008.03.019]
- 15 **Kara MA**, Peters FP, Rosmolen WD, Krishnadath KK, ten Kate FJ, Fockens P, Bergman JJ. High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in Barrett's esophagus: a prospective randomized crossover study. *Endoscopy* 2005; **37**: 929-936 [PMID: 16189764 DOI: 10.1055/s-2005-870433]
- 16 **Sami SS**, Subramanian V, Butt WM, Bejkar G, Coleman J, Mannath J, Ragunath K. High definition versus standard definition white light endoscopy for detecting dysplasia in patients with Barrett's esophagus. *Dis Esophagus* 2015; **28**: 742-749 [PMID: 25209721 DOI: 10.1111/dote.12283]
- 17 **Sharma P**, Hawes RH, Bansal A, Gupta N, Curvers W, Rastogi A, Singh M, Hall M, Mathur SC, Wani SB, Hoffman B, Gaddam S, Fockens P, Bergman JJ. Standard endoscopy with random biopsies versus narrow band imaging targeted biopsies in Barrett's oesophagus: a prospective, international, randomised controlled trial. *Gut* 2013; **62**: 15-21 [PMID: 22315471 DOI: 10.1136/gutjnl-2011-300962]
- 18 **Curvers W**, Baak L, Kiesslich R, Van Oijen A, Rabenstein T, Ragunath K, Rey JF, Scholten P, Seitz U, Ten Kate F, Fockens P, Bergman J. Chromoendoscopy and narrow-band imaging compared with high-resolution magnification endoscopy in Barrett's esophagus. *Gastroenterology* 2008; **134**: 670-679 [PMID: 18242603 DOI: 10.1053/j.gastro.2008.01.003]
- 19 **Curvers WL**, van Vilsteren FG, Baak LC, Böhmer C, Mallant-Hent RC, Naber AH, van Oijen A, Ponsioen CY, Scholten P, Schenk E, Schoon E, Seldenrijk CA, Meijer GA, ten Kate FJ, Bergman JJ. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicenter, randomized, crossover study in general practice. *Gastrointest Endosc* 2011; **73**: 195-203 [PMID: 21168835 DOI: 10.1016/j.gie.2010.10.014]
- 20 **Kiesslich R**, Jung M. Magnification endoscopy: does it improve mucosal surface analysis for the diagnosis of gastrointestinal neoplasias? *Endoscopy* 2002; **34**: 819-822 [PMID: 12244505 DOI: 10.1055/s-2002-34259]
- 21 **Sharma P**, Weston AP, Topalovski M, Cherian R, Bhattacharyya A, Sampliner RE. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. *Gut* 2003; **52**: 24-27 [PMID: 12477754 DOI: 10.1136/gut.52.1.24]
- 22 **Meining A**, Rösch T, Kiesslich R, Muders M, Sax F, Heldwein W. Inter- and intra-observer variability of magnification chromoendoscopy for detecting specialized intestinal metaplasia at the gastroesophageal junction. *Endoscopy* 2004; **36**: 160-164 [PMID: 14765313 DOI: 10.1055/s-2004-814183]
- 23 **Kouklakis GS**, Kountouras J, Dokas SM, Molyvas EJ, Vourvoulakis GP, Minopoulos GI. Methylene blue chromoendoscopy for the detection of Barrett's esophagus in a Greek cohort. *Endoscopy* 2003; **35**: 383-387 [PMID: 12701007 DOI: 10.1055/s-2003-38768]
- 24 **Kiesslich R**, Hahn M, Herrmann G, Jung M. Screening for specialized columnar epithelium with methylene blue: chromoendoscopy in patients with Barrett's esophagus and a normal control group. *Gastrointest Endosc* 2001; **53**: 47-52 [PMID: 11154488 DOI: 10.1067/mge.2001.111041]
- 25 **Sharma P**, Topalovski M, Mayo MS, Weston AP. Methylene blue chromoendoscopy for detection of short-segment Barrett's esophagus. *Gastrointest Endosc* 2001; **54**: 289-293 [PMID: 11522967 DOI: 10.1067/mge.2001.115728]
- 26 **Canto MI**, Setrakian S, Willis J, Chak A, Petras R, Powe NR, Sivak MV. Methylene blue-directed biopsies improve detection of intestinal metaplasia and dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2000; **51**: 560-568 [PMID: 10805842 DOI: 10.1067/mge.2000.104655]
- 27 **Wo JM**, Ray MB, Mayfield-Stokes S, Al-Sabbagh G, Gebrail F, Slone SP, Wilson MA. Comparison of methylene blue-directed biopsies and conventional biopsies in the detection of intestinal metaplasia and dysplasia in Barrett's esophagus: a preliminary study. *Gastrointest Endosc* 2001; **54**: 294-301 [PMID: 11522968 DOI: 10.1067/mge.2001.115732]
- 28 **Ngamruengphong S**, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 2009; **69**: 1021-1028 [PMID: 19215918 DOI: 10.1016/j.gie.2008.06.056]
- 29 **Oliver JR**, Wild CP, Sahay P, Dexter S, Hardie LJ. Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. *Lancet* 2003; **362**: 373-374 [PMID: 12907012 DOI: 10.1016/S0140-6736(03)14026-3]
- 30 **Stevens PD**, Lightdale CJ, Green PH, Siegel LM, Garcia-Carrasquillo RJ, Rotterdam H. Combined magnification endoscopy with chromoendoscopy for the evaluation of Barrett's esophagus. *Gastrointest Endosc* 1994; **40**: 747-749 [PMID: 7859976]
- 31 **Fortun PJ**, Anagnostopoulos GK, Kaye P, James M, Foley S, Samuel S, Shonde A, Badreldin R, Campbell E, Hawkey CJ, Ragunath K. Acetic acid-enhanced magnification endoscopy in the diagnosis of specialized intestinal metaplasia, dysplasia and early cancer in Barrett's oesophagus. *Aliment Pharmacol Ther* 2006; **23**: 735-742 [PMID: 16556175 DOI: 10.1111/j.1365-2036.2006.02823.x]
- 32 **Tholloor S**, Bhattacharyya R, Tsagkournis O, Longcroft-Wheaton G, Bhandari P. Acetic acid chromoendoscopy in Barrett's esophagus surveillance is superior to the standardized random biopsy protocol: results from a large cohort study (with video). *Gastrointest Endosc* 2014; **80**: 417-424 [PMID: 24713305 DOI: 10.1016/j.gie.2014.01.041]
- 33 **Hoffman A**, Kiesslich R, Bender A, Neurath MF, Nafe B, Herrmann G, Jung M. Acetic acid-guided biopsies after magnifying endoscopy compared with random biopsies in the detection of

- Barrett's esophagus: a prospective randomized trial with crossover design. *Gastrointest Endosc* 2006; **64**: 1-8 [PMID: 16813794 DOI: 10.1016/j.gie.2005.09.031]
- 34 **Gono K**, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; **9**: 568-577 [PMID: 15189095 DOI: 10.1117/1.1695563]
 - 35 **Goda K**, Kato T, Tajiri H. Endoscopic diagnosis of early Barrett's neoplasia: perspectives for advanced endoscopic technology. *Dig Endosc* 2014; **26**: 311-321 [PMID: 24754238 DOI: 10.1111/den.12294]
 - 36 **Anagnostopoulos GK**, Yao K, Kaye P, Hawkey CJ, Ragunath K. Novel endoscopic observation in Barrett's oesophagus using high resolution magnification endoscopy and narrow band imaging. *Aliment Pharmacol Ther* 2007; **26**: 501-507 [PMID: 17635385 DOI: 10.1111/j.1365-2036.2007.03374.x]
 - 37 **Sharma P**, Bansal A, Mathur S, Wani S, Cherian R, McGregor D, Higbee A, Hall S, Weston A. The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. *Gastrointest Endosc* 2006; **64**: 167-175 [PMID: 16860063 DOI: 10.1016/j.gie.2005.10.044]
 - 38 **Mannath J**, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Endoscopy* 2010; **42**: 351-359 [PMID: 20200809 DOI: 10.1055/s-0029-1243949]
 - 39 **Hamamoto Y**, Endo T, Noshio K, Arimura Y, Sato M, Imai K. Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. *J Gastroenterol* 2004; **39**: 14-20 [PMID: 14767729 DOI: 10.1007/s00535-003-1239-z]
 - 40 **Curvers WL**, Bohmer CJ, Mallant-Hent RC, Naber AH, Ponsioen CI, Ragunath K, Singh R, Wallace MB, Wolfsen HC, Song LM, Lindeboom R, Fockens P, Bergman JJ. Mucosal morphology in Barrett's esophagus: interobserver agreement and role of narrow band imaging. *Endoscopy* 2008; **40**: 799-805 [PMID: 18828075 DOI: 10.1055/s-2008-1077596]
 - 41 **Singh R**, Anagnostopoulos GK, Yao K, Karageorgiou H, Fortun PJ, Shonde A, Garsed K, Kaye PV, Hawkey CJ, Ragunath K. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. *Endoscopy* 2008; **40**: 457-463 [PMID: 18459090 DOI: 10.1055/s-2007-995741]
 - 42 **Alvarez Herrero L**, Curvers WL, Bansal A, Wani S, Kara M, Schenk E, Schoon EJ, Lynch CR, Rastogi A, Pondugula K, Weusten B, Sharma P, Bergman JJ. Zooming in on Barrett oesophagus using narrow-band imaging: an international observer agreement study. *Eur J Gastroenterol Hepatol* 2009; **21**: 1068-1075 [PMID: 19318970 DOI: 10.1097/MEG.0b013e3283271e87]
 - 43 **Osawa H**, Yamamoto H, Yamada N, Yoshizawa M, Sunada K, Kita H, Ajibe H, Satoh K, Sugano K. Diagnosis of endoscopic Barrett's esophagus by transnasal flexible spectral imaging color enhancement. *J Gastroenterol* 2009; **44**: 1125-1132 [PMID: 19714289 DOI: 10.1007/s00535-009-0121-z]
 - 44 **Pohl J**, May A, Rabenstein T, Pech O, Nguyen-Tat M, Fissler-Eckhoff A, Ell C. Comparison of computed virtual chromoendoscopy and conventional chromoendoscopy with acetic acid for detection of neoplasia in Barrett's esophagus. *Endoscopy* 2007; **39**: 594-598 [PMID: 17611913 DOI: 10.1055/s-2007-966649]
 - 45 **Hoffman A**, Korczynski O, Tresch A, Hansen T, Rahman F, Goetz M, Murthy S, Galle PR, Kiesslich R. Acetic acid compared with i-scan imaging for detecting Barrett's esophagus: a randomized, comparative trial. *Gastrointest Endosc* 2014; **79**: 46-54 [PMID: 23953402 DOI: 10.1016/j.gie.2013.07.013]
 - 46 **Kara MA**, Smits ME, Rosmolen WD, Bultje AC, Ten Kate FJ, Fockens P, Tytgat GN, Bergman JJ. A randomized crossover study comparing light-induced fluorescence endoscopy with standard videoendoscopy for the detection of early neoplasia in Barrett's esophagus. *Gastrointest Endosc* 2005; **61**: 671-678 [PMID: 15855970 DOI: 10.1016/S0016-5107(04)02777-4]
 - 47 **Niepsuj K**, Niepsuj G, Cebula W, Zieleznik W, Adamek M, Sielańczyk A, Adamczyk J, Kurek J, Sieroń A. Autofluorescence endoscopy for detection of high-grade dysplasia in short-segment Barrett's esophagus. *Gastrointest Endosc* 2003; **58**: 715-719 [PMID: 14595307 DOI: 10.1016/S0016-5107(03)02018-2]
 - 48 **Kara MA**, Peters FP, Fockens P, ten Kate FJ, Bergman JJ. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. *Gastrointest Endosc* 2006; **64**: 176-185 [PMID: 16860064 DOI: 10.1016/j.gie.2005.11.050]
 - 49 **Kara MA**, Peters FP, Ten Kate FJ, Van Deventer SJ, Fockens P, Bergman JJ. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. *Gastrointest Endosc* 2005; **61**: 679-685 [PMID: 15855971 DOI: 10.1016/S0016-5107(04)02577-5]
 - 50 **Curvers WL**, Singh R, Song LM, Wolfsen HC, Ragunath K, Wang K, Wallace MB, Fockens P, Bergman JJ. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. *Gut* 2008; **57**: 167-172 [PMID: 17965067 DOI: 10.1136/gut.2007.134213]
 - 51 **Curvers WL**, Alvarez Herrero L, Wallace MB, Wong Kee Song LM, Ragunath K, Wolfsen HC, Prasad GA, Wang KK, Subramanian V, Weusten BL, Ten Kate FJ, Bergman JJ. Endoscopic tri-modal imaging is more effective than standard endoscopy in identifying early-stage neoplasia in Barrett's esophagus. *Gastroenterology* 2010; **139**: 1106-1114 [PMID: 20600033 DOI: 10.1053/j.gastro.2010.06.045]
 - 52 **Kiesslich R**, Gossner L, Goetz M, Dahlmann A, Vieth M, Stolte M, Hoffman A, Jung M, Nafe B, Galle PR, Neurath MF. In vivo histology of Barrett's esophagus and associated neoplasia by confocal laser endomicroscopy. *Clin Gastroenterol Hepatol* 2006; **4**: 979-987 [PMID: 16843068 DOI: 10.1016/j.cgh.2006.05.010]
 - 53 **Dunbar KB**, Okolo P, Montgomery E, Canto MI. Confocal laser endomicroscopy in Barrett's esophagus and endoscopically inapparent Barrett's neoplasia: a prospective, randomized, double-blind, controlled, crossover trial. *Gastrointest Endosc* 2009; **70**: 645-654 [PMID: 19559419 DOI: 10.1016/j.gie.2009.02.009]
 - 54 **Canto MI**, Anandasabapathy S, Brugge W, Falk GW, Dunbar KB, Zhang Z, Woods K, Almario JA, Schell U, Goldblum J, Maitra A, Montgomery E, Kiesslich R. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). *Gastrointest Endosc* 2014; **79**: 211-221 [PMID: 24219822 DOI: 10.1016/j.gie.2013.09.020]
 - 55 **Bertani H**, Frazzoni M, Dabizzi E, Pigò F, Losi L, Manno M, Manta R, Bassotti G, Conigliaro R. Improved detection of incident dysplasia by probe-based confocal laser endomicroscopy in a Barrett's esophagus surveillance program. *Dig Dis Sci* 2013; **58**: 188-193 [PMID: 22875309 DOI: 10.1007/s10620-012-2332-z]
 - 56 **Sharma P**, Meining AR, Coron E, Lightdale CJ, Wolfsen HC, Bansal A, Bajbouj M, Galmiche JP, Abrams JA, Rastogi A, Gupta N, Michalek JE, Lauwers GY, Wallace MB. Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc* 2011; **74**: 465-472 [PMID: 21741642 DOI: 10.1016/j.gie.2011.04.004]
 - 57 **Kwon RS**, Wong Kee Song LM, Adler DG, Conway JD, Diehl DL, Farraye FA, Kantsevoy SV, Kaul V, Kethu SR, Mamula P, Pedrosa MC, Rodriguez SA, Tierney WM. Endocytoscopy. *Gastrointest Endosc* 2009; **70**: 610-613 [PMID: 19788978 DOI: 10.1016/j.gie.2009.06.030]
 - 58 **Pohl H**, Koch M, Khalifa A, Papanikolaou IS, Scheiner K, Wiedenmann B, Rösch T. Evaluation of endocytoscopy in the surveillance of patients with Barrett's esophagus. *Endoscopy* 2007; **39**: 492-496 [PMID: 17554642 DOI: 10.1055/s-2007-966340]
 - 59 **Tomizawa Y**, Iyer PG, Wongkeesong LM, Buttar NS, Lutzke LS, Wu TT, Wang KK. Assessment of the diagnostic performance and interobserver variability of endocytoscopy in Barrett's esophagus: a pilot ex-vivo study. *World J Gastroenterol* 2013; **19**: 8652-8658 [PMID: 24379583 DOI: 10.3748/wjg.v19.i46.8652]

- 60 **Evans JA**, Poneros JM, Bouma BE, Bressner J, Halpern EF, Shishkov M, Lauwers GY, Mino-Kenudson M, Nishioka NS, Tearney GJ. Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2006; **4**: 38-43 [PMID: 16431303 DOI: 10.1016/S1542-3565(05)00746-9]
- 61 **Cobb MJ**, Hwang JH, Upton MP, Chen Y, Oelschlager BK, Wood DE, Kimmey MB, Li X. Imaging of subsquamous Barrett's epithelium with ultrahigh-resolution optical coherence tomography: a histologic correlation study. *Gastrointest Endosc* 2010; **71**: 223-230 [PMID: 19846077 DOI: 10.1016/j.gie.2009.07.005]
- 62 **Isenberg G**, Sivak MV, Chak A, Wong RC, Willis JE, Wolf B, Rowland DY, Das A, Rollins A. Accuracy of endoscopic optical coherence tomography in the detection of dysplasia in Barrett's esophagus: a prospective, double-blinded study. *Gastrointest Endosc* 2005; **62**: 825-831 [PMID: 16301020 DOI: 10.1016/j.gie.2005.07.048]
- 63 **Poneros JM**, Brand S, Bouma BE, Tearney GJ, Compton CC, Nishioka NS. Diagnosis of specialized intestinal metaplasia by optical coherence tomography. *Gastroenterology* 2001; **120**: 7-12 [PMID: 11208708 DOI: 10.1053/gast.2001.20911]
- 64 **Vakoc BJ**, Shishko M, Yun SH, Oh WY, Suter MJ, Desjardins AE, Evans JA, Nishioka NS, Tearney GJ, Bouma BE. Comprehensive esophageal microscopy by using optical frequency-domain imaging (with video). *Gastrointest Endosc* 2007; **65**: 898-905 [PMID: 17383652 DOI: 10.1016/j.gie.2006.08.009]
- 65 **Suter MJ**, Vakoc BJ, Yachinski PS, Shishkov M, Lauwers GY, Mino-Kenudson M, Bouma BE, Nishioka NS, Tearney GJ. Comprehensive microscopy of the esophagus in human patients with optical frequency domain imaging. *Gastrointest Endosc* 2008; **68**: 745-753 [PMID: 18926183 DOI: 10.1016/j.gie.2008.05.014]
- 66 **Swager A**, Boerwinkel DF, de Bruin DM, Weusten BL, Faber DJ, Meijer SL, van Leeuwen TG, Curvers WL, Bergman JJ. Volumetric laser endomicroscopy in Barrett's esophagus: a feasibility study on histological correlation. *Dis Esophagus* 2015 May 8; Epub ahead of print [PMID: 25951873 DOI: 10.1111/dote.12371]
- 67 **Sauk J**, Coron E, Kava L, Suter M, Gora M, Gallagher K, Rosenberg M, Ananthakrishnan A, Nishioka N, Lauwers G, Woods K, Brugge W, Forcione D, Bouma BE, Tearney G. Interobserver agreement for the detection of Barrett's esophagus with optical frequency domain imaging. *Dig Dis Sci* 2013; **58**: 2261-2265 [PMID: 23508980 DOI: 10.1007/s10620-013-2625-x]
- 68 **Backman V**, Wallace MB, Perelman LT, Arendt JT, Gurjar R, Müller MG, Zhang Q, Zonios G, Kline E, McGilligan JA, Shapshay S, Valdez T, Badizadegan K, Crawford JM, Fitzmaurice M, Kabani S, Levin HS, Seiler M, Dasari RR, Itzkan I, Van Dam J, Feld MS. Detection of preinvasive cancer cells. *Nature* 2000; **406**: 35-36 [PMID: 10894529 DOI: 10.1038/35017638]
- 69 **Wallace MB**, Perelman LT, Backman V, Crawford JM, Fitzmaurice M, Seiler M, Badizadegan K, Shields SJ, Itzkan I, Dasari RR, Van Dam J, Feld MS. Endoscopic detection of dysplasia in patients with Barrett's esophagus using light-scattering spectroscopy. *Gastroenterology* 2000; **119**: 677-682 [PMID: 10982761 DOI: 10.1053/gast.2000.16511]
- 70 **Georgakoudi I**, Van Dam J. Characterization of dysplastic tissue morphology and biochemistry in Barrett's esophagus using diffuse reflectance and light scattering spectroscopy. *Gastrointest Endosc Clin N Am* 2003; **13**: 297-308 [PMID: 12916661 DOI: 10.1016/S1052-5157(03)00008-4]
- 71 **Badizadegan K**, Backman V, Boone CW, Crum CP, Dasari RR, Georgakoudi I, Keefe K, Munger K, Shapshay SM, Sheetse EE, Feld MS. Spectroscopic diagnosis and imaging of invisible pre-cancer. *Faraday Discuss* 2004; **126**: 265-279; discussion 303-311 [PMID: 14992412 DOI: 10.1039/b305410a]
- 72 **Bergholt MS**, Zheng W, Lin K, Ho KY, Teh M, Yeoh KG, So JB, Huang Z. In vivo diagnosis of esophageal cancer using image-guided Raman endoscopy and biomolecular modeling. *Technol Cancer Res Treat* 2011; **10**: 103-112 [PMID: 21381788 DOI: 10.7785/tcrt.2012.500185]
- 73 **Bergholt MS**, Zheng W, Ho KY, Teh M, Yeoh KG, Yan So JB, Shabbir A, Huang Z. Fiberoptic confocal raman spectroscopy for real-time in vivo diagnosis of dysplasia in Barrett's esophagus. *Gastroenterology* 2014; **146**: 27-32 [PMID: 24216327 DOI: 10.1053/j.gastro.2013.11.002]

P- Reviewer: Mirnezami AH S- Editor: Kong JX

L- Editor: A E- Editor: Wu HL



Efforts to increase image quality during endoscopy: The role of pronase

Gwang Ha Kim, Yu Kyung Cho, Jae Myung Cha, Sun-Young Lee, Il-Kwun Chung

Gwang Ha Kim, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan 602-739, South Korea

Yu Kyung Cho, Department of Internal Medicine, the Catholic University of Korea, College of Medicine, Seoul 137-701, South Korea

Jae Myung Cha, Department of Internal Medicine, Kyung Hee University Hospital at Gang Dong, Kyung Hee University School of Medicine, Seoul 134-727, South Korea

Sun-Young Lee, Department of Internal Medicine, Konkuk University School of Medicine, Seoul 143-729, South Korea

Il-Kwun Chung, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan 330-721, South Korea

Author contributions: Kim GH and Chung IK contributed to the review of the literature and initial draft of manuscript; Cho YK, Cha JM and Lee SY contributed to revising and final approval of the manuscript.

Conflict-of-interest statement: All authors declare no conflict-of-interest related to this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Il-Kwun Chung, MD, PhD, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, 23-20 Bongmyung-dong, Dongnam-gu, Cheonan 330-721, South Korea. euschung@schmc.ac.kr
Telephone: +82-41-5703679
Fax: +82-41-5745762

Received: August 22, 2015

Peer-review started: August 26, 2015

First decision: October 30, 2015

Revised: December 1, 2015

Accepted: December 18, 2015

Article in press: December 20, 2015

Published online: March 10, 2016

Abstract

Clear visualization of the gastrointestinal mucosal surface is essential for thorough endoscopy. An unobstructed assessment can reduce the need for additional time-consuming manipulations such as frequent washing and suction, which tend to prolong total procedure time. However, mucus, foam, and bubbles often hinder clear visibility during endoscopy. Premedication with pronase, a compound of mixed proteolytic enzymes, has been studied in order to improve mucosal visibility during endoscopy. Although its effects differ according to the location in the stomach, premedication with pronase 10 to 20 min before endoscopy significantly improves mucosal visibility without affecting the accuracy of *Helicobacter pylori* identification. The effects of pronase as premedication also extend to chromoendoscopy, narrow-band imaging, magnifying endoscopy, and endoscopic ultrasonography. In addition, endoscopic flushing with pronase during endoscopy may improve the quantity and the quality of a biopsy to some degree. Although improved mucosal visibility does not necessarily improve clinical outcomes, premedication with pronase may be helpful for increasing the detection rate of early cancers.

Key words: Endoscopy; Premedication; Pronase

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The present review discusses the role of

pronase in increasing image quality during endoscopy. Premedication with pronase 10 to 20 min before endoscopy significantly improves mucosal visibility without affecting the accuracy of *Helicobacter pylori* identification. The effects of pronase as premedication are also applicable in advanced endoscopic procedures such as narrow-band imaging, magnifying endoscopy, or endoscopic ultrasonography. Although improved mucosal visibility does not necessarily improve clinical outcomes, premedication with pronase may be helpful for increasing the detection rate of early cancers.

Kim GH, Cho YK, Cha JM, Lee SY, Chung IK. Efforts to increase image quality during endoscopy: The role of pronase. *World J Gastrointest Endosc* 2016; 8(5): 267-272 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i5/267.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i5.267>

INTRODUCTION

Esophagogastroduodenoscopy (EGD) is commonly performed to diagnose and treat benign and malignant diseases, especially early gastric cancer in the upper gastrointestinal tract. Clear visualization of the gastrointestinal mucosal surface is essential for thorough EGD, particularly when using advanced endoscopic methods such as narrow-band imaging (NBI) or magnifying endoscopy (ME). Furthermore, clear visualization can decrease the need for additional time-consuming manipulations such as frequent washing and suction, which may prolong the total procedure time. In other words, proper premedication before EGD is important to obtain satisfactory visualization of the gastrointestinal mucosa. However, mucus, foam, and bubbles often hinder clear visibility during EGD^[1]. To overcome these problems, mucolytic and defoaming agents have been applied in EGD.

In most endoscopic centers, simethicone or dimethylpolysiloxane (DMPS) is commonly used to eliminate bubbles and foam during EGD^[1,2]. Simethicone is a mixture of polydimethylsiloxanes that reduces the surface tension of air bubbles and results in the coalescence of small bubbles into larger ones, which may then pass more easily with belching or flatulence^[3]. DMPS, which is similar to simethicone, also has the effect of eliminating foam and bubbles. Several studies have shown that simethicone is a suitable premedication to improve the endoscopic view of EGD^[4,5]. However, despite premedication with these defoaming agents, great deal of mucus can still be encountered during EGD^[6].

Pronase, a compound of mixed proteolytic enzymes, was isolated from the culture filtrate of *Streptomyces griseus* in 1962, and has been used as a base material in the preparation of anti-inflammatory and digestive enzymes^[7]. Because of its mucolytic effects^[8], pronase was used to remove gastric mucus for roentgenographic

examination in 1964^[9]. It has also been applied as a premedication for endoscopy since 1991^[10]. However, the effectiveness of premedication with pronase for improving mucosal visibility during EGD has been the subject of a few clinical trials. Similarly, a limited number of systematic reviews have been performed to address its efficacy in improving mucosal visibility during advanced endoscopy such as NBI or ME as well as conventional endoscopy. Therefore, the aim of this review is to evaluate the role of pronase in increasing imaging quality of various endoscopic examinations based on the published literature.

METHODS TO IDENTIFY STUDIES

Two reviewers (Kim GH and Chung IK) performed a literature search using PubMed and Embase databases. Key words included pronase, premedication, and endoscopy. Relevant review articles were also investigated and additional studies were identified by searching the bibliography of published articles. We focused on studies that described premedication with pronase to increase imaging quality during endoscopy.

THE EFFECTS OF PRONASE ON MUCOSAL VISIBILITY DURING CONVENTIONAL ENDOSCOPY

Table 1 summarizes studies of the effects of pronase as premedication for conventional endoscopy. In most studies, the mucosal visibility score was classified from 1 to 4 (1, no adherent mucus; 2, mild mucus, but not obscuring vision; 3, large amount of mucus obscuring vision; and 4, heavy adherent mucus). All studies showed the superior effects of pronase for improving mucosal visibility in the stomach, but this effect differed according to the location in the stomach. In a recent meta-analysis that included three studies until 2012^[11], significant improvement in mucosal visibility was noted only with pronase use in the antrum and fundus. Mucosal visibility in the greater curvature of the upper body did not improve despite pronase premedication, which suggests that this area needs to be cautiously observed^[12,13]. In our study, even though the grade of mucosal visibility in the upper body and fundus was high compared to other sites, a significant difference in mucosal visibility grade during EGD was observed in the fundus and upper body of the stomach^[7].

Improving visibility can also lead to reduce the need of additional manipulation for washing to clear the surface of the gastrointestinal mucosa, which results in shortening the total EGD procedure time^[8,10,13]. However, pronase only induces mucolysis, but itself does not have a defoaming effect. Therefore, if a defoaming agent is used simultaneously as premedication in addition to pronase, it is expected that mucosal visibility will be improved vs using pronase alone. In fact, many studies have reported a combination of pronase

Table 1 Summary of studies about premedication with pronase for visualization of the mucosa during conventional endoscopy

Ref.	Year	Study design	Premedication group (n)	Mucosal visibility
Fujii <i>et al</i> ^[8]	1998	Prospective	A: DMPS (34) B: DMPS + SB (32)	C > A, B
Kuo <i>et al</i> ^[6]	2002	Prospective	C: DMPS + SB + pronase (34) A: DMPS (34) B: DMPS + water (30) C: Pronase + water (31) D: Pronase + SB + water (32) E: Pronase + SB + DMPS + water (33)	E > A, B, C, D
Chang <i>et al</i> ^[12]	2007	Prospective	A: DMPS (39) B: DMPS + water (35) C: Pronase + SB + DMPS + water (34) D: N-acetylcystein + DMPS + water (39)	C = D > A, B
Bhandari <i>et al</i> ^[30]	2010	Prospective	A: Drinking of simethicone + pronase + water (35) B: Endoscopic flushing of simethicone + water (37) C: Endoscopic flushing of simethicone + pronase + water (40)	A > B, C
Lee <i>et al</i> ^[13]	2012	Prospective	A: DMPS + SB + pronase within 10 min (100) B: DMPS + SB within 10 min (100) C: DMPS + SB + pronase within 20 min (100) D: DMPS + SB within 20 min (100)	A = C > B, D
Woo <i>et al</i> ^[26]	2013	Prospective	A: Pronase + SB + DMPS within 10 min (98) B: Pronase + SB + DMPS between 10-30 min (97) C: Pronase + SB + DMPS at 30 min (99)	A = B > C
Kim <i>et al</i> ^[7]	2015	Prospective	A: Simethicone + SB + pronase (71) B: Simethicone (72)	A > B

DMPS: Dimethylpolysiloxane; SB: Sodium bicarbonate.

with defoaming agents such as DMPS significantly improves visibility during conventional endoscopy or chromoendoscopy^[6,8,10]. Therefore, when pronase is used to improve visibility during EGD, we recommend the concurrent use of a defoaming agent.

THE EFFECTS OF PRONASE ON MUCOSAL VISIBILITY DURING ADVANCED ENDOSCOPY

Table 2 summarizes studies that explored the effects of pronase as premedication for advanced endoscopy.

Chromoendoscopy

Chromoendoscopy requires a clear field in order for the dye to bind to the targeted mucosa rather than the overlying mucus^[14,15]. Gastric mucus prevents the dye from spraying onto the gastric mucosa and is a frequent source of artifacts during endoscopic imaging. The mucolytic effect of pronase during conventional endoscopy is sustained during chromoendoscopy. In a randomized controlled trial of chromoendoscopy with methylene blue, premedication with pronase came to significantly improve the visibility of the gastric wall both before and after methylene blue spraying and also to significantly shorten the time of the chromoendoscopic examination^[8].

NBI and ME

Recently, NBI has been reported to improve the visibility of mucosal structure and the accuracy of detection for

precancerous conditions^[16]. Like conventional endoscopy, the presence of foam, bubbles, or mucus on the gastric mucosa can obstruct mucosal visualization during NBI endoscopy. Therefore, a premedication with defoaming and mucolytic agents can be an effective method to improve visibility and possibly the diagnostic performance of NBI endoscopy. In our study comparing the visibility score and diagnostic performance of NBI endoscopy for patients with precancerous conditions with or without pronase premedication, a combination of pronase with simethicone significantly improved visibility during NBI endoscopy in the proximal part of the stomach, and it also improved the negative predictive value of NBI endoscopy compared with that of white light endoscopy^[17].

ME with NBI (ME-NBI) is reported to have high accuracy for diagnosing corpus gastritis, intestinal metaplasia and early gastric cancer^[18-21]. In particular, the microvascular and microsurface patterns observed during ME-NBI are clinically helpful for distinguishing cancerous from noncancerous lesions. As mucosal visibility during EGD is essential in finding subtle mucosal abnormalities associated with early neoplasia, mucosal visibility is especially important during ME-NBI in that this procedure has time-consuming and complicated nature. In a randomized study, we showed that premedication with pronase improved mucosal visibility during ME-NBI of the stomach and reduced the frequency of water flushing needed to clear the mucosa^[7].

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) plays an important

Table 2 Summary of studies about premedication with pronase for visualization of the mucosa during advanced endoscopy

Examination	Ref.	Year	Study design	Premedication group (n)	Mucosal visibility
Chromoendoscopy	Fujii <i>et al</i> ^[8]	1998	Prospective	A: DMPS (34) B: DMPS + SB (32) C: DMPS + SB + pronase (34)	C > A, B
NBI endoscopy	Cha <i>et al</i> ^[17]	2014	Prospective	A: Pronase + SB (28) B: Simethicone (27)	A > B
ME-NBI	Kim <i>et al</i> ^[7]	2015	Prospective	A: Simethicone + SB + pronase (71) B: Simethicone (72)	A > B
EUS	Sakai <i>et al</i> ^[24]	2003	Prospective	A: DMPS (29) B: DMPS + SB (29) C: DMPS + SB + pronase (29)	C > A, B
	Han <i>et al</i> ^[25]	2011	Prospective	A: Saline (60) B: Pronase + SB (62) C: Pronase + SB + simethicone (61)	B > A > C

NBI: Narrow-band imaging; ME-NBI: Magnifying endoscopy with narrow-band imaging; EUS: Endoscopic ultrasonography; DMPS: Dimethylpolysiloxane; SB: Sodium bicarbonate.

role in assessing benign and malignant gastrointestinal diseases. It is especially useful for diagnosing subepithelial lesions and the staging of early gastric cancer^[22,23]. However, artifacts caused by gastric mucus can potentially affect visibility during EUS, which inhibits the ability to evaluate superficial mucosal lesions. Reducing gastric cavity and mucosal surface artifacts caused by mucus may be helpful in improving EUS performance. A randomized study evaluating the effect of pronase in improving EUS images showed that premedication with pronase reduced artifacts during EUS *via* a mucolytic effect that disrupts the surface mucus gel layer of the stomach^[24]. In another similar randomized controlled study, premedication with pronase decreased the number of gastric wall and lumen hyperechoic artifacts observed in patients given either saline solution or pronase/simethicone^[25]. Unlike pronase, the use of simethicone led to turbidity and echogenicity, which did not improve visibility during EUS. Although a more accurate diagnosis is not necessarily gleaned from better-quality images, obtaining good EUS images through premedication with pronase may lead to improve the diagnostic accuracy for superficial mucosal lesions during EUS.

CONSIDERATIONS IN USING PRONASE AS PREMEDICATION

To improve the effect of pronase on removing gastric mucus, several factors must be considered^[10]. First is intragastric pH. Mucolysis by pronase is found to be maximal at pH 6 to 8. Therefore, it is necessary to neutralize the acidity of the gastric juice with a neutralizer such as sodium bicarbonate and to prevent subsequent hypersecretion of gastric juice with an anticholinergic agents such as scopolamine butylbromide^[8]. The second consideration is the amount of pronase and the volume of oral solution. Based on previous findings^[6,8,10,13], 2000 units or more (usually 20000 units) of pronase and 80 mL to 100 mL of oral solution are needed to achieve

adequate effects. The third consideration relates to position change of the patient. Rotation from supine, left or right lateral, to prone position several times is helpful for completely removing gastric mucus^[8]. However, in two recent studies, similar effects of pronase were shown without position changes before EGD^[12,13]. The argument for not changing position before EGD stems from the fact that the ingested solution flows into the gastric fundus, then gradually into the gastric antrum by the way of the gastric body after premedication with pronase.

When is the optimal time for taking pronase to maximize its mucolytic effect before EGD? In previous studies, premedication with pronase was administered 10 to 20 min before EGD^[8,12]. In a recent study comparing premedication times of 10 min and 20 min before EGD, mucosal visibility score did not differ between the two groups^[13]. In another recent study evaluating the optimal time of medication with pronase, administration of pronase within 30 min before EGD significantly improved endoscopic visualization compared to administration at 30 min before EGD^[26]. These results suggest that if pronase is given within 30 min before EGD, the duration of premedication does not play a significant role in satisfactory mucosa visualization.

OTHER ADDITIVE EFFECTS OF PRONASE

Effect of pronase on Helicobacter pylori

Because *Helicobacter pylori* (*H. pylori*) strains reside in the surface mucous gel layer as well as on the surface of gastric epithelial cells, premedication with pronase could reduce the accuracy of *H. pylori* identification in biopsy specimens *via* its mucolytic effect. However, the use of pronase seems not to influence the identification of *H. pylori* by culture and rapid urease test of biopsy specimens in many studies^[6,8,12].

Pronase can disrupt gastric mucus and so reduce the thickness of the surface mucous gel layer, which enhances drug delivery to improve the eradication

rate of *H. pylori*^[6,27,28]. Therefore, it is assumed that supplements of pronase in addition to anti-*H. pylori* regimen could increase the eradication rate of *H. pylori*. Earlier randomized controlled studies showed the additive effect of pronase in improvement of *H. pylori* eradication rates^[27,28], but a recent randomized controlled study did not confirm this effect^[29].

Effect of pronase on gastric biopsy

Although pronase improves visibility, a patient's positioning may prevent it from reaching some portions of the stomach in sufficient quantity. In these situations, the endoscopist aid distribution to the target lesion through endoscopic flushing of pronase. Although endoscopic flushing is not able to provide equivalent improvements in mucosal visibility during EGD when compared with the oral administration of pronase^[30], it can be helpful for improving the visibility of a target lesion. Furthermore, patients receiving endoscopic flushing with pronase in a limited area exhibited decrease in thickness of mucus, increase in depth of biopsy, improved anatomical orientation, and improved overall diagnostic assessment of the second biopsy specimens compared with a control group^[31]. Therefore, endoscopic flushing with pronase during EGD can be recommended in order to improve the quantity and quality of endoscopic biopsies.

CONCLUSION

During EGD, foam, bubbles, and mucus often obstruct visibility. Premedication is therefore usually administered prior to an endoscopic procedure in order to remove foam and mucus. Satisfactory visibility achieved through premedication with proper agents can reduce the need to carry out flushing during the procedure, thus shortening the duration of an endoscopy. The use of pronase as premedication improves mucosal visualization in advanced endoscopy as well as in conventional endoscopy without affecting the accuracy of *H. pylori* identification. Although the use of pronase does not necessarily result in a higher detection rate of early cancers or improve clinical outcomes, improved mucosal visibility may be helpful for increasing the detection rate of early cancers. Large randomized clinical trials will be needed to confirm the utility of pronase for identifying early cancers.

REFERENCES

- 1 Banerjee B, Parker J, Waits W, Davis B. Effectiveness of pre-procedure simethicone drink in improving visibility during esophagogastroduodenoscopy: a double-blind, randomized study. *J Clin Gastroenterol* 1992; **15**: 264-265 [PMID: 1479177]
- 2 Bertoni G, Gumina C, Conigliaro R, Ricci E, Staffetti J, Mortilla MG, Pacchione D. Randomized placebo-controlled trial of oral liquid simethicone prior to upper gastrointestinal endoscopy. *Endoscopy* 1992; **24**: 268-270 [PMID: 1612040 DOI: 10.1055/s-2007-1010479]
- 3 Shiotani A, Opekun AR, Graham DY. Visualization of the small intestine using capsule endoscopy in healthy subjects. *Dig Dis Sci* 2007; **52**: 1019-1025 [PMID: 17380402 DOI: 10.1007/s10620-006-9558-6]
- 4 Ge ZZ, Chen HY, Gao YJ, Hu YB, Xiao SD. The role of simeticone in small-bowel preparation for capsule endoscopy. *Endoscopy* 2006; **38**: 836-840 [PMID: 17001575 DOI: 10.1055/s-2006-944634]
- 5 Sudduth RH, DeAngelis S, Sherman KE, McNally PR. The effectiveness of simethicone in improving visibility during colonoscopy when given with a sodium phosphate solution: a double-blind randomized study. *Gastrointest Endosc* 1995; **42**: 413-415 [PMID: 8566629]
- 6 Kuo CH, Sheu BS, Kao AW, Wu CH, Chuang CH. A defoaming agent should be used with pronase premedication to improve visibility in upper gastrointestinal endoscopy. *Endoscopy* 2002; **34**: 531-534 [PMID: 12170403 DOI: 10.1055/s-2002-33220]
- 7 Kim GH, Cho YK, Cha JM, Lee SY, Chung IK. Effect of pronase as mucolytic agent on imaging quality of magnifying endoscopy. *World J Gastroenterol* 2015; **21**: 2483-2489 [PMID: 25741158 DOI: 10.3748/wjg.v21.i8.2483]
- 8 Fujii T, Iishi H, Tatsuta M, Hirasawa R, Uedo N, Hifumi K, Omori M. Effectiveness of premedication with pronase for improving visibility during gastroendoscopy: a randomized controlled trial. *Gastrointest Endosc* 1998; **47**: 382-387 [PMID: 9609431]
- 9 Koga M, Arakawa K. On the application of enzymatic mucinolysis in x-ray diagnosis of the stomach. *Nihon Igaku Hoshasen Gakkai Zasshi* 1964; **24**: 1011-1031 [PMID: 14280614]
- 10 Ida K, Okuda J, Nakazawa S, Yoshino J, Ito M, Yokoyama Y, Ogawa N. Clinical evaluation of premedication with KPD (Pronase) in gastroendoscopy-placebo-controlled double blind study in dye scattering endoscopy. *Clin Rep* 1991; **25**: 1793-1804
- 11 Chen HW, Hsu HC, Hsieh TY, Yeh MK, Chang WK. Premedication to improve esophagogastroduodenoscopic visibility: a meta-analysis and systemic review. *Hepatogastroenterology* 2014; **61**: 1642-1648 [PMID: 25436356]
- 12 Chang CC, Chen SH, Lin CP, Hsieh CR, Lou HY, Suk FM, Pan S, Wu MS, Chen JN, Chen YF. Premedication with pronase or N-acetylcysteine improves visibility during gastroendoscopy: an endoscopist-blinded, prospective, randomized study. *World J Gastroenterol* 2007; **13**: 444-447 [PMID: 17230616]
- 13 Lee GJ, Park SJ, Kim SJ, Kim HH, Park MI, Moon W. Effectiveness of premedication with pronase for visualization of the mucosa during endoscopy: A randomized, controlled trial. *Clin Endosc* 2012; **45**: 161-164 [PMID: 22866258 DOI: 10.5946/ce.2012.45.2.161]
- 14 Shaw D, Blair V, Framp A, Harawira P, McLeod M, Guilford P, Parry S, Charlton A, Martin I. Chromoendoscopic surveillance in hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy? *Gut* 2005; **54**: 461-468 [PMID: 15753528 DOI: 10.1136/gut.2004.049171]
- 15 Tamura S, Ookawauchi K, Onishi S, Yokoyama Y, Yamada T, Higashidani Y, Tadokoro T, Onishi S. The usefulness of magnifying chromoendoscopy: pit pattern diagnosis can predict histopathological diagnosis precisely. *Am J Gastroenterol* 2002; **97**: 2934-2935 [PMID: 12425584 DOI: 10.1111/j.1572-0241.2002.07086.x]
- 16 Capelle LG, Haringsma J, de Vries AC, Steyerberg EW, Biermann K, van Dekken H, Kuipers EJ. Narrow band imaging for the detection of gastric intestinal metaplasia and dysplasia during surveillance endoscopy. *Dig Dis Sci* 2010; **55**: 3442-3448 [PMID: 20393882 DOI: 10.1007/s10620-010-1189-2]
- 17 Cha JM, Won KY, Chung IK, Kim GH, Lee SY, Cho YK. Effect of pronase premedication on narrow-band imaging endoscopy in patients with precancerous conditions of stomach. *Dig Dis Sci* 2014; **59**: 2735-2741 [PMID: 24861034 DOI: 10.1007/s10620-014-3218-z]
- 18 Yao K. Gastric microvascular architecture as visualized by magnifying endoscopy: body and antral mucosa without pathologic change demonstrate two different patterns of microvascular architecture. *Gastrointest Endosc* 2004; **59**: 596-597; author reply 597 [PMID: 15044912]
- 19 Yao K, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy

- for diagnosing and delineating early gastric cancer. *Endoscopy* 2009; **41**: 462-467 [PMID: 19418401 DOI: 10.1055/s-0029-1214594]
- 20 **Kang HM**, Kim GH, Park do Y, Cheong HR, Baek DH, Lee BE, Song GA. Magnifying endoscopy of gastric epithelial dysplasia based on the morphologic characteristics. *World J Gastroenterol* 2014; **20**: 15771-15779 [PMID: 25400462 DOI: 10.3748/wjg.v20.i42.15771]
- 21 **An JK**, Song GA, Kim GH, Park do Y, Shin NR, Lee BE, Woo HY, Ryu DY, Kim DU, Heo J. Marginal turbid band and light blue crest, signs observed in magnifying narrow-band imaging endoscopy, are indicative of gastric intestinal metaplasia. *BMC Gastroenterol* 2012; **12**: 169 [PMID: 23185997 DOI: 10.1186/1471-230X-12-169]
- 22 **Kim GH**, Park do Y, Kim S, Kim DH, Kim DH, Choi CW, Heo J, Song GA. Is it possible to differentiate gastric GISTs from gastric leiomyomas by EUS? *World J Gastroenterol* 2009; **15**: 3376-3381 [PMID: 19610138]
- 23 **Kim GH**, Park do Y, Kida M, Kim DH, Jeon TY, Kang HJ, Kim DU, Choi CW, Lee BE, Heo J, Song GA. Accuracy of high-frequency catheter-based endoscopic ultrasonography according to the indications for endoscopic treatment of early gastric cancer. *J Gastroenterol Hepatol* 2010; **25**: 506-511 [PMID: 20074167 DOI: 10.1111/j.1440-1746.2009.06111.x]
- 24 **Sakai N**, Tatsuta M, Iishi H, Nakaizumi A. Pre-medication with pronase reduces artefacts during endoscopic ultrasonography. *Aliment Pharmacol Ther* 2003; **18**: 327-332 [PMID: 12895217]
- 25 **Han JP**, Hong SJ, Moon JH, Lee GH, Byun JM, Kim HJ, Choi HJ, Ko BM, Lee MS. Benefit of pronase in image quality during EUS. *Gastrointest Endosc* 2011; **74**: 1230-1237 [PMID: 21963063 DOI: 10.1016/j.gie.2011.07.044]
- 26 **Woo JG**, Kim TO, Kim HJ, Shin BC, Seo EH, Heo NY, Park J, Park SH, Yang SY, Moon YS, Lee NY. Determination of the optimal time for premedication with pronase, dimethylpolysiloxane, and sodium bicarbonate for upper gastrointestinal endoscopy. *J Clin Gastroenterol* 2013; **47**: 389-392 [PMID: 23442831 DOI: 10.1097/MCG.0b013e3182758944]
- 27 **Kimura K**, Ido K, Saifuku K, Taniguchi Y, Kihira K, Satoh K, Takimoto T, Yoshida Y. A 1-h topical therapy for the treatment of *Helicobacter pylori* infection. *Am J Gastroenterol* 1995; **90**: 60-63 [PMID: 7801950]
- 28 **Gotoh A**, Akamatsu T, Shimizu T, Shimodaira K, Kaneko T, Kiyosawa K, Ishida K, Ikeno T, Sugiyama A, Kawakami Y, Ota H, Katsuyama T. Additive effect of pronase on the efficacy of eradication therapy against *Helicobacter pylori*. *Helicobacter* 2002; **7**: 183-191 [PMID: 12047324]
- 29 **Bang CS**, Kim YS, Park SH, Kim JB, Baik GH, Suk KT, Yoon JH, Kim DJ. Additive effect of pronase on the eradication rate of first-line therapy for *Helicobacter pylori* infection. *Gut Liver* 2015; **9**: 340-345 [PMID: 25167799 DOI: 10.5009/gnl13399]
- 30 **Bhandari P**, Green S, Hamanaka H, Nakajima T, Matsuda T, Saito Y, Oda I, Gotoda T. Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: a prospective, randomized, controlled, blinded trial. *Scand J Gastroenterol* 2010; **45**: 357-361 [PMID: 20148732 DOI: 10.3109/00365520903483643]
- 31 **Lee SY**, Han HS, Cha JM, Cho YK, Kim GH, Chung IK. Endoscopic flushing with pronase improves the quantity and quality of gastric biopsy: a prospective study. *Endoscopy* 2014; **46**: 747-753 [PMID: 25019968 DOI: 10.1055/s-0034-1365811]

P- Reviewer: Ciaccio E, Raczy I, Sivandzadeh GR **S- Editor:** Ji FF

L- Editor: A **E- Editor:** Wu HL



Raman spectroscopy for early real-time endoscopic optical diagnosis based on biochemical changes during the carcinogenesis of Barrett's esophagus

Hong Shi, Su-Yu Chen, Kai Lin

Hong Shi, Su-Yu Chen, Department of Gastrointestinal Endoscopy, Fujian Provincial Tumor Hospital, Teaching Hospital of Fujian Medical University, Fuzhou 350014, Fujian Province, China

Kai Lin, Department of General Surgery, Fuzhou Seventh Hospital, Fuzhou 350014, Fujian Province, China

Author contributions: Shi H and Chen SY were responsible for the study concept and design; all authors conducted endoscopic operations together; Chen SY and Lin K drafted the manuscript; Shi H revised and finalized the manuscript.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Hong Shi, MD, Department of Gastrointestinal Endoscopy, Fujian Provincial Tumor Hospital, Teaching Hospital of Fujian Medical University, No 420 FuMa Road, Fuzhou 350014, Fujian Province, China. endoshihong@hotmail.com
Telephone: +86-591-83660063
Fax: +86-591-83660063

Received: August 27, 2015
Peer-review started: October 1, 2015
First decision: November 30, 2015
Revised: December 16, 2015
Accepted: January 8, 2016
Article in press: January 11, 2016
Published online: March 10, 2016

Abstract

Raman spectroscopy is a spectroscopic technique based on the inelastic scattering of monochromatic light that represents the molecular composition of the interrogated volume to provide a direct molecular fingerprint. Several investigations have revealed that confocal Raman spectroscopy can differentiate non-dysplastic Barrett's esophagus from esophageal high-grade dysplasia and adenocarcinoma with high sensitivity and specificity. An automated on-line Raman spectral diagnostic system has made it possible to use Raman spectroscopy to guide accurate target biopsy instead of multiple random forceps-biopsies, this novel system is expected to improve *in vivo* precancerous diagnosis and tissue characterization of Barrett's esophagus.

Key words: Raman spectroscopy; Barrett's esophagus; Confocal; High-grade dysplasia; Diagnosis

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Raman spectroscopy is a very sensitive tool to detect subtle biochemical and molecular changes, which is crucial for differentiating nondysplastic from high-grade dysplastic Barrett's esophagus. With an increased accuracy of updated algorithms and a real time automatic analysis system, Raman spectroscopy is expected to improve *in vivo* precancerous diagnosis and tissue characterization of Barrett's esophagus.

Shi H, Chen SY, Lin K. Raman spectroscopy for early real-time endoscopic optical diagnosis based on biochemical changes during the carcinogenesis of Barrett's esophagus. *World J Gastrointest Endosc* 2016; 8(5): 273-275 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i5/273.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i5.273>

INTRODUCTION

Confirmed by the presence of intestinal metaplasia with or without goblet cells from a squamous to a columnar-lined esophageal epithelium^[1,2], Barrett's esophagus is a metaplastic precursor of esophageal adenocarcinoma. Given the poor prognosis that has remained relatively constant, with current 5-year survival rates of only 8% to 15%^[3], early identification of Barrett's esophagus associated with high-grade dysplasia followed by targeted endoscopic resection is the most critical measure to prevent progression to invasive esophageal malignancy^[4]. According to the current diagnostic guidelines, patients with Barrett's esophagus are recommended to undergo strict biopsy samplings (typically 4-quadrant random samplings) for every 2 cm of Barrett's mucosa during endoscopic surveys at intervals of 3 to 5 years. This approach may produce a large number of negative biopsies and increase the risk of bleeding. Considering the elevated incidence of esophageal adenocarcinoma, the need for new advanced endoscopic technologies that can transition standard Barrett's esophagus surveillance from random biopsies to a real-time "optical biopsy" is imperative.

Optical spectroscopy is a technique that utilizes microstructural information contained in light-tissue interactions to enhance suspicious tissue recognition during standard endoscopy^[5], including fluorescence, elastic scattering, and inelastic (Raman) scattering.

Principle of raman spectroscopy

Raman spectroscopy represents a unique optical vibrational technique based on the inelastic scattering of a monochromatic laser light source. Inelastic scattering is a phenomenon in which the frequency of the scattered photon is shifted up or down with respect to the incident excitation light depending on the specific vibrational motions of the molecules in the tissue being interrogated, which is called the Raman effect. This shift of frequency provides unique information on the scattering molecules.

Taking the unique advantage of the ability of Raman spectroscopy to harvest a wealth of direct molecular fingerprint information from inter and/or intracellular components such as proteins, lipids, carbohydrates and DNA in cells and tissue, Raman spectroscopy has shown great promise for histo-pathologic assessments at the biochemical and molecular levels^[6]. Because the progression from non-dysplastic Barrett's esophagus to esophagus adenocarcinoma manifests a progressive series of molecular and biochemical changes, Raman spectroscopy may provide the capability to analyze the carcinogenesis process. Furthermore, the majority of biological molecules are Raman active, each with its own unique fingerprint. As a result, Raman spectroscopy is a very sensitive tool to detect subtle biochemical and molecular changes, which is crucial for differentiating nondysplastic from high-grade dysplastic Barrett's esophagus.

Overall configuration of the raman spectroscopy system

Briefly, the Raman spectroscopy system consists of four major components^[6]: A light generator (near-infrared diode laser); light collection optics; a wavelength selector (filter or spectrophotometer); and a detector (photodiode array, charge coupled device or photomultiplier tube). Compared with an ultraviolet ray illumination source, near infrared excitation not only minimizes spectral disruption from tissue fluorescence but also produces reduced mutagenic effects and deeper penetration capability.

The combination of Raman spectroscopy and an endoscopic system is realized by a Raman probe, which is coupled to an optical cable containing the excitation and collection fibers, with an outer diameter enabling easy passage through the instrument channel of an endoscope. Currently, the two novel confocal Raman probes^[3,4] have the following advantages: They ensure the precise interrogation of the epithelium (with a volume of $< 0.02 \text{ mm}^3$), which is closely related to early onset of Barrett's carcinogenesis, because the ratio of the epithelium to stromal Raman photons collected is 19-fold higher than that collected using previous volume-type Raman probes; and they provide the capacity for reproducible and objective Raman measurements achieved in a direct contact mode.

Clinical application

Water molecules, the predominant constituents of living tissue, have a negligible influence on Raman signals due to the limited change in the polarity of the -OH bond, which enables Raman spectroscopic analysis of fresh, unprepared tissue, both *ex vivo* and *in vivo*.

Robles^[5] summarized some clinical research on Raman spectroscopic technology for classification of malignant changes in Barrett's esophagus, carried out by two groups, from Gloucestershire Royal Hospital^[3], United Kingdom and the National University of Singapore^[4], Singapore. The latter demonstrated for the first time that confocal Raman spectroscopy can be used to target dysplasia identification and subsequent biopsy in Barrett's esophagus in real-time, which has also been used to diagnose gastric^[7] and colorectal^[8] lesions. The characteristics of the two abovementioned confocal probes were compared and listed in Table 1.

At present, most biomedical Raman research on pre-cancer and early cancer diagnosis remain focused on the fingerprint (FP) Raman spectra, which contain rich biochemical information regarding the tissue; however, some extremely weak tissue Raman signals in certain organ sites may be overwhelmed by the tissue autofluorescence (AF) background. Because the high-wavenumber (HW) Raman spectral range exhibits stronger tissue Raman signals with less AF interference, it has been integrated with the FP Raman spectra to improve the real-time *in vivo* diagnosis of esophageal squamous cell carcinoma (ESCC) during endoscopic examination, resulting in a predictive diagnostic sensitivity of 92.7% and specificity of 93.6% for ESCC

Table 1 Comparison of two endoscopic confocal raman spectroscopic systems

Technical parameters	Developed by Almond <i>et al.</i> ^[3]	Developed by Bergholt <i>et al.</i> ^[4]
λex	830 nm	785 nm
Diameter of probe	2.7 mm	1.8 mm
Range of Raman spectra	400-1850 cm ⁻¹	800-1800 cm ⁻¹
Acquisition times	1 s	0.2 s
Classification model	Principal component fed linear discriminant analysis	Partial least-squares discriminant analysis ^[9]
Diagnostic way	<i>Ex vivo</i>	Real-time <i>in vivo</i>
Sensitivity and specificity for detecting HGD in BE	86% and 88%	87.0% and 84.7%

HGD: High grade dysplasia; BE: Barrett's esophagus.

identification^[10].

CONCLUSION

Despite some limitations, such as only identifying molecular features, susceptibility to interference of fluorescence from impurities or from the sample itself, and thermal damage to tissues, confocal Raman spectroscopy uncovers the biochemical and molecular changes occurring in the epithelium during Barrett's carcinogenesis. This technique is expected to improve *in vivo* precancerous diagnosis and tissue characterization of Barrett's esophagus with increased accuracy based upon updated algorithms and the on-line real time automatic analysis system.

REFERENCES

1 Playford RJ. New British Society of Gastroenterology (BSG)

guidelines for the diagnosis and management of Barrett's oesophagus. *Gut* 2006; **55**: 442 [PMID: 16531521]

- 2 Sampliner RE. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol* 2002; **97**: 1888-1895 [PMID: 12190150]
- 3 Almond LM, Hutchings J, Lloyd G, Barr H, Shepherd N, Day J, Stevens O, Sanders S, Wadley M, Stone N, Kendall C. Endoscopic Raman spectroscopy enables objective diagnosis of dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2014; **79**: 37-45 [PMID: 23886354 DOI: 10.1016/j.gie.2013.05.028]
- 4 Bergholt MS, Zheng W, Ho KY, Teh M, Yeoh KG, Yan So JB, Shabbir A, Huang Z. Fiber-optic confocal raman spectroscopy for real-time *in vivo* diagnosis of dysplasia in Barrett's esophagus. *Gastroenterology* 2014; **146**: 27-32 [PMID: 24216327 DOI: 10.1053/j.gastro.2013.11.002]
- 5 Robles LY, Singh S, Fisichella PM. Emerging enhanced imaging technologies of the esophagus: spectroscopy, confocal laser endomicroscopy, and optical coherence tomography. *J Surg Res* 2015; **195**: 502-514 [PMID: 25819772 DOI: 10.1016/j.jss.2015.02.045]
- 6 Kim HH. Endoscopic Raman Spectroscopy for Molecular Fingerprinting of Gastric Cancer: Principle to Implementation. *Biomed Res Int* 2015; **2015**: 670121 [PMID: 26106612 DOI: 10.1155/2015/670121]
- 7 Bergholt MS, Zheng W, Ho KY, Teh M, Yeoh KG, So JB, Shabbir A, Huang Z. Fiber-optic Raman spectroscopy probes gastric carcinogenesis *in vivo* at endoscopy. *J Biophotonics* 2013; **6**: 49-59 [PMID: 23288709 DOI: 10.1002/jbio.201200138]
- 8 Bergholt MS, Lin K, Wang J, Zheng W, Xu H, Huang Q, Ren JL, Ho KY, Teh M, Srivastava S, Wong B, Yeoh KG, Huang Z. Simultaneous fingerprint and high-wavenumber fiber-optic Raman spectroscopy enhances real-time *in vivo* diagnosis of adenomatous polyps during colonoscopy. *J Biophotonics* 2015 Apr 7; Epub ahead of print [PMID: 25850576 DOI: 10.1002/jbio.201400141]
- 9 Bergholt MS, Duraipandian S, Zheng W, Huang Z. Multivariate reference technique for quantitative analysis of fiber-optic tissue Raman spectroscopy. *Anal Chem* 2013; **85**: 11297-11303 [PMID: 24160634 DOI: 10.1021/ac402059v]
- 10 Wang J, Lin K, Zheng W, Ho KY, Teh M, Yeoh KG, Huang Z. Simultaneous fingerprint and high-wavenumber fiber-optic Raman spectroscopy improves *in vivo* diagnosis of esophageal squamous cell carcinoma at endoscopy. *Sci Rep* 2015; **5**: 12957 [PMID: 26243571 DOI: 10.1038/srep12957]

P- Reviewer: Amorniyotin S, Teoh AYB, Watari J
S- Editor: Qiu S L- Editor: A E- Editor: Wu HL



Retrospective Study

Endoscopic mucosal resection of colorectal adenomas > 20 mm: Risk factors for recurrence

Alexander Briedigkeit, Omar Sultanie, Bernd Sido, Franz Ludwig Dumoulin

Alexander Briedigkeit, Omar Sultanie, Franz Ludwig Dumoulin, Department of Medicine and Gastroenterology, Gemeinschaftskrankenhaus Bonn, 53113 Bonn, Germany

Bernd Sido, Department of General and Abdominal Surgery, Gemeinschaftskrankenhaus Bonn, 53113 Bonn, Germany

Author contributions: Briedigkeit A collected and analyzed the data, and drafted the manuscript; Sultanie O and Sido B provided analytical oversight; Dumoulin FL performed EMRs and designed and supervised the study; all authors have read and approved the final version to be published.

Institutional review board statement: The study was approved by the Institutional Review Board of the Gemeinschaftskrankenhaus Bonn (Chair Bremekamp C). A formal ethical approval is not required for retrospective studies by German Federal Law. This statement may be verified by contacting the chairman of the Ethics Committee of the University of Bonn (Professor Racké K, email: ethik@uni-bonn.de).

Informed consent statement: All patients gave informed consent for an anonymized data analysis along with the informed consent for interventional endoscopy. According to German Federal Law informed consent of patients is not required for retrospective data analysis.

Conflict-of-interest statement: The authors have no conflict of interest to disclose.

Data sharing statement: An anonymized dataset is available from the corresponding author at the email address given below.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Franz Ludwig Dumoulin, MD, PhD,

Department of Medicine and Gastroenterology, Gemeinschaftskrankenhaus Bonn, Bonner Talweg 4-6, 53113 Bonn, Germany. f.dumoulin@gk-bonn.de
Telephone: +49-228-5081561
Fax: +49-228-5081562

Received: August 16, 2015
Peer-review started: August 17, 2015
First decision: September 23, 2015
Revised: October 21, 2015
Accepted: January 16, 2016
Article in press: January 19, 2016
Published online: March 10, 2016

Abstract

AIM: To evaluate risk factors for local recurrence after endoscopic mucosal resection of colorectal adenomas > 20 mm.

METHODS: Retrospective data analysis of 216 endoscopic mucosal resections for colorectal adenomas > 20 mm in 179 patients (40.3% female; median age 68 years; range 35-91 years). All patients had at least 1 follow-up endoscopy with a minimum control interval of 2 mo (mean follow-up 6 mo/2.0-43.4 mo). Possible factors associated with local recurrence were analyzed by univariate and multivariate analysis.

RESULTS: Median size of the lesions was 30 mm (20-70 mm), 69.0% were localized in the right-sided (cecum, ascending and transverse) colon. Most of the lesions (85.6%) showed a non-pedunculated morphology and the majority of resections was in piecemeal technique (78.7%). Histology showed carcinoma or high-grade intraepithelial neoplasia in 51/216 (23.6%) lesions including 4 low risk carcinomas (pT1a, L0, V0, R0 - G1/G2). Histologically proven recurrence was observed in 33/216 patients (15.3%). Patient age > 65 years, polyp size > 30 mm, non-

pedunculated morphology, localization in the right-sided colon, piecemeal resection and tubular-villous histology were found as associated factors in univariate analysis. On multivariate analysis, only localization in the right-sided colon (HR = 6.842/95%CI: 1.540-30.394; $P = 0.011$), tubular-villous histology (HR = 3.713/95%CI: 1.617-8.528; $P = 0.002$) and polyp size > 30 mm (HR = 2.563/95%CI: 1.179-5.570; $P = 0.017$) were significantly associated risk factors for adenoma recurrence.

CONCLUSION: Meticulous endoscopic follow-up is warranted after endoscopic mucosal resection of adenomas localized in the right-sided colon larger than > 30 mm, with tubular-villous histology.

Key words: Colorectal adenoma; Endoscopic mucosal resection; Piecemeal resection; Local recurrence rate; Tubular-villous adenoma

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic mucosal resection of larger adenomas is burdened with relatively high rates of local recurrence. In this retrospective analysis, size > 30 mm, non-pedunculated morphology, right-sided localization, piecemeal resection and histology were all associated with local recurrence. In addition, right-sided localization, tubular-villous histology and size > 30 mm were independently associated with local recurrence. These findings emphasize the necessity of meticulous endoscopic follow-up, they might also argue in favor of *en bloc* resection of larger colorectal lesions, in particular in the right-sided colon.

Briedigkeit A, Sultanie O, Sido B, Dumoulin FL. Endoscopic mucosal resection of colorectal adenomas > 20 mm: Risk factors for recurrence. *World J Gastrointest Endosc* 2016; 8(5): 276-281 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i5/276.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i5.276>

INTRODUCTION

Screening colonoscopy and removal of detected adenomas is now recognized as an effective measure to prevent colorectal cancer^[1-3]. However, efficacy of screening endoscopy is hampered not only by a low adenoma detection rate but also by incomplete removal of advanced adenomas^[4].

Endoscopic mucosal resection (EMR) is the current standard for the treatment of colorectal adenomas in Western countries^[5-7]. While widely used, EMR is burdened by incomplete adenoma resections even for smaller lesions up to 20 mm^[8]. The technique is also used for lesions > 20 mm where it is performed in piecemeal technique, *i.e.*, the adenoma is removed in fragments. As a consequence of fragmentation it is impossible to histologically confirm the completeness of

resection. Endoscopic control is therefore recommended after 2-6 mo by current guidelines^[9-12]. Reported recurrence rates during endoscopic follow-up vary from 5%-27% in retrospective studies^[13-23]. In a recently published well-conducted prospective study the recurrence rate was 32%^[24]. Since the majority of colorectal lesions harbors only low-grade intraepithelial neoplasia, local recurrence is usually not viewed as a treatment failure^[22,25]. Nevertheless, all patients need close endoscopic observation and those with recurrences often need several EMR interventions during follow-up^[26]. Moreover, there is a concern about late local recurrences and even subsequent cancer after a negative first control endoscopy^[13,22,24,27]. Many of these problems could be overcome by the use of endoscopic submucosal dissection (ESD) - which allows *en bloc* resection of larger adenomas, but colorectal ESD is still largely considered an experimental therapy in the Western world^[11].

Several risk factors for local recurrence after EMR (*e.g.*, lesion size, localization, morphology, resection in piecemeal technique, histological features) have been reported in retrospective studies^[18,22,28-30]. The purpose of this study was to analyze risk factors in a cohort of larger colorectal adenomas with preferentially right-sided localization. The results of this study should have an impact on the choice of the resection strategy (*e.g.*, EMR vs ESD vs laparoscopic surgery) as well as on the intensity of endoscopic follow-up.

MATERIALS AND METHODS

Patients and data collection

A single experienced interventional endoscopist (FLD) performed 688 EMRs over a five-year period (03/2008-03/2013). Of these, 216 EMRs in 179 patients, 87 female (40.3%) and 129 male (59.7%), with a median age of 68 years (35-91) met the inclusion criteria of polyp size > 20 mm, at least one endoscopic control 2-6 mo after EMR and sufficient data of follow-up examinations. The median follow-up time was 6 mo (range: 2-43.4 mo).

EMR procedure

EMRs were carried out under conscious sedation with propofol (B Braun Melsungen, Melsungen, German) and occasionally midazolam (Roche Pharma AG, Basel, Switzerland) using standard endoscopes (GIF 1-TQ160, CF-H180 AL, PCF 180 AL; Olympus Europe, Hamburg Germany). After detailed endoscopic inspection, lesions were classified according to the Paris classification^[31] and the size of the lesion was estimated by comparison to an opened snare. Submucosal injection of normal saline with 0.01% indigo carmine (Novaplus, Lake Forrest, IL, United States) was performed with a small bore injector needle (25G, Olympus Europe, Hamburg, Germany). EMR was then carried out with different snare types according to the size and shape of the lesions (Snaremaster®, Olympus Europe, Hamburg,

Table 1 Characteristics of the resected lesions *n* (%)

No. of polyps	<i>n</i> = 216
Size (median/range)	30 mm (20.0-70.0)
Localization	
Right-sided colon (cecum, ascending, transverse)	149 (69.0)
Left-sided colon (descending, sigmoid) or rectum	67 (31.0)
Morphology of polyps (Paris classification ^[31])	
Pedunculated (0-Ip)	31 (14.4)
Non-pedunculated (0-Is; 0-IIa/b/c)	185 (85.6)
Resection in piecemeal technique	170 (78.7)
Final histology	
Low-risk invasive adeno-carcinoma	4 (1.9)
Tubular-villous adenoma	102 (47.2)
Tubular adenoma	65 (30.1)
Serrated adenoma	45 (20.8)

Germany; Acusnare®, Cook Medical Germany, Mönchengladbach, Germany) using standard power settings on an Erbe VAI0 200S electrosurgical unit (Erbe Elektromedizin, Tübingen, Germany). Careful APC coagulation of resection bed or margins was performed if deemed necessary. Resected specimens were retrieved and fixed in phosphate buffered formaldehyde solution for histopathology. To prevent delayed bleeding hemoclips (EZ clip; Olympus Europe, Hamburg, Germany) were used in most procedures.

Endoscopic follow-up after EMR

According to the German S3 guideline on colorectal carcinoma^[11] control endoscopies were done 2-6 mo after EMR. If longer follow-up endoscopies without signs of recurrence were available the longest follow-up interval was counted.

Statistical analysis

Univariate (Kaplan Meier) analysis was carried out to describe the distributions of baseline variables. Cox regression analysis was then used to evaluate various combinations and interactions of prognostic variables in a multivariate manner. Data analysis was done using the SPSS package (student's edition; SPSS Inc. Somers, NY, United States). A *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 216 adenomas with a median size of 30 mm (range 20-70 mm) were resected. Most adenomas were localized in the right-sided colon (69%), had a flat or sessile morphology (85.6%) and were resected in piecemeal technique (78.7%). Histological analysis revealed tubular adenoma (30.1%), tubular-villous adenoma (47.2%), serrated adenoma (20.8%) and invasive cancer in four lesions (1.9%). High-grade intraepithelial neoplasia was detected in 47 lesions (21.8%). While piecemeal fragments did show lateral margins with adenoma tissue, positive vertical margins were not detected. All four colorectal cancers were low risk (pT1a, L0, V0, R0 - G1/G2) and did not recur

Table 2 Histology by localization of the lesions *n* (%)

Histology	Right-sided colon (<i>n</i> = 149)	Left-sided colon (<i>n</i> = 67)
Low-risk invasive adeno-carcinoma	1 (0.7)	3 (4.5)
Tubular-villous adenoma	63 (42.3)	39 (58.2)
Tubular adenoma	42 (28.2)	23 (34.3)
Serrated adenoma	43 (28.9)	2 (3.0)

during follow-up (Tables 1 and 2).

After a median follow-up interval of 6 mo (range 2-43.4) a total number of 33 recurrences were detected, resulting in a local recurrence rate of 15.3%. All recurrences showed the same histology as the initially resected lesion and by the time of writing all patients with recurrences had been treated endoscopically by EMR and/or argon plasma coagulation. Univariate (Kaplan-Meier) analysis (Table 3) detected significant differences in the recurrence rates for age group (< 65 years: 11.4%/> 65 years: 19.2%), adenoma size (< 30 mm: 12.4%/> 30 mm: 22.2%), localization (left-sided colon: 3.0%/right-sided colon: 20.8%), morphology (pedunculated: 0%/non-pedunculated: 17.8%), resection technique (*en bloc*: 6.5%/piecemeal: 17.6%) and histology (tubular, serrated, carcinoma: 7.1%/ tubular-villous 24.3%) but not for time interval of follow-up or histology of serrated adenoma. On multivariate (Cox regression) analysis only localization in the right-sided colon (HR = 6.842), histology of tubular-villous adenoma (HR = 3.713) and size > 30 mm (HR = 2.563) were independently associated with local recurrence. We did not detect an association of recurrence with high-grade intraepithelial neoplasia (OR = 0.549/95%CI: 0.193-1.562; *P* = 0.279) (Table 4).

DISCUSSION

In this retrospective analysis of EMRs for 216 large colorectal adenomas (median size 30 mm) with preferential proximal localization (69% right-sided colon) we observed a recurrence rate of 15.3% after a median follow-up of 6 mo. Univariate analysis showed significantly higher recurrence rates for patient age > 65 years, adenoma size > 30 mm, proximal localization, non-pedunculated morphology, resection in piecemeal technique and tubular-villous histology. Multivariate analysis revealed only adenoma size > 30 mm, right-sided localization and tubular-villous histology as risk factors independently associated with local recurrence.

Many of the above mentioned factors have been described in the literature (Table 5). Interestingly, and in contrast to most other reports, the strongest risk factor for adenoma recurrence identified in this study was a right-sided localization (HR = 6.842). These findings are in line with data from Cipolletta *et al.*^[30] who reported a similar association for lesions with predominantly right-sided localization. In the present study, 69% of the lesions were located in the right-sided colon and the

Table 3 Risk factors for recurrence (univariate analysis)¹

Variable	Recurrence (fraction/%)	OR (95%CI)	P value ²
Age			
< 65 yr	10/96 (11.4%)	2.492	0.011
> 65 yr	23/120 (19.2%)	(1.182-5.252)	
Size			
< 30 mm	19/153 (12.4%)	2.472	0.005
> 30 mm	14/63 (22.2%)	(1.233-4.957)	
Morphology			
Paris 0-Ip (pedunculated)	0/31 (0%)	26.386	0.018
Paris 0-Is, 0-II a, b, c (sessile/flat)	33/185 (17.8%)	(0.473-1472.565)	
Localization			
Right-sided colon	31/149 (20.8%)	7.475	0.002
Left-sided colon or rectum	2/67 (3.0%)	(1.787-31.264)	
Resection technique			
Piecemeal (fragmented)	30/170 (17.6%)	3.741	0.01
<i>En bloc</i>	3/46 (6.5%)	(1.139-12.292)	
Histology			
Tubular-villous adenoma	25/103 (24.3%)	3.417	0.002
Tubular, serrated, carcinoma	8/113 (7.1%)	(1.533-7.614)	

¹The overall recurrence rate was 33/216 (15.3%); ²As calculated with the Kaplan-Meier method.

recurrence rate was 20.9% (vs 3.0% for localization in left-sided colon or rectum). Our interpretation is, that this association is driven by the higher technical difficulty for the treatment of right-sided lesions, resulting in lower complete resection rates, in particular since all pedunculated lesions were localized in the left-sided colon. Since relatively high recurrence rates have been reported after resection of serrated lesions^[8] it is tempting to speculate on a correlation of a serrated histology with local recurrence rates but in the current study we did not find any statistically significant association. Interestingly, contradictory findings with higher recurrence rates for left-sided rather than right-sided localization have been reported from a retrospective study with predominantly left-sided adenomas^[28]. Thus, the diverging findings most probably reflect a difference in the study population, in particular with respect to adenoma characteristics (size, localization, morphology, *en bloc* resection rate), rather than true differences.

In addition, a larger size of the lesion^[14,22,23,30] and resection in piecemeal technique^[19,23,29,30] or a resection in more than 5 fragments^[18] have been reported as risk factors for recurrence. Our findings of a significant association of piecemeal resection (univariate analysis only) and of adenoma size > 30 mm (multivariate) with local recurrence after EMR are in complete agreement with the aforementioned studies.

Finally, we identified tubular-villous histology as a risk factor for local recurrence. Since tubular-villous adenoma represents a more advanced neoplastic lesion these data are in line with Lim *et al.*^[28] who reported an association of recurrence with high-grade intraepithelial neoplasia (not significantly associated in our dataset). Such associations could reflect biological

Table 4 Risk factors for recurrence (multivariate analysis)¹

Variable	HR (95%CI)	P value
Size > 30 mm	2.563 (1.179-5.570)	0.017
Localization right-sided colon	6.842 (1.540-30.394)	0.011
Histology tubular-villous adenoma	3.713 (1.617-8.528)	0.002

¹The factors age, morphology, resection technique were not significant in multivariate analysis.

Table 5 Reported associations with adenoma recurrence from the literature

Ref.	Lesions (n)	Size	Localization	Piecemeal resection
Luigiano <i>et al.</i> ^[14]	148	> 40 mm		
Lim <i>et al.</i> ^[28]	239		Left-sided	
Mannath <i>et al.</i> ^[29]	121			Yes
Sakamoto <i>et al.</i> ^[18]	222			Yes
				(> 5 pieces)
Woodward <i>et al.</i> ^[19]	423			Yes
Cipolletta <i>et al.</i> ^[30]	1012	> 30 mm	Right-sided	Yes
Moss <i>et al.</i> ^[22]	799	> 40 mm		
Oka <i>et al.</i> ^[23]	1029	> 40 mm		Yes
Briedigkeit <i>et al.</i> (this study)	216	> 30 mm	Right-sided	Yes
				(univariate only)

differences between the different types of histology (serrated vs tubular vs tubular-villous) but the study size was probably too small to definitively address such differences in greater detail. The same holds true for age, morphology and resection technique with significant associations only on univariate but not on multivariate analysis.

The presented study has several limits. In particular, the retrospective design and the relatively short follow up interval (which results from the current guideline in our country^[11]) might have underestimated the true recurrence rate. In addition, the relatively low number of adenoma recurrences could have reduced the probability of correctly identifying associated risk factors. Nevertheless, the data underscore the necessity of meticulous endoscopic follow-up, in particular after EMR of larger adenomas with right-sided localization and tubular-villous histology, and probably also for adenomas resected in piecemeal technique. In these situations alternative procedures with higher *en bloc* resection rates such as colorectal ESD^[23,32] or laparoscopic surgery should be considered.

ACKNOWLEDGMENTS

We are indebted to Mrs. Jennifer Nadal (Institute for Medical Biometrics, Informatics and Epidemiology, University of Bonn, Germany) who reviewed the statistics reported in this study. In addition, we gratefully acknowledge the following colleagues for referring patients and for providing follow-up data: Bockelmann N, Bönninghausen G, Fehring C, Gille K, Klassen PM, Lindstaedt H, May P, Mayershofer R, Nordhoff S, Oeyen

M, Rosenhauer von Deimling K, Plaßmann D, Robertz-Vaupel GM, Respondek A, Schmidt C, Schulte-Witte H, Vogt M, Zumfelde P.

COMMENTS

Background

Endoscopic mucosal resection of colorectal adenomas is the standard treatment in the Western world. However, the effectiveness for endoscopic mucosal resection (EMR) is limited for larger adenomas with reported recurrence rates of more than 30%.

Research frontiers

The identification of risk factors associated with local adenoma recurrence may be useful to identify patients in need for a more intensive follow-up and - possibly - to guide treatment methods.

Innovations and breakthroughs

This study shows an increased risk for recurrence after EMR of adenomas with proximal localization, larger size (> 30 mm) and tubular-villous histology.

Applications

The results can be used to determine the follow-up strategy, which should be more stringent for adenomas with the above-mentioned criteria. Moreover, resection strategy for colorectal adenomas with particular high recurrence risk should preferably be an *en bloc* resection (either by endoscopic submucosal dissection or laparoscopic surgery).

Peer-review

The study is a well written paper, addressing an important issue regarding treatment of these borderline lesions.

REFERENCES

- 1 **Zauber AG**, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Wayne JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]
- 2 **Brenner H**, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ* 2014; **348**: g2467 [PMID: 24922745 DOI: 10.1136/bmj.g2467]
- 3 **Løberg M**, Kalager M, Holme Ø, Hoff G, Adami HO, Bretthauer M. Long-term colorectal-cancer mortality after adenoma removal. *N Engl J Med* 2014; **371**: 799-807 [PMID: 25162886 DOI: 10.1056/NEJMoa1315870]
- 4 **Singh S**, Singh PP, Murad MH, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109**: 1375-1389 [PMID: 24957158 DOI: 10.1038/ajg.2014.171]
- 5 **Repici A**, Pellicano R, Strangio G, Danese S, Fagoonee S, Malesci A. Endoscopic mucosal resection for early colorectal neoplasia: pathologic basis, procedures, and outcomes. *Dis Colon Rectum* 2009; **52**: 1502-1515 [PMID: 19617768 DOI: 10.1007/DCR.0b013e3181a74d9b]
- 6 **Elmunzer BJ**. Endoscopic resection of sessile colon polyps. *Gastroenterology* 2013; **144**: 30-31 [PMID: 23127574 DOI: 10.1053/j.gastro.2012.09.063]
- 7 **Kaltenbach T**, Soetikno R. Endoscopic resection of large colon polyps. *Gastrointest Endosc Clin N Am* 2013; **23**: 137-152 [PMID: 23168124 DOI: 10.1016/j.giec.2012.10.005]
- 8 **Pohl H**, Srivastava A, Bensen SP, Anderson P, Rothstein RI, Gordon SR, Levy LC, Toor A, Mackenzie TA, Rosch T, Robertson DJ. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. *Gastroenterology* 2013; **144**: 74-80.e1 [PMID: 23022496 DOI: 10.1053/j.gastro.2012.09.043]
- 9 **Davila RE**, Rajan E, Baron TH, Adler DG, Egan JV, Faigel DO, Gan SI, Hirota WK, Leighton JA, Lichtenstein D, Qureshi WA, Shen B, Zuckerman MJ, VanGuilder T, Fanelli RD. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc* 2006; **63**: 546-557 [PMID: 16564851 DOI: 10.1016/j.gie.2006.02.002]
- 10 **Hassan C**, Quintero E, Dumonceau JM, Regula J, Brandão C, Chaussade S, Dekker E, Dinis-Ribeiro M, Ferlitsch M, Gimeno-García A, Hazewinkel Y, Jover R, Kalager M, Loberg M, Pox C, Rembacken B, Lieberman D. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2013; **45**: 842-851 [PMID: 24030244 DOI: 10.1055/s-0033-1344548]
- 11 **Pox C**, Aretz S, Bischoff SC, Graeven U, Hass M, Heußner P, Hohenberger W, Holstege A, Hübner J, Kolligs F, Kreis M, Lux P, Ockenga J, Porschen R, Post S, Rahner N, Reinacher-Schick A, Riemann JF, Sauer R, Sieg A, Schepbach W, Schmitt W, Schmoll HJ, Schulmann K, Tannapfel A, Schmigel W. [S3-guideline colorectal cancer version 1.0]. *Z Gastroenterol* 2013; **51**: 753-854 [PMID: 23955142 DOI: 10.1055/s-0033-1350264]
- 12 **Tanaka S**, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Kudo SE, Tsuruta O, Sugihara K, Watanabe T, Saitoh Y, Igarashi M, Toyonaga T, Ajioka Y, Ichinose M, Matsui T, Sugita A, Sugano K, Fujimoto K, Tajiri H. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2015; **27**: 417-434 [PMID: 25652022 DOI: 10.1111/den.12456]
- 13 **Khashab M**, Eid E, Rusche M, Rex DK. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. *Gastrointest Endosc* 2009; **70**: 344-349 [PMID: 19249767 DOI: 10.1016/j.gie.2008.10.037]
- 14 **Luigiano C**, Consolo P, Scaffidi MG, Strangio G, Giacobbe G, Alibrandi A, Pallio S, Tortora A, Melita G, Familiari L. Endoscopic mucosal resection for large and giant sessile and flat colorectal polyps: a single-center experience with long-term follow-up. *Endoscopy* 2009; **41**: 829-835 [PMID: 19750448 DOI: 10.1055/s-0029-1215091]
- 15 **Ferrara F**, Luigiano C, Ghersi S, Fabbri C, Bassi M, Landi P, Polifemo AM, Billi P, Cennamo V, Consolo P, Alibrandi A, D'Imperio N. Efficacy, safety and outcomes of 'inject and cut' endoscopic mucosal resection for large sessile and flat colorectal polyps. *Digestion* 2010; **82**: 213-220 [PMID: 20588036 DOI: 10.1159/000284397]
- 16 **Ah Soune P**, Ménard C, Salah E, Desjeux A, Grimaud JC, Barthet M. Large endoscopic mucosal resection for colorectal tumors exceeding 4 cm. *World J Gastroenterol* 2010; **16**: 588-595 [PMID: 20128027]
- 17 **Buchner AM**, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. *Gastrointest Endosc* 2012; **76**: 255-263 [PMID: 22657404 DOI: 10.1016/j.gie.2012.02.060]
- 18 **Sakamoto T**, Matsuda T, Otake Y, Nakajima T, Saito Y. Predictive factors of local recurrence after endoscopic piecemeal mucosal resection. *J Gastroenterol* 2012; **47**: 635-640 [PMID: 22223177 DOI: 10.1007/s00535-011-0524-5]
- 19 **Woodward TA**, Heckman MG, Cleveland P, De Melo S, Raimondo M, Wallace M. Predictors of complete endoscopic mucosal resection of flat and depressed gastrointestinal neoplasia of the colon. *Am J Gastroenterol* 2012; **107**: 650-654 [PMID: 22552236 DOI: 10.1038/ajg.2011.473]
- 20 **Carvalho R**, Areia M, Brito D, Saraiva S, Alves S, Cadime AT. Endoscopic mucosal resection of large colorectal polyps: prospective evaluation of recurrence and complications. *Acta Gastroenterol Belg* 2013; **76**: 225-230 [PMID: 23898560]
- 21 **Maguire LH**, Shellito PC. Endoscopic piecemeal resection of large colorectal polyps with long-term followup. *Surg Endosc* 2014; **28**: 2641-2648 [PMID: 24695984 DOI: 10.1007/s00464-014-3516-8]
- 22 **Moss A**, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, Zanati S, Burgess NG, Sonson R, Byth K, Bourke MJ. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is

- infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut* 2015; **64**: 57-65 [PMID: 24986245 DOI: 10.1136/gutjnl-2013-305516]
- 23 **Oka S**, Tanaka S, Saito Y, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Tsuruta O, Sano Y, Yamano H, Shimizu S, Yahagi N, Watanabe T, Nakamura H, Fujii T, Ishikawa H, Sugihara K. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. *Am J Gastroenterol* 2015; **110**: 697-707 [PMID: 25848926 DOI: 10.1038/ajg.2015.96]
 - 24 **Knabe M**, Pohl J, Gerges C, Ell C, Neuhaus H, Schumacher B. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. *Am J Gastroenterol* 2014; **109**: 183-189 [PMID: 24343549 DOI: 10.1038/ajg.2013.419]
 - 25 **Belle S**, Haase L, Pilz LR, Post S, Ebert M, Kaehler G. Recurrence after endoscopic mucosal resection-therapy failure? *Int J Colorectal Dis* 2014; **29**: 209-215 [PMID: 24146064 DOI: 10.1007/s00384-013-1783-9]
 - 26 **Arebi N**, Swain D, Suzuki N, Fraser C, Price A, Saunders BP. Endoscopic mucosal resection of 161 cases of large sessile or flat colorectal polyps. *Scand J Gastroenterol* 2007; **42**: 859-866 [PMID: 17558911 DOI: 10.1080/00365520601137280]
 - 27 **Wei XB**, Xin L, Hao J. Malignant recurrence and distal metastasis after complete local resection of colorectal "high-grade intraepithelial neoplasia": incidence and risk factors. *Int J Colorectal Dis* 2014; **29**: 1467-1475 [PMID: 25155620 DOI: 10.1007/s00384-014-2001-0]
 - 28 **Lim TR**, Mahesh V, Singh S, Tan BH, Elsadig M, Radhakrishnan N, Conlong P, Babbs C, George R. Endoscopic mucosal resection of colorectal polyps in typical UK hospitals. *World J Gastroenterol* 2010; **16**: 5324-5328 [PMID: 21072895]
 - 29 **Mannath J**, Subramanian V, Singh R, Telakis E, Ragunath K. Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. *Dig Dis Sci* 2011; **56**: 2389-2395 [PMID: 21327705 DOI: 10.1007/s10620-011-1609-y]
 - 30 **Cipolletta L**, Rotondano G, Bianco MA, Buffoli F, Gizzi G, Tessari F. Endoscopic resection for superficial colorectal neoplasia in Italy: a prospective multicentre study. *Dig Liver Dis* 2014; **46**: 146-151 [PMID: 24183949 DOI: 10.1016/j.dld.2013.09.019]
 - 31 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541]
 - 32 **Uraoka T**, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection: is it suitable in western countries? *J Gastroenterol Hepatol* 2013; **28**: 406-414 [PMID: 23278302 DOI: 10.1111/jgh.12099]

P- Reviewer: Fogli L, Mentos O, Zhu YL **S- Editor:** Gong XM

L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 March 25; 8(6): 282-318





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmänn, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hirotoshi Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hirotoshi Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

MINIREVIEWS

- 282 Endoscopic retrograde cholangiopancreatography in periampullary diverticulum: The challenge of cannulation

Altonbary AY, Bahgat MH

ORIGINAL ARTICLE

Retrospective Cohort Study

- 288 Determination of the cut-off score of an endoscopic scoring method to predict whether elderly patients with dysphagia can eat pureed diets

Sakamoto T, Horiuchi A, Makino T, Kajiyama M, Tanaka N, Hyodo M

Retrospective Study

- 295 Use of automated irrigation pumps improves quality of bowel preparation for colonoscopy

Ravi S, Sabbagh R, Antaki F

- 301 Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis

Hirayama Y, Ando T, Hirooka Y, Watanabe O, Miyahara R, Nakamura M, Yamamura T, Goto H

SYSTEMATIC REVIEWS

- 310 Systematic review comparing endoscopic, percutaneous and surgical pancreatic pseudocyst drainage

Teoh AYB, Dhir V, Jin ZD, Kida M, Seo DW, Ho KY

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 6 March 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Xiao-Lei Wang, MD, PhD, Associate Professor, Department of Gastroenterology, Tongji Hospital, Tongji University, Shanghai 200065, China

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Su-Qing Liu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Shui-Qiu*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lei Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
March 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Endoscopic retrograde cholangiopancreatography in periampullary diverticulum: The challenge of cannulation

Ahmed Youssef Altonbary, Monir Hussein Bahgat

Ahmed Youssef Altonbary, Monir Hussein Bahgat, Department of Hepatology and Gastroenterology, Mansoura Specialized Medical Hospital, Mansoura 35516, Egypt

Author contributions: Altonbary AY and Bahgat MH contributed equally the conception, design and performance of this study; Altonbary AY wrote the manuscript; Bahgat MH revised the manuscript for important intellectual content.

Conflict-of-interest statement: Neither of the authors has any conflict of interest related to the publication of this study.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ahmed Youssef Altonbary, MD, Department of Hepatology and Gastroenterology, Mansoura Specialized Medical Hospital, Dakahlia Governorate, Mansoura 35516, Egypt. a.tonbary@gmail.com
Telephone: +2-100-5100091
Fax: +2-50-2200878

Received: December 6, 2015

Peer-review started: December 7, 2015

First decision: December 22, 2015

Revised: January 5, 2016

Accepted: January 29, 2016

Article in press: January 31, 2016

Published online: March 25, 2016

Abstract

Periampullary diverticulum (PAD) is duodenal outpouching defined as herniation of the mucosa or submucosa that occurs *via* a defect in the muscle layer within an area of 2 to 3 cm around the papilla. Although PAD is

usually asymptomatic and discovered incidentally during endoscopic retrograde cholangiopancreatography (ERCP), it is associated with different pathological conditions such as common bile duct obstruction, pancreatitis, perforation, bleeding, and rarely carcinoma. ERCP has a low rate of success in patients with PAD, suggesting that this condition may complicate the technical application of the ERCP procedure. Moreover, cannulation of PAD can be challenging, time consuming, and require the higher level of skill of more experienced endoscopists. A large portion of the failures of cannulation in patients with PAD can be attributed to inability of the endoscopist to detect the papilla. In cases where the papilla is identified but does not point in a suitable direction for cannulation, different techniques have been described. Endoscopists must be aware of papilla identification in the presence of PAD and of different cannulation techniques, including their technical feasibility and safety, to allow for an informed decision and ensure the best outcome. Herein, we review the literature on this practical topic and propose an algorithm to increase the success rate of biliary cannulation.

Key words: Periampullary diverticulum; Cannulation techniques; Tips; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Presence of periampullary diverticulum (PAD) is thought to complicate the application of endoscopic retrograde cholangiopancreatography, which is already a technically difficult procedure. To improve success rates, different techniques have been developed to achieve successful biliary cannulation in patients with PAD. For patients with PAD, endoscopists must be aware of papilla identification and the different available cannulation techniques, as well as the technical feasibility and safety of each.

Altonbary AY, Bahgat MH. Endoscopic retrograde cholangiopancreatography in periampullary diverticulum: The challenge of cannulation. *World J Gastrointest Endosc* 2016; 8(6): 282-287 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i6/282.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i6.282>

INTRODUCTION

Periampullary diverticulum (PAD) is duodenal outpunching defined as herniation of the mucosa or submucosa that occurs *via* a defect in the muscle layer within an area of 2 to 3 cm around the papilla. Prevalence of PAD increases with age, and overall prevalence among the elderly is reportedly 65%^[1]. The formation of PAD is related to progression of duodenal motility disorders. Furthermore, increased intraduodenal pressure and progressive weakening of intestinal smooth muscles are known as the main underlying etiologies for this defect^[2]. PAD is sub-classified into two categories according to the location of the papilla with respect to the diverticulum. In type I, or peri-diverticular papilla, the papilla is located at the edge of the diverticulum or within a radius of 2 cm from the diverticular edge. In type II, or intra-diverticular papilla (IDP), the papilla is located inside the diverticulum or lying between two adjacent diverticula^[3].

Although PAD is usually asymptomatic and discovered incidentally in patients during endoscopic retrograde cholangiopancreatography (ERCP), it is associated with different pathological conditions such as common bile duct (CBD) obstruction, pancreatitis, perforation, bleeding, and rarely carcinoma^[4-7]. Several hypotheses have been put forth to explain the observed higher incidence of biliary stone formation in the presence of PAD. First, it was proposed that dysfunction in the sphincter of Oddi, which in turn causes reflux of pancreatic fluid and intestinal content, can lead to biliary stone formation^[8]. Second, it was proposed that diverticula cause spasm of the sphincter, thereby increasing biliary tract pressure that may in turn produce jaundice and cholangitis as well as predispose for choledocholithiasis^[9]. Finally, it was proposed that PAD may compress the distal part of the CBD to cause functional biliary stasis, and this hypothesis was supported by the observation of increased incidence of pigment biliary stones^[10,11].

Reported success rates of cannulation in patients with PAD have varied from 61% to 95.4%, a range that is significantly lower than that observed in patients without PAD^[12]. In recent years, new techniques and new devices for successful biliary cannulation have been developed to improve rates of success in patients with PAD. For patients with PAD, endoscopists must be aware of papilla identification and the different cannulation techniques available, including the technical feasibility and safety of each, in order to make an informed decision and ensure the best outcome. Herein, we review the literature on this practical topic that was

obtained through an electronic search of the literature databases of Google Scholar and PubMed using the following terms alone or in combination: ERCP, difficult cannulation, cannulation techniques, and periampullary diverticulum.

TIPS FOR PAPILLARY ORIENTATION AND CANNULATION

The presence of PAD is thought to complicate the application of ERCP, an already technically difficult procedure^[2]. Cannulation of IDP can be challenging, time consuming and require the higher level of skill of more experienced endoscopists. A large portion of the failures of cannulation in patients with PAD has been attributed to inability of the endoscopist to detect the papilla^[6]. However, in some studies, the finding of PAD during an ERCP was suggested as an indicator of an easier cannulation attempt, with a reported success rate of 94.9% compared to that of 94.8% in non-PAD patients after exclusion of cases with undetectable papillas that were considered to be likely IDPs^[7]. In ERCP, identification of the papilla is the first major obstacle, especially in the presence of large diverticula. Thus, it is extremely helpful to know the following tips^[13]: (1) in most cases, the papilla is located on the lower edge of the diverticulum or just inside, somewhere between the positions of 4 o'clock and 8 o'clock; (2) large diverticula are usually divided from proximal to distal by a ridge-like septum. This mostly involves the bile duct, with the ridge terminating at the papilla; (3) a catheter can be used to straighten and evert the folds to identify a hidden papilla within the diverticulum; (4) cannulation with the tip of the duodenoscope within the sac is also possible, but care must be taken to avoid perforation; and (5) in contrast to the usual papillary anatomy, the presence of PAD alters the biliary direction. It is often not acutely angulated superiorly, but runs more directly. Thus, acute angulation of the sphincterotome is not necessary.

TECHNIQUES FOR DIFFICULT CANNULATION

To address cases where the papilla is identified but does not point in a suitable direction for cannulation, the below-described techniques are available for consideration (Table 1).

Two-devices in one-channel method

A biopsy forceps is used to pull the duodenal mucosa adjacent to the papilla, bringing the papillary orifice out of the diverticulum. Another instrument, either a cannula or sphincterotome, is then inserted into the working channel of the endoscope together with the biopsy forceps. With coordination of the two instruments, biliary cannulation can be attempted (Figure 1A). A report of this technique applied to two PAD cases showed successful cannulation for both and with no complications in either (success rate

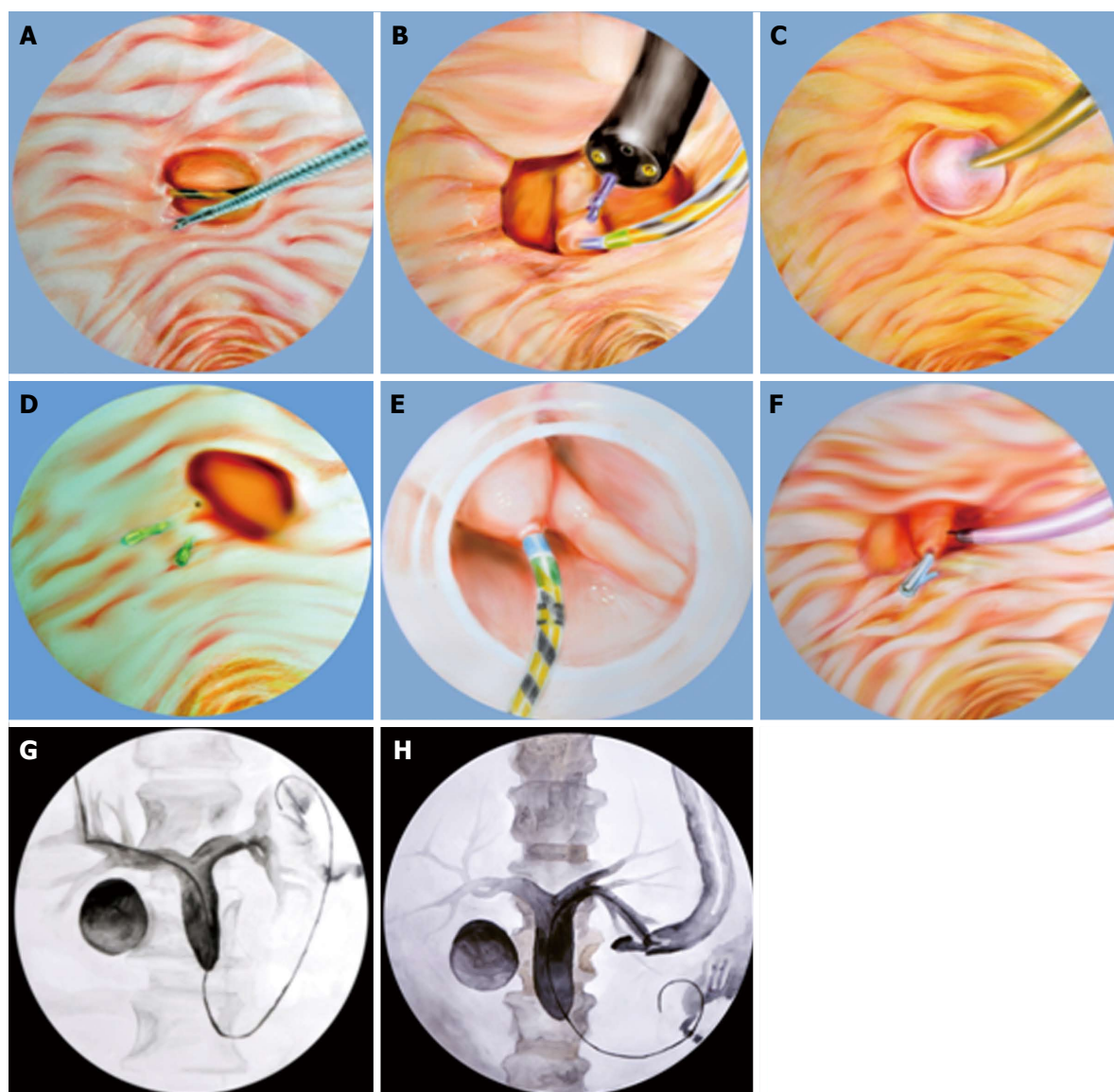


Figure 1 Techniques for difficult cannulation. A: Two-devices in one-channel method; B: Double endoscope method; C: Balloon dilation of the narrow diverticular neck; D: Endoclip-assisted cannulation; E: Cap-assisted cannulation; F: Pancreatic duct stent placement followed by pre-cut biliary sphincterotomy; G: Percutaneous ultrasound-guided rendezvous technique; H: Endoscopic ultrasound-guided rendezvous technique.

Table 1 Techniques for difficult cannulation

Two-devices in one-channel method
Reversed guidewire method
Double endoscope method
Balloon dilation of the narrow diverticular neck
Endoclip-assisted cannulation
Cap-assisted cannulation
Pancreatic duct stent placement followed by pre-cut biliary sphincterotomy
Percutaneous ultrasound-guided rendezvous technique
EUS-guided rendezvous technique

EUS: Endoscopic ultrasound.

100%)^[14].

Reversed guidewire method

A second guidewire is advanced in reverse (stiff end forward) through the working channel of the duo-

denoscope, alongside the sphincterotome. This wire is then used to push the mucosa adjacent to the papilla toward the lumen of the duodenum and to straighten the folds, anchoring the papilla in a better configuration and creating a suitable direction for cannulation. A report of this technique applied to one PAD case showed successful cannulation with no complication (success rate 100%)^[15].

Double endoscope method

A forward-viewing gastroscope is inserted inside the diverticulum for better visualization of the papilla. A foreign body forceps is used to grasp the tissue just beside the papilla in order to bring it into a better orientation. The gastroscope holding the papilla is left in place, to avoid backsliding after opening of the forceps. A side-viewing duodenoscope is inserted alongside the gastroscope. With both endoscopes positioned simu-

Itaneously in the duodenum, the CBD can be cannulated (Figure 1B). A report of this technique applied to one PAD case showed successful cannulation with no complication (success rate 100%)^[16].

Balloon dilation of the narrow diverticular neck

In narrow-necked papillary diverticula with the papilla located in the fundus of the diverticulum, endoscopic balloon dilation of the narrow diverticular neck, using a 15-mm stone retrieval balloon, can be done safely, bringing the papillary orifice into view. Cannulation of the bile duct can be attempted without any complications (Figure 1C). A report of this technique applied to three PAD cases showed successful cannulation and no complications (success rate 100%)^[17].

Endoclip-assisted cannulation

One or more endoclips can be used to rotate the IDP externally and to fix it on the outside rim of the diverticulum. This manipulation can successfully evert and fix the papilla on the diverticular margin in a better position, resulting in successful biliary cannulation (Figure 1D). A report of this technique applied to two PAD cases showed successful cannulation with no complications (success rate 100%)^[18].

Cap-assisted cannulation

A transparent cap is attached to the tip of a forward-viewing endoscope. At first, selective biliary cannulation can be attempted through the papillary orifice. If selective biliary cannulation fails, endoscopic fistulotomy can be attempted. Fistulotomy is performed between the lower two-thirds and the upper one-third of the papillary roof. To gain biliary access after the fistulotomy, needle puncture is made and a soft-tipped guidewire is advanced (Figure 1E). A report of this technique applied to twelve PAD cases showed successful cannulation in all cases (success rate 100%) and a minor complication (bleeding at the site of fistulotomy) in two patients (complications rate 16.5%); primary hemostasis was achieved by hemoclippping in one patient and by saline-epinephrine mixture spray in the other^[19].

Pancreatic duct stent placement followed by pre-cut biliary sphincterotomy

In the case of pancreatic duct cannulation, placement of a main pancreatic duct stent keeps the papilla out of the diverticulum, thereby facilitating pre-cut needle knife sphincterotomy and selective cannulation of the CBD (Figure 1F). A report of this technique applied to eight cases showed successful cannulation in seven of the patients (success rate 87.5%), with two of those requiring a second ERCP for success. In addition, two patients developed post-ERCP pancreatitis (complication rate 25%)^[20].

Percutaneous ultrasound-guided rendezvous technique

After the percutaneous ultrasound-guided transhepatic biliary puncture is performed a sterile guidewire is

inserted into the CBD, then into the papilla. A snare or forceps is then used to grasp the guidewire and pull it back through the working channel of the duodenoscope for subsequent over-the-wire cannulation (Figure 1G)^[21]. However, it is sometimes difficult to grasp the guidewire, which may be damaged or kinked, during the withdrawal through the working channel of the duodenoscope; thus, passing a catheter over it is difficult or sometimes impossible^[22]. A study on the percutaneous-ultrasound guided rendezvous technique applied to a total of fourteen patients showed success in 13 (success rate 93%) with complication (retroperitoneal perforation) experienced in only 1 (complication rate 7%)^[21].

Endoscopic ultrasound-guided rendezvous technique

When the echoendoscope is positioned in the stomach or duodenum, and the bile ducts can be visualized by the endoscopic ultrasound (EUS), a 19-gauge or 22-gauge needle are used to puncture the bile ducts. After aspiration of bile, contrast is injected through the EUS needle to facilitate display the intra- and extra-hepatic bile ducts. After confirmation of bile duct puncture, a guidewire is advanced distally through the CBD and across the papilla under fluoroscopic guidance. The endoscope exchange is performed after passage of the guidewire through the papilla into the duodenum. In this process, the echoendoscope is removed, leaving the guidewire in place, after which a duodenoscope is passed up to the papilla alongside the EUS-placed guidewire. Finally, a snare or forceps is used to grasp the guidewire and pull it back out of the working channel of the duodenoscope for subsequent over-the-wire cannulation. After access to the CBD is achieved, a standard ERCP can be performed (Figure 1H). A study on the EUS-guided rendezvous technique applied to a total of 45 patients showed success in 36 (success rate 80%) with complications (bile leakage and pneumoperitoneum) experienced in only 2 (complication rate 4%)^[23].

PROPOSED ALGORITHM

We propose an algorithm based on the previous techniques to increase the success rate of cannulation (Figure 2). It is important to note, however, that this algorithm has several limitations. First, it is based on a small number of published cases for most of the techniques. Second, the success rates are comparable in most of the techniques and the choice depends on the endoscopist's preference and experience. Finally, percutaneous ultrasound-guided and EUS-guided rendezvous techniques are not available in all centers.

Feasibility and safety of therapeutic maneuvers

When therapeutic maneuvers are performed in patients with PAD the potential risks of complications are a concern, primarily because of the thin mucosa and the absence of sphincter muscle present in the ampullary area^[24]. Currently, endoscopic papillary large balloon dilation (EPLBD) combined with limited endoscopic

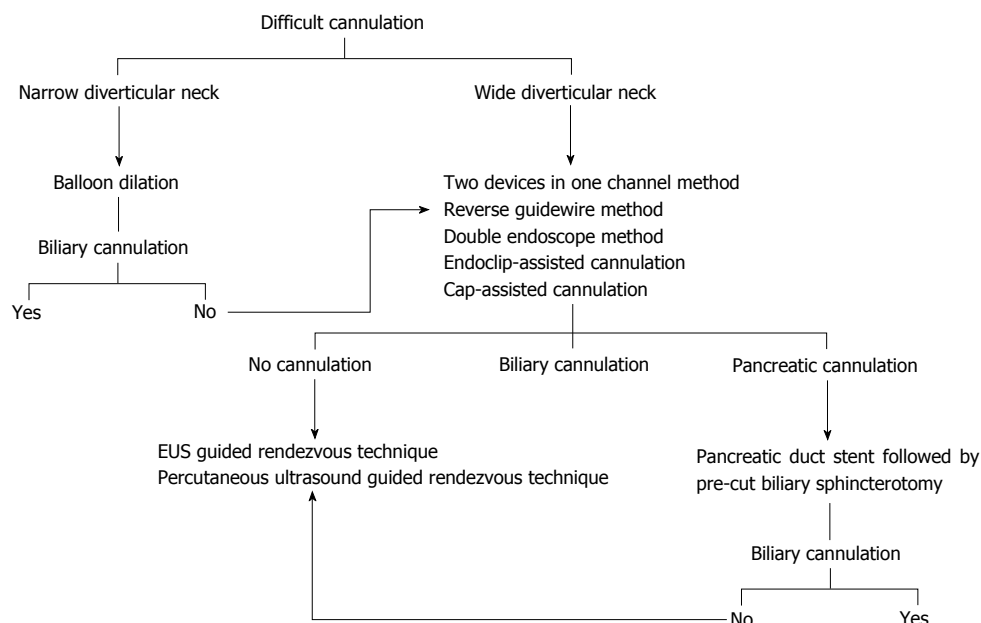


Figure 2 Proposed algorithm to ensure the best outcome. EUS: Endoscopic ultrasound.

sphincterotomy (ES) (EPLBD + ES) is regarded as an effective maneuver for treating difficult CBD stones. It has been reported that perforation and hemorrhage are less frequent in cases treated with EPLBD + ES than in those treated with standard ES alone^[25,26]. The tendency toward a shorter ballooning time in patients with PAD can be explained by the lack of sphincter muscle and the ease of ampullary widening facilitated by EPLBD, which suggest that EPLBD is a safe method for retrieval of CBD stones in patients with PAD^[24]. Moreover, the complication rates of ERCP are similar in patients with or without PAD and the therapeutic outcome is not affected by the presence of PAD^[3,7].

CONCLUSION

PAD represents a technical barrier to the successful application of ERCP. Cannulation of IDP can be challenging, time consuming and require the skill of more experienced endoscopists. In cases where the papilla is identified but does not point in a suitable direction for cannulation, a number of feasible techniques are available for consideration. Moreover, complication rates of ERCP are similar in patients with and without PAD, and therapeutic outcome is not affected by the presence of PAD.

REFERENCES

- 1 Shemesh E, Klein E, Czerniak A, Coret A, Bat L. Endoscopic sphincterotomy in patients with gallbladder in situ: the influence of periampullary duodenal diverticula. *Surgery* 1990; **107**: 163-166 [PMID: 2099745]
- 2 Lobo DN, Balfour TW, Iftikhar SY. Periampullary diverticula: consequences of failed ERCP. *Ann R Coll Surg Engl* 1998; **80**: 326-331 [PMID: 9849331]
- 3 Boix J, Lorenzo-Zúñiga V, Añños F, Domènech E, Morillas

- RM, Gassull MA. Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 208-211 [PMID: 16921297 DOI: 10.1097/00129689-200608000-00002]
- 4 Oddo F, Chevallier P, Souci J, Baque J, Buckley MJ, Fabiani P, Diaine B, Coussement A. [Radiologic aspects of the complications of duodenal diverticula]. *J Radiol* 1999; **80**: 134-140 [PMID: 10209709]
- 5 Yoneyama F, Miyata K, Ohta H, Takeuchi E, Yamada T, Kobayashi Y. Excision of a juxtaapillary duodenal diverticulum causing biliary obstruction: report of three cases. *J Hepatobiliary Pancreat Surg* 2004; **11**: 69-72 [PMID: 15754050 DOI: 10.1007/s00534-003-0854-7]
- 6 Tyagi P, Sharma P, Sharma BC, Puri AS. Periampullary diverticula and technical success of endoscopic retrograde cholangiopancreatography. *Surg Endosc* 2009; **23**: 1342-1345 [PMID: 18818967 DOI: 10.1007/s00464-008-0167-7]
- 7 Panteris V, Vezakis A, Filippou G, Filippou D, Karamanolis D, Rizos S. Influence of juxtaapillary diverticula on the success or difficulty of cannulation and complication rate. *Gastrointest Endosc* 2008; **68**: 903-910 [PMID: 18635174 DOI: 10.1016/j.gie.2008.03.1092]
- 8 Yildiran MI, Başoğlu M, Yılmaz I, Atamanalp SS, Balık AA, Aydınli B, Öztürk G. Periampullary diverticula causing pancreaticobiliary disease. *Dig Dis Sci* 2004; **49**: 1943-1945 [PMID: 15628730 DOI: 10.1007/s10620-004-9597-9]
- 9 Hagège H, Berson A, Pelletier G, Fritsch J, Choury A, Liguory C, Etienne JP. Association of juxtaapillary diverticula with choledocholithiasis but not with cholecystolithiasis. *Endoscopy* 1992; **24**: 248-251 [PMID: 1612038 DOI: 10.1055/s-2007-1010476]
- 10 Miyazaki S, Sakamoto T, Miyata M, Yamasaki Y, Yamasaki H, Kuwata K. Function of the sphincter of Oddi in patients with juxtaapillary duodenal diverticula: evaluation by intraoperative biliary manometry under a duodenal pressure load. *World J Surg* 1995; **19**: 307-312 [PMID: 7754640 DOI: 10.1007/BF00308647]
- 11 Shinagawa N, Fukui T, Mashita K, Kitano Y, Yura J. The relationship between juxtaapillary duodenal diverticula and the presence of bacteria in the bile. *Jpn J Surg* 1991; **21**: 284-291 [PMID: 1906956 DOI: 10.1007/BF02470948]
- 12 Zoepf T, Zoepf DS, Arnold JC, Benz C, Riemann JF. The relationship between juxtaapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients.

- Gastrointest Endosc* 2001; **54**: 56-61 [PMID: 11427842 DOI: 10.1067/mge.2001.115334]
- 13 **Pohl J.** Periampullary Diverticulum: Cannulation and Sphincterotomy. *Video J Encyclop GI Endosc* 2013; **1**: 516-517 [DOI: 10.1016/S2212-0971(13)70226-7]
 - 14 **Fujita N,** Noda Y, Kobayashi G, Kimura K, Yago A. ERCP for intradiverticular papilla: two-devices-in-one-channel method. Endoscopic Retrograde Cholangiopancreatography. *Gastrointest Endosc* 1998; **48**: 517-520 [PMID: 9831843 DOI: 10.1016/S0016-5107(98)70096-3]
 - 15 **Elmunzer BJ,** Boettcher NC. Reverse guidewire anchoring of the papilla for difficult cannulation due to a periampullary diverticulum. *Gastrointest Endosc* 2015; **82**: 957 [PMID: 26142553 DOI: 10.1016/j.gie.2015.05.054]
 - 16 **Külling D,** Haskell E. Double endoscope method to access intradiverticular papilla. *Gastrointest Endosc* 2005; **62**: 811-812 [PMID: 16246708 DOI: 10.1016/j.gie.2005.06.035]
 - 17 **Tóth E,** Lindström E, Fork FT. An alternative approach to the inaccessible intradiverticular papilla. *Endoscopy* 1999; **31**: 554-556 [PMID: 10533741 DOI: 10.1055/s-1999-59]
 - 18 **Huang CH,** Tsou YK, Lin CH, Tang JH. Endoscopic retrograde cholangiopancreatography (ERCP) for intradiverticular papilla: endoclip-assisted biliary cannulation. *Endoscopy* 2010; **42** Suppl 2: E223-E224 [PMID: 20931451 DOI: 10.1055/s-0029-1215008]
 - 19 **Myung DS,** Park CH, Koh HR, Lim SU, Jun CH, Ki HS, Park SY, Rew JS. Cap-assisted ERCP in patients with difficult cannulation due to periampullary diverticulum. *Endoscopy* 2014; **46**: 352-355 [PMID: 24549783]
 - 20 **Fogel EL,** Sherman S, Lehman GA. Increased selective biliary cannulation rates in the setting of periampullary diverticula: main pancreatic duct stent placement followed by pre-cut biliary sphincterotomy. *Gastrointest Endosc* 1998; **47**: 396-400 [PMID: 9609434 DOI: 10.1016/S0016-5107(98)70226-3]
 - 21 **Calvo MM,** Bujanda L, Heras I, Cabriada JL, Bernal A, Orive V, Miguelez J. The rendezvous technique for the treatment of choledocholithiasis. *Gastrointest Endosc* 2001; **54**: 511-513 [PMID: 11577321 DOI: 10.1067/mge.2001.118441]
 - 22 **Dickey W.** Parallel cannulation technique at ERCP rendezvous. *Gastrointest Endosc* 2006; **63**: 686-687 [PMID: 16564873 DOI: 10.1016/j.gie.2005.10.029]
 - 23 **Tarantino I,** Barresi L, Fabbri C, Traina M. Endoscopic ultrasound guided biliary drainage. *World J Gastrointest Endosc* 2012; **4**: 306-311 [PMID: 22816011 DOI: 10.4253/wjge.v4.i7.306]
 - 24 **Kim HG,** Cheon YK, Cho YD, Moon JH, Park do H, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304 [PMID: 19750573 DOI: 10.3748/wjg.v19.i41.7168]
 - 25 **Kim HG,** Cheon YK, Cho YD, Moon JH, Park DH, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304 [PMID: 19750573 DOI: 10.3748/wjg.15.4298]
 - 26 **Minami A,** Hirose S, Nomoto T, Hayakawa S. Small sphincterotomy combined with papillary dilation with large balloon permits retrieval of large stones without mechanical lithotripsy. *World J Gastroenterol* 2007; **13**: 2179-2182 [PMID: 17465497 DOI: 10.3748/wjg.v13.i15.2179]

P- Reviewer: Gkekas I, Kitamura K, Oner OZ **S- Editor:** Qi Y

L- Editor: A **E- Editor:** Liu SQ



Retrospective Cohort Study

Determination of the cut-off score of an endoscopic scoring method to predict whether elderly patients with dysphagia can eat pureed diets

Torao Sakamoto, Akira Horiuchi, Toshiyuki Makino, Masashi Kajiyama, Naoki Tanaka, Masamitsu Hyodo

Torao Sakamoto, Department of Rehabilitation, Showa Inan General Hospital, Komagane 399-4117, Japan

Akira Horiuchi, Toshiyuki Makino, Masashi Kajiyama, Naoki Tanaka, Digestive Disease Center, Showa Inan General Hospital, Komagane 399-4117, Japan

Masamitsu Hyodo, Department of Otolaryngology, Head and Neck Surgery, Kochi Medical School, Kochi Prefecture 783-8505, Japan

Author contributions: All the authors contributed to this paper.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at horichi.akira@sihp.jp.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Akira Horiuchi, MD, Digestive Disease Center, Showa Inan General Hospital, 3230 Akaho, Komagane 399-4117, Japan. horichi.akira@sihp.jp
Telephone: +81-265-822121
Fax: +81-265-822118

Received: October 26, 2015

Peer-review started: October 27, 2015

First decision: December 11, 2015

Revised: December 21, 2015

Accepted: January 16, 2016

Article in press: January 19, 2016

Published online: March 25, 2016

Abstract

AIM: To identify the cut-off value for predicting the ability of elderly patients with dysphagia to swallow pureed diets using a new endoscopy scoring method.

METHODS: Endoscopic swallowing evaluation of pureed diets were done in patients ≥ 65 years with dysphagia. The Hyodo-Komagane score for endoscopic swallowing evaluation is expressed as the sum (0-12) of four degrees (0-3) with four parameters: (1) salivary pooling in the vallecula and piriform sinuses; (2) the response of glottal closure reflex induced by touching the epiglottis with the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" following swallowing of test jelly; and (4) pharyngeal clearance after swallowing of test jelly. We used receiver operating characteristic (ROC) curve analysis to retrospectively analyze the association between the total score and successful oral intake of pureed diets.

RESULTS: One hundred and seventy-eight patients were enrolled including 113 men (63%), mean age 83 years (range, 66-98). One hundred and twenty-six patients (71%) were able to eat pureed diets during the observation period (mean \pm SD, 19 \pm 14 d). In ROC analysis, the cut-off value of the score for eating the pureed diets was 7 (sensitivity = 0.98; specificity = 0.91).

CONCLUSION: The Hyodo-Komagane endoscopic score is useful to predict the ability to eat pureed diets in elderly patients with dysphagia.

Key words: Dysphagia; Endoscopy; Pureed diets; Percutaneous endoscopic gastrostomy

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Predicting successful oral intake in elderly patients with dysphagia remains a challenge. The scoring method for endoscopic swallowing evaluation was based on final score (from 0 to 12) using four parameters; (1) the salivary pooling in the vallecula and piriform sinuses; (2) the response of glottal closure reflex induced by touching the epiglottis with the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" after the swallowing of test jelly; and (4) the extent of pharyngeal clearance after test jelly is swallowed. A total score of 7 or less during endoscopic swallowing evaluation reliably predicted the ability to eat pureed diets.

Sakamoto T, Horiuchi A, Makino T, Kajiyama M, Tanaka N, Hyodo M. Determination of the cut-off score of an endoscopic scoring method to predict whether elderly patients with dysphagia can eat pureed diets. *World J Gastrointest Endosc* 2016; 8(6): 288-294 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i6/288.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i6.288>

INTRODUCTION

With aging of the population, dysphagia is becoming an important medical and social issue^[1]. Pneumonia is the fourth most common cause of mortality in the elderly in Japan; the majority of cases in hospital-acquired pneumonia are reported to be related to aspiration^[2]. Pureed diets are often used as an initial dysphagia diet for patients with moderate to severe dysphagia because, if the dysphagic patients can fulfill their nutritional requirements by eating pureed diets, they can avoid enteral feeding using a percutaneous endoscopic gastrostomy (PEG) tube. Wilkinson *et al*^[3] previously reported PEG should be considered for people unable to tolerate a pureed diet 14 d after their stroke despite the fact that half will recover sufficiently to manage oral intake. They suggested that the texture of the pureed diet is likely to be most useful factor predictive of the need for PEG. No methods for predicting successful oral intake of pureed diets in elderly patients with dysphagia have been established.

Endoscopic and videofluoroscopic examinations are often used to evaluate swallowing and to quantify the risk of aspiration^[4-7]. Our facility uses a team approach that includes a gastroenterologist and a speech therapist. Swallowing is evaluated by endoscopy using an

endoscope normally used for transnasal esophagogastroduodenoscopy. We previously used this approach to study factors that influenced swallowing of pureed diets^[8]. Saliva pooling and pharyngeal residues of pureed foods were shown to predict impaired swallowing of pureed foods. However, endoscopic determination of whether patients could swallow pureed diets was not always reproducible or safe especially for severely dysphagic patients. Irreproducibility was possibly related to variability in the texture and physical characteristics of the pureed diet despite being prepared in the same facility.

We previously developed a scoring system for endoscopic swallowing evaluation using blue-dyed water^[9]. We modified the test meal to contain a test jelly instead of blue-dyed water so that elderly patients with severe dysphagia could undergo endoscopic examination of swallowing safely even unable to swallow pureed diets and the data would be reproducible. The aim of this study was to validate the revised scoring system to predict the ability to eat pureed diets in elderly patients with dysphagia.

MATERIALS AND METHODS

Patients

From January 2012 to November 2014, 205 hospitalized patients who underwent endoscopic swallowing evaluation at Showa Inan General Hospital, a municipal local hospital, were consecutively enrolled. We included dysphagia patients able to sit in a chair or up in bed with assistance and whose oral intake had been observed at least for 5 d after endoscopic swallowing evaluation. Subjects were included irrespective of whether oral intake of dysphagic diets was successful or unsuccessful. Exclusion criteria included an age less than 65 years old or the presence of an acute infection.

Study design

Verbal and written informed consent for the endoscopic examination of swallowing was obtained from all patients. Gastroenterologists, who were experienced in transnasal esophagogastroduodenoscopy and PEG, performed the endoscopic swallowing evaluation along with a speech therapist. Results of endoscopic swallowing examination including the new scoring system (Hyodo-Komagane score) were recorded in the endoscopic database. Determination of the validity of the proposed endoscopic swallowing score was based on a retrospective review of the patients' charts with special attention to the Hyodo-Komagane score and the status of oral intake of diets. This retrospective analysis was approved by the ethics committee of Showa Inan General Hospital.

Procedure

Participants underwent the endoscopic swallowing evaluation while sitting in a chair or sitting up in bed. Two minutes prior to inserting the endoscope, 0.2-0.5

Table 1 Hyodo-Komagane score

A: Salivary pooling in vallecula and piriform sinuses
0 No pooling
1 Pooling at the only vallecula
2 Pooling in vallecula and piriform sinuses and no penetration ¹ into larynx
3 Pooling in vallecula and piriform sinuses and penetration into larynx
B: The response of glottal closure reflex induced by touching the epiglottis with the endoscope
0 Marked reflex by one touching
1 Slow and/or weak reflex by one touching
2 Reflex by two or three touchings
3 No reflex despite three touchings
C: The location of the bolus at the time of swallow onset assessed by "white-out" ² following swallowing of test jelly
0 Pharyngeal
1 Vallecula
2 Piriform sinuses
3 No swallowing
D: The extent of pharyngeal clearance after swallowing of test jelly
0 No residues
1 Pharyngeal residues remain, but are absent after swallowing is attempted two or three times
2 Pharyngeal residues remain, but do not penetrate into larynx
3 Pharyngeal residues remain and penetrate into larynx

¹When saliva or test jelly enters the glottis (opening to the trachea) and moves as far as the vestibule above the true vocal folds, this is termed as "penetration"; ²"white-out" is defined as the period when the videoendoscopic image is obscured owing to pharyngeal closure. Total score (A + B + C + D) = 0-12.

mL of 4% lidocaine was applied to the nasal cavities of each participant using a nasal spray. An endoscope (GIF-XP260N, Olympus, Tokyo, Japan) was used for endoscopic swallowing evaluations. This is a forward-viewing upper gastrointestinal videoscope with an ultra-miniature, resolution charged-coupled device with a 120 degree field of view. The insertion diameter is 5.5 mm and the videoscope has a tip deflection capability of 210/120 up/down in a single plane. The lubricated endoscope was passed transnasally, typically on the floor of the nose, to obtain a superior view of the hypopharynx. The endoscope was moved throughout the study between swallowing and post-swallow positions to collect the data as described previously^[8]. Images of the oropharynx, hypopharynx and larynx were displayed on a monitor and recorded on the digital video recorder (Sony EVO-550H, Tokyo, Japan).

Hyodo-Komagane scoring method

All patients underwent endoscopic swallowing evaluation at least once prior to starting oral intake. First, salivary pooling in the vallecula and piriform sinuses was evaluated. The response of the glottal closure reflex was also evaluated by touching the epiglottis with the tip of endoscope. When glottal closure reflex was not elicited by touching the epiglottis, the result was confirmed by attempting to touch the epiglottis with the endoscope at least three times before absence of glottal closure reflex was declared. The swallowing trial was then performed following ingestion of a 3 mL of test diet contained in a spoon. The interior larynx and airway were examined before and after each swallow for the presence of food within the laryngeal vestibule and/or aspiration of test materials below the true vocal folds. Silent aspiration, defined as lack of cough or gag reflex when the test

materials passed into the trachea, was also noted.

This scoring system was based on our previously clinic-based scoring for endoscopic swallowing evaluation using a blue-dyed water test meal^[9]. Table 1 shows the modified scoring method that consists of four parameters: (1) salivary pooling in the vallecula and piriform sinuses (Figure 1); (2) the response of glottal closure reflex induced by touching the epiglottis with the tip of the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" following swallowing of test jelly; and (4) the extent of pharyngeal clearance after swallowing of test jelly. The four parameters above are scored using a 4 point scale of 0 to 3 (Table 1). The final Hyodo-Komagane score is expressed as the total score (0 to 12) of the four parameters. All patients for whom the endoscopic swallowing evaluation was performed during the time period of the study had the score recorded in the clinical chart.

Test diets

Test jelly, that is gelatin jelly (Isotonic jelly[®], Nutri Co., Ltd., Yokkaichi, Japan) is shown in Figure 2. The characteristics were as follows: Hardness, 5000 N/m²; cohesiveness, 0.4; adhesiveness, 89 J/m³. The swallowing of test jelly was attempted for all subjects who underwent endoscopic swallowing evaluation. When the test jelly was absent from pharyngeal cavity after swallowing was attempted two or three times, swallowing of test jelly was regarded as successful. If swallowing of the test jelly was successful, swallowing of a semi-solid diet (Elental[®] jelly, Ajinomoto Pharmaceutical Co., Tokyo, Japan) and pureed diets was attempted.

The semi-solid diet (Elental[®] jelly) was made by adding a thickening agent (Jelly mix[®], Ajinomoto

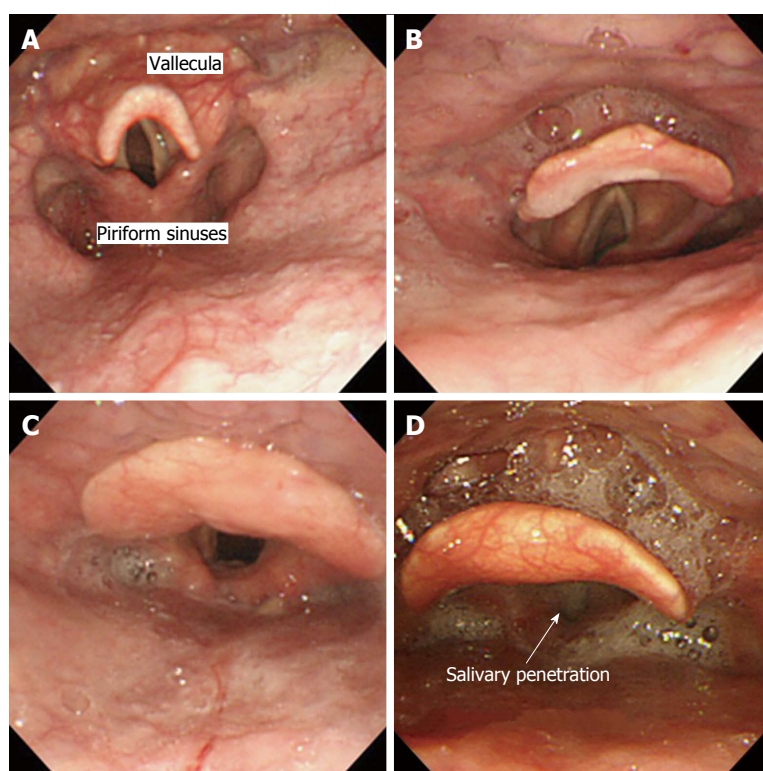


Figure 1 Endoscopic images of Hyodo-Komagane score. Salivary pooling in vallecule and piriform sinuses. A: A-0 no pooling; B: A-1 pooling at the only vallecule; C: A-2 pooling in vallecule and piriform sinuses and no penetration into larynx; D: A-3 pooling in vallecule and piriform sinuses and penetration into larynx.



Figure 2 Test jelly used in this study (Isotonic jelly®, Nutri Co., Ltd., Yokkaichi, Japan).

Pharmaceutical Co.) which contained 11.7% agar, sugar, stabilizer, and other ingredients to an elemental diet, Elental®. The thickening agent (5.8 g) was dissolved with 150 mL of hot water, and 80 g of Elental® was added to the solution which was then cooled to harden. The texture characteristics were: Hardness, $17000 \pm 640 \text{ N/m}^2$; cohesiveness, 0.14 ± 0.0066 ; adhesiveness, $150 \pm 49 \text{ J/m}^3$.

Assessment of oral intake of pureed diets

Except for patients in whom pureed diet was noted to penetrate into the larynx after swallowing the pureed diet, feeding of pureed diets was attempted and assessed once each day by a speech therapist throughout the subjects' hospitalization, irrespective of

Hyodo-Komagane score. When patients were able to eat sufficient pureed diet to meet their daily nutritional requirements for at least 5 d, they were judged to be able to be managed with pureed diets. Dysphagia diets at next higher level were then attempted at the discretion of the speech therapist. The status of oral intake of dysphagia diets was noted.

Statistical analysis

Sensitivity and specificity of variables were based on receiver operating characteristic (ROC) curve analysis. In a ROC curve the true positive rate (sensitivity) is plotted in function of the false positive rate ($100 - \text{specificity}$) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve is a measure of how well a parameter can distinguish between two groups (successful/unsuccessful). Statistical analysis was performed by using JMP® 9.0.2 version software (SAS Institute, Inc., Japan).

RESULTS

One hundred and seventy-eight dysphagic subjects were included in this study. Their demographic and clinical data are shown in Table 2. There were 113 men (63%) with a mean age of 83 years (range: 66-98). Approximately 70% (124 patients) were 80 years and over. Severe comorbid diseases such as cerebrovascular disease (38%), aspiration pneumonia (32%), and

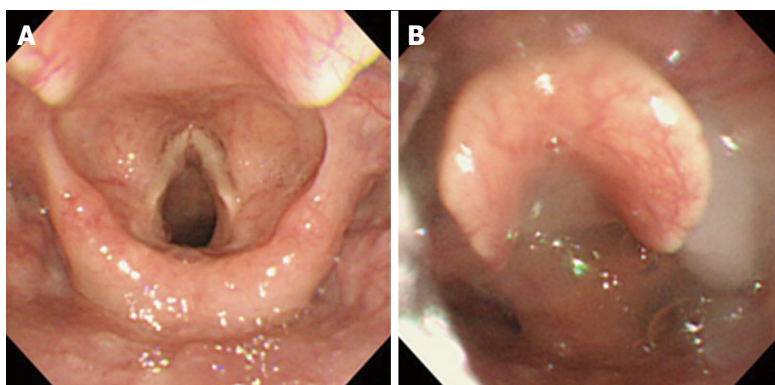


Figure 3 Endoscopic image of Hyodo-Komagane score. A: Before swallowing of test jelly; B: D-3 pharyngeal residues remain and penetrate into larynx after swallowing of test jelly.

Table 2 Demographic and clinical data in 178 patients who underwent endoscopic evaluation of swallowing

	<i>n</i> (%)
Gender male, female	113 (63), 65 (37)
Mean age range (yr)	83 (66-98)
65-69	11 (6)
70-79	43 (24)
80-89	88 (50)
90 and over	36 (20)
Comorbid diseases	
CVD	68 (38)
Aspiration pneumonia	57 (32)
Neuromuscular disease	35 (20)
Others	18 (10)

Values are *n* (%) of patients except for mean age. CVD: Cerebrovascular disease.

neuromuscular disease (20%) were common. Patients who had developed new cerebrovascular disease, myocardial infarction, and aspiration pneumonia within two weeks were not included. Fifty-two patients had remaining pharyngeal residue seen to penetrate into the larynx after swallowing the test jelly (D-3) (Figure 3). In nine of these patients the pureed diet also penetrated into larynx. With these patients feeding trials were not attempted to avoid aspiration pneumonia. In the remaining 169 patients, swallowing trials of the pureed diet were attempted. Overall, 126 (71%) of 178 patients were able to eat pureed diets or a higher level of dysphagia diet that fulfilled their daily nutritional needs [the observation period: Mean \pm SD (range), 19 \pm 14 d (5-58 d)]. The remaining 43 patients were judged to fail the subsequent pureed food tests because the amount they ate was less than their daily nutritional needs.

Figure 4 shows the distribution of Hyodo-Komagane scores among the 178 patients who underwent endoscopic swallowing evaluation (lower scores are better). Using ROC curve analysis of the Hyodo-Komagane scores, the area under the curve was 98.3% (95%CI: 0.097-0.996) (Figure 5). The optimal cut-off value of successful oral intake of pureed diets was a score of 7 (sensitivity = 0.98; specificity = 0.91). In 115 patients

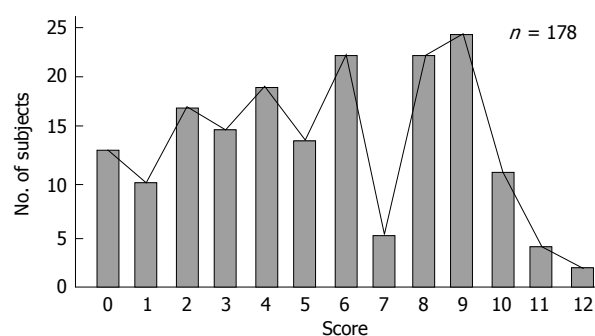


Figure 4 Distribution of a new scoring (Hyodo-Komagane score) in 178 patients undergoing endoscopic evaluation of swallowing.

with Hyodo-Komagane scores of 7 or less only one patient was not able to maintain adequate nutritional status with pureed diets (his Hyodo-Komagane score was 6). Ten (53%) of the 19 patients whose scores were 8 were able to eat pureed diets after a rehabilitation using the semi-solid diet made from an elemental diet. Oral intake of pureed diets was unsuccessful for those with scores of 9 or higher on the Hyodo-Komagane score (Table 3). For patients who could not eat pureed diets, enteral feeding was employed.

Adverse events

No adverse events such as cardiopulmonary events or aspiration pneumonia occurred in included subjects of this study.

DISCUSSION

The aim of this study was to obtain a cut-off value of the Hyodo-Komagane score that reliably predicted the ability to eat pureed diets in elderly patients with dysphagia. The Hyodo-Komagane scoring system differs from the original Hyodo score^[9] with regard to the assessment of salivary pooling in that it uses a test jelly instead of blue-dyed water as the test meal. Jelly was used because it is very difficult for severe dysphagic patients to swallow water. In addition, we previously demonstrated a low agreement in judging the presence or absence of glottal closure response as whether the

Table 3 Association between Hyodo-Komagane score and oral intake of pureed diets

Score	Oral intake of pureed diets
0-7	Successful 100%
8 ¹	Successful in some cases
9-12	Unsuccessful

¹Some patients were able to eat pureed diets after a rehabilitation.

reflex was elicited depended on how and whether the endoscopists actually touched the epiglottis^[9]. Because it is difficult to be confident that the tip of the endoscope touches the epiglottis, we attempted to touch the epiglottis with the endoscope at least three times prior to scoring the reflex of glottal closure as absent. We speculate that this increased the reliability of making that determination and thus the Hyodo-Komagane modification of the scoring system improved both the validity and reliability of Hyodo score.

Dysphasia diets vary considerably from facility to facility. Dysphagia diets are designed to adjust food/liquid intake in terms of amount, consistency, and timing of the meal to achieve maximal nutritional intake and minimize swallowing difficulty. Traditional oral dysphagia diets typically involve a stepwise progression of bolus consistencies. A pureed diet is the basic level of swallowing for severe dysphagia patients. When dysphagia patients can swallow pureed diets, they generally do not require enteral nutrition including PEG^[3,8]. The aim of this study was to develop methods to prospectively assess whether elderly patients with severe dysphagia could eat pureed diets. ROC analysis of this study suggested that the cut-off value of the Hyodo-Komagane score for eating the pureed diets is 7 (sensitivity = 0.98; specificity = 0.91) for predicting successful oral intake of pureed diets in elderly patients with dysphagia.

In the Hyodo-Komagane score the extent of pharyngeal clearance after swallowing of test jelly was regarded as important. Pharyngeal residue has consistently been identified to be greater using endoscopic evaluation of swallowing than when using videofluoroscopy^[10] and penetration/aspiration was also perceived to be more severe with endoscopic evaluation of swallowing compared to videofluoroscopy images^[11]. Penetration/aspiration is thought to be a clinically important variable in patients with swallowing dysfunction and is likely to be associated with an increased risk of aspiration/pneumonia. However, the agreement between the gastroenterologists regarding the presence of penetration/aspiration was found to be poor in our previous study^[8]. Here, we scored penetration/aspiration only when penetration of saliva or the pharyngeal residues of test jelly into the larynx occurred. These phenomena were adopted as A-3 or D-3 in Hyodo-Komagane score.

In addition, the response of glottal closure reflex induced by touching the epiglottis with the endoscope was examined to assess the relationship between the

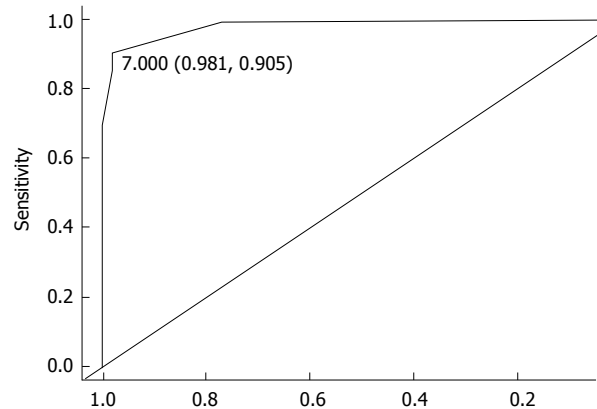


Figure 5 Receiver operating characteristic curve to evaluate the prediction capability of the Hyodo-Komagane score for successful oral intake of pureed diets.

sensory and motor components of the swallow. The relationship between laryngopharyngeal sensation and motor function has been well documented^[12] and patients with impaired pharyngeal squeeze at different levels of sensory deficits are at significantly greater risk for aspiration of pureed foods compared with those with normal squeeze^[13]. While the use of 0.5 mL of 4% lidocaine during endoscopic swallowing evaluation has been reported to impair swallowing ability in patients with dysphagia, this result did not achieve statistical significance and was associated with a reduction in subjective pain and discomfort^[14]. A recent study confirmed that 0.2 mL of 4% lidocaine improved examination tolerability and did not impair the swallowing activity in dysphagic patients during endoscopic swallowing evaluation^[15]. Therefore, we speculated that the amount (0.2-0.5 mL) of lidocaine used in this study had minimal effects on testing the sensory aspects of swallowing.

Our study has some limitations. This study was retrospective and comparative data using established competitive techniques are absent in part because there was no gold standard for detection of failure to swallow. Comparison with the other commonly used method such as with a videofluoroscopic swallowing study may provide useful comparative data in subsequent studies. Finally, all subjects were older than 65 years. It is unknown whether the prediction based on the Hyodo-Komagane endoscopic score are applicable to those less than 65 years old.

In conclusion, the modified scoring method for endoscopic swallowing evaluation was based on final score (from 0 to 12) using four parameters: (1) the salivary pooling in the vallecula and piriform sinuses; (2) the response of glottal closure reflex induced by touching the epiglottis with the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" after the swallowing of test jelly; and (4) the extent of pharyngeal clearance after test jelly is swallowed. A total score of 7 or less during endoscopic swallowing evaluation reliably predicted the ability to eat pureed

diets. The use of the modified scoring system appears to be a reliable method to decide whether the elderly patients can eat pureed diets or requires enteral feeding.

ACKNOWLEDGMENTS

The authors thank David Y Graham, MD for helping with preparation of the manuscript in English.

COMMENTS

Background

Pureed diets are often used as an initial dysphagia diet for patients with moderate to severe dysphagia because, if the dysphagic patients can fulfill their nutritional requirements by eating pureed diets, they can avoid enteral feeding using a percutaneous endoscopic gastrostomy tube. However, no methods for predicting successful oral intake of pureed diets in elderly patients with dysphagia have been established.

Research frontiers

The authors' group pioneered a scoring system for endoscopic swallowing evaluation in elderly patients with dysphagia; the authors think that the method for predicting successful oral intake of pureed diets in elderly patients with dysphagia should be established and they provide support to their hypothesis with this paper, reporting that the Hyodo-Komagane endoscopic score is useful to predict the ability to eat pureed diets in elderly patients with dysphagia.

Innovations and breakthroughs

Endoscopic and videofluoroscopic examinations have been used to evaluate swallowing and to quantify the risk of aspiration. However, endoscopic determination of whether patients could swallow pureed diets was not always reproducible or safe especially for severely dysphagic patients. Irreproducibility was possibly related to variability in the texture and physical characteristics of the pureed diet despite being prepared in the same facility. This paper shows a new scoring system for endoscopic swallowing evaluation using a test jelly so that elderly patients with severe dysphagia can undergo endoscopic examination of swallowing safely even unable to swallow pureed diets; in addition, the cut-off value of the score for eating the pureed diets was defined as 7 (sensitivity = 0.98; specificity = 0.91).

Applications

Elderly patients with dysphagia will benefit from the use of Hyodo-Komagane endoscopic score which is useful to predict the ability to eat pureed diets. If evaluated with this scoring system, avoiding unfavorable enteral feeding.

Terminology

When saliva or test jelly enters the glottis (opening to the trachea) and moves as far as the vestibule above the true vocal folds, this is termed as penetration; aspiration is defined when the test materials passed into the trachea below the true vocal folds. White-out is defined as the period when the videoendoscopic image is obscured owing to pharyngeal closure.

Peer-review

This is a nice study, well-conceived and written.

REFERENCES

1 Annual Health, Labour and Welfare Report, For the Realization

of a Society of Health and Longevity. Ministry of Health, Labour and Welfare, Japan, 2014. Available from: URL: <http://www.mhlw.go.jp/english/wp/wp-hw8/dl/summary.pdf>

- 2 Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. *J Am Geriatr Soc* 2008; **56**: 577-579 [PMID: 18315680 DOI: 10.1111/j.1532-5415.2008.01597.x]
- 3 Wilkinson TJ, Thomas K, MacGregor S, Tillard G, Wyles C, Sainsbury R. Tolerance of early diet textures as indicators of recovery from dysphagia after stroke. *Dysphagia* 2002; **17**: 227-232 [PMID: 12140651 DOI: 10.1007/s00455-002-0060-9]
- 4 Langmore SE, Schatz K, Olson N. Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. *Ann Otol Rhinol Laryngol* 1991; **100**: 678-681 [PMID: 1872520]
- 5 Kidder TM, Langmore SE, Martin BJ. Indications and techniques of endoscopy in evaluation of cervical dysphagia: comparison with radiographic techniques. *Dysphagia* 1994; **9**: 256-261 [PMID: 7805425]
- 6 Wu CH, Hsiao TY, Chen JC, Chang YC, Lee SY. Evaluation of swallowing safety with fiberoptic endoscope: comparison with videofluoroscopic technique. *Laryngoscope* 1997; **107**: 396-401 [PMID: 9121321]
- 7 Leder SB, Sasaki CT, Burrell MI. Fiberoptic endoscopic evaluation of dysphagia to identify silent aspiration. *Dysphagia* 1998; **13**: 19-21 [PMID: 9391224 DOI: 10.1007/PL00009544]
- 8 Sakamoto T, Horiuchi A, Nakayama Y. Transnasal endoscopic evaluation of swallowing: a bedside technique to evaluate ability to swallow pureed diets in elderly patients with dysphagia. *Can J Gastroenterol* 2013; **27**: 459-462 [PMID: 23936875]
- 9 Hyodo M, Nishikubo K, Hirose K. [New scoring proposed for endoscopic swallowing evaluation and clinical significance]. *Nihon Jibiinkoka Gakkai Kaiho* 2010; **113**: 670-678 [PMID: 20845709 DOI: 10.3950/jibiinkoka.113.670]
- 10 Kelly AM, Leslie P, Beale T, Payten C, Drinnan MJ. Fibreoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? *Clin Otolaryngol* 2006; **31**: 425-432 [PMID: 17014453 DOI: 10.1111/j.1749-4486.2006.01292.x]
- 11 Kelly AM, Drinnan MJ, Leslie P. Assessing penetration and aspiration: how do videofluoroscopy and fiberoptic endoscopic evaluation of swallowing compare? *Laryngoscope* 2007; **117**: 1723-1727 [PMID: 17906496 DOI: 10.1097/MLG.0b013e318123e6a]
- 12 Setzen M, Cohen MA, Mattucci KF, Perlman PW, Ditkoff MK. Laryngopharyngeal sensory deficits as a predictor of aspiration. *Otolaryngol Head Neck Surg* 2001; **124**: 622-624 [PMID: 11391251 DOI: 10.1067/mhn.2001.116035]
- 13 Perlman PW, Cohen MA, Setzen M, Belafsky PC, Guss J, Mattucci KF, Ditkoff M. The risk of aspiration of pureed food as determined by flexible endoscopic evaluation of swallowing with sensory testing. *Otolaryngol Head Neck Surg* 2004; **130**: 80-83 [PMID: 14726914 DOI: 10.1016/j.otohns.2003.09.026]
- 14 Fife TA, Butler SG, Langmore SE, Lester S, Wright SC, Kemp S, Grace-Martin K, Lintzenich CR. Use of topical nasal anesthesia during flexible endoscopic evaluation of swallowing in dysphagic patients. *Ann Otol Rhinol Laryngol* 2015; **124**: 206-211 [PMID: 25204714 DOI: 10.1177/0003489414550153]
- 15 O'Dea MB, Langmore SE, Krisciunas GP, Walsh M, Zanchetti LL, Scheel R, McNally E, Kaneoka AS, Guarino AJ, Butler SG. Effect of Lidocaine on Swallowing During FEES in Patients With Dysphagia. *Ann Otol Rhinol Laryngol* 2015; **124**: 537-544 [PMID: 25667217 DOI: 10.1177/0003489415570935]

P-Reviewer: Garg P S-Editor: Qi Y
L-Editor: A E-Editor: Liu SQ



Retrospective Study

Use of automated irrigation pumps improves quality of bowel preparation for colonoscopy

Sujan Ravi, Rana Sabbagh, Fadi Antaki

Sujan Ravi, Department of Internal Medicine, University of Alabama at Birmingham, Birmingham, AL 35233, United States

Sujan Ravi, Rana Sabbagh, Fadi Antaki, Division of Gastroenterology, John D. Dingell Veterans Affairs Medical Center and Wayne State University School of Medicine, Detroit, MI 48201, United States

Sujan Ravi, Rana Sabbagh, Detroit Medical Center, Detroit, MI 48201, United States

Author contributions: Ravi S, Sabbagh R and Antaki F designed the study; Ravi S and Sabbagh R collected data; Ravi S and Antaki F performed data analysis and interpretation, drafting of manuscript and draft revision; Ravi S, Sabbagh R and Antaki F approved the final manuscript.

Supported by Resources and the use of facilities at the John D. Dingell VA Medical Center, Detroit, MI, United States (the views expressed in this article are those of the authors and do not represent those of the Department of Veterans Affairs or the United States Government).

Institutional review board statement: The study was approved by the Wayne State University Institutional Review Board (IRB# 025911M1E(V)) and the John D. Dingell Veterans Affairs Medical Center Research Committee.

Informed consent statement: A waiver of informed consent was granted by the Wayne State University Institutional Review Board (IRB) as the study satisfied the following criteria: (1) risk is no more than minimal, (2) the waiver does not adversely affect the rights and welfare of research participants and (3) the research could not be practicably carried out without the waiver. All research participants had signed informed consent for the colonoscopy procedure.

Conflict-of-interest statement: None of the authors have any financial conflict of interest in relationship to the submitted manuscript.

Data sharing statement: No other data is available.

Open-Access: This article is an open-access article which was

selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Fadi Antaki, MD, AGAF, Associate Professor of Medicine, Division of Gastroenterology, John D. Dingell Veterans Affairs Medical Center and Wayne State University School of Medicine, 4646 John R Road, C-3825, Detroit, MI 48201, United States. fadi.antaki@va.gov
Telephone: +1-313-5763389
Fax: +1-313-5761237

Received: June 28, 2015

Peer-review started: July 6, 2015

First decision: August 16, 2015

Revised: October 23, 2015

Accepted: January 16, 2016

Article in press: January 19, 2016

Published online: March 25, 2016

Abstract

AIM: To evaluate the effectiveness of automated irrigation pumps (AIPs) in improving the quality of the bowel preparation and the yield of colonoscopy.

METHODS: A retrospective observational study was conducted at a single medical center. Outpatient colonoscopies performed during a 4-mo time period when AIPs were not in use, were compared to colonoscopies performed during control period. The main outcomes measured were quality of bowel preparation, procedures aborted due to poor preparation, recommendations to repeat at short interval due to sub-optimal bowel preparation and adenoma detection rates.

RESULTS: One thousand and thirty-seven colonoscopies were included. A higher proportion of cases did not achieve a satisfactory bowel preparation when AIPs were not used (24.4% *vs* 10.3%, $P < 0.01$). The number of procedures aborted due to inadequate preparation was not significantly different, however a repeat procedure at a short interval was recommended in a higher proportion of cases when AIPs were not used (21.3% *vs* 6.9%, $P < 0.01$). Good or excellent preparation was 2.91 (95%CI: 2.04-4.15) times more likely when AIPs were used. Detection of polyps and adenomas was not significantly different.

CONCLUSION: AIP use during colonoscopy results in a higher proportion of colonic preparation rated as satisfactory, although polyp detection rate is not significantly affected. Recommendations for repeat colonoscopy at shorter interval significantly decrease with the use of AIPs. This study supports the use of the irrigation pumps in endoscopy units to improve the quality of colonoscopy.

Key words: Automated irrigation pumps; Adenoma; Quality; Polyps; Bowel preparation; Surveillance interval; Colonoscopy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The use of automated irrigation pumps during colonoscopy results in higher quality of preparation and decreases recommendations for repeating colonoscopy at short interval.

Ravi S, Sabbagh R, Antaki F. Use of automated irrigation pumps improves quality of bowel preparation for colonoscopy. *World J Gastrointest Endosc* 2016; 8(6): 295-300 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i6/295.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i6.295>

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer deaths in the United States^[1,2]. Colonoscopy is used for screening to detect early cancer, and may also prevent CRC by detection and removal of the CRC neoplastic precursor, the adenomatous polyp^[3-5]. Improving the yield of colonoscopy has attracted much attention in recent years^[6]. In the past, manual irrigation using water-filled syringes, was used to clean any retained fecal matter or colonic contents, in order to allow for a detailed examination of the colonic mucosa and therefore to improve the yield of colonoscopy^[7,8]. Automated irrigation pumps (AIPs), which are operated by a foot pedal and connect to the auxiliary channel of newer generation endoscopes have largely replaced the manual irrigation method, as they are much more efficient and

convenient. It is, however, not known whether the AIPs increase the detection of polyps during colonoscopy when compared to the manual method. Moreover, the efficacy of these AIPs in decreasing the rate of procedures prematurely repeated due to inadequate bowel preparation has also never been studied. The aim of this study is to evaluate the effectiveness of AIPs in improving the quality of the bowel preparation, improving the yield of colonoscopy and decreasing the rate of repeat colonoscopy for inadequate bowel preparation.

MATERIALS AND METHODS

Study design

The study was conducted at the John D. Dingell Veterans Affairs Medical Center (JDDVAMC) in Detroit, Michigan. It was approved by the Wayne State University Institutional Review Board and the JDDVAMC Research Committee.

A retrospective chart review was performed for colonoscopies completed during the study periods. The use of AIPs was suspended at the endoscopy unit of the JDDVAMC for a period of 4 mo in 2009 for administrative reasons; therefore patients who underwent colonoscopy during this period constituted the main study group. For these procedures, manual irrigation was performed at the request of endoscopist, when retained fecal or bilious material was encountered. It was done by a technician using syringes filled with 60 mL of sterile water through the suction channel of the endoscope. Patients who underwent colonoscopy in an eight-month period in 2008 and 2009 constituted the control groups. They were selected to match the level of training of the gastroenterology fellows involved and the calendar year of the study group. Standard bowel preparation for both groups consisted of conventional dosing of a 4-L polyethylene glycol solution and 15 mg of Bisacodyl the evening prior to endoscopy. Colonoscopies that were aborted due to reasons other than poor colonic preparations, procedures repeated at a short interval (such as for follow-up after piecemeal polypectomy), colonoscopies performed on hospitalized patients, and those performed by non-gastroenterologists were excluded from the study.

Information was collected by review of the medical records about each patient's demographics, indication for the procedure, history of prior adenomatous polyps or cancer, involvement of a gastroenterology fellow, use of the AIPs, quality of the colonic preparation, detection of polyps and adenomas, with all associated details, and if the procedure was aborted due to sub-optimal preparation or if it was advised to repeat the procedure sooner than recommended by guidelines due to the quality of the preparation.

Colonoscopy was performed using Olympus Q160 and Q180 endoscopes (Olympus America Inc., Center Valley, PA). Some procedures were performed by an

Table 1 Baseline characters of the study population

	Manual flushes	Automated irrigation pumps	<i>P</i> value
<i>n</i>	328	709	
Age, yr (mean, 95%CI)	60.0 (59.0-61.1)	60.3 (59.6-61.1)	0.70
Gender, <i>n</i> (%)			0.34
Female	18 (5.5)	49 (6.9)	
Male	310 (94.5)	660 (93.1)	
Race, <i>n</i> (%)			0.47
African-American	176 (53.7)	359 (50.6)	
Caucasian	146 (44.5)	341 (48.1)	
Others	6 (1.8)	9 (1.3)	
Performed by: <i>n</i> (%)			0.42
Attending physician alone	65 (19.8)	156 (22.0)	
GI fellow with attending physician	263 (80.2)	553 (78.0)	
Indications, <i>n</i> (%)			0.09
Screening	191 (58.2)	373 (52.6)	
Diagnostic	137 (41.8)	336 (47.4)	
History of CRC/polyps, <i>n</i> (%)			0.55
No	238 (72.6)	527 (74.3)	
Yes	90 (27.4)	182 (25.7)	

GI: Gastroenterology; CRC: Colorectal cancer.

attending physician alone (board-certified in Gastroenterology), while, in other cases, the attending physician directly supervised a gastroenterology fellow. Attending physicians involved in the procedures were the same during the different study periods. AIPs (OPF, Olympus America Inc., Center Valley, PA) were available in every procedure room and routinely connected to the endoscope during the control period. Indications for colonoscopy were classified into either screening or diagnosis. The bowel preparation was determined by the attending physician for every case and reported in the endoscopy report using the Aronchick scale^[9], as excellent, good, fair or poor. For our study, we considered the bowel preparation to be satisfactory if the procedure report described it as either good or excellent, no retained fecal material was mentioned in the findings and no recommendation for repeat at short interval for sub-optimal bowel preparation was made.

The primary outcomes were quality of the bowel preparation and the number of procedures aborted or repeated early due to sub-optimal preparation. The secondary outcomes evaluated were detection rates for polyps and adenomas.

Statistical analysis

SAS version 9.3 (SAS Institute, Cary, NC) was used for statistical analyses. For the preliminary descriptive analyses, χ^2 test was used for the description of categorical variables and a two-sided *t*-test was used for continuous variables for the comparison of means. Multivariable logistic regression model was used to compare the outcomes between the groups. Odds ratio was considered to be statistically significant if the *P* value was less than 0.05.

RESULTS

Information was collected for a total of 1037 colono-

scopies. AIPs were used for 709 procedures. Mean age of the group was 60.23 years. Majority was male (93.5%). The study group included 535 (51.6%) African-Americans and 487 (47%) Caucasians. Five hundred and sixty-four colonoscopies were performed for screening or surveillance (54.4%), while 473 (45.6%) were performed for diagnostic purposes. Two hundred and seventy-two (26.2%) of the patients had a prior history of polyps/CRC. The two groups were not significantly different in the demographic factors, endoscopist, indication for the procedure or history of polyps or CRC (Table 1).

A significantly higher proportion of cases did not achieve a satisfactory bowel preparation when manual flushes were used as compared to when AIPs were used (24.4% vs 10.3%, *P* < 0.01) (Table 2). Although the number of procedures aborted due to poor preparation was slightly higher in the group with manual flushes, this was not statistically different (*P* = 0.10). However a repeat procedure at a short interval was recommended in a significantly higher proportion of cases when manual flushes were used (21.3% vs 6.9%, *P* < 0.01). On multivariate logistic regression analysis, after adjusting for indication, history of polyps or CRC, sex, age and race, odds of calling bowel preparation satisfactory was 2.91 (95%CI: 2.04-4.15) times more likely when AIPs were used in comparison to manual flushes. When adjusted for the same variables, the detection of polyps and adenomas was not significantly different between the two groups.

DISCUSSION

Colonoscopy is a cost-effective (USD 11900 per year of life gained)^[10] tool for screening and prevention of CRC through the detection and removal of pre-cancerous, adenomatous polyps. However sub-optimal bowel preparation limits the effectiveness of colonoscopy as it

Table 2 Colonoscopy results stratified by the use of the automated irrigation pumps

	Manual flushes	Automated irrigation pumps	Odds ratio (95%CI) P value
<i>n</i>	328	709	
Prep quality, <i>n</i> (%)			2.91 (2.04-4.15) <i>P</i> < 0.01
Sub-optimal prep	80 (24.4)	73 (10.3)	
Satisfactory prep	248 (75.6)	636 (89.7)	
Procedure aborted due to poor prep, <i>n</i> (%)			2.45 (0.92-6.50) <i>P</i> = 0.10
No	323 (98.5)	684 (96.5)	
Yes	5 (1.5)	25 (3.5)	
Recommendation to repeat early due to prep quality, <i>n</i> (%)			0.27 (0.18-0.40) <i>P</i> < 0.01
No	258 (78.7)	660 (93.1)	
Yes	70 (21.3)	49 (6.9)	
Polyp detection, <i>n</i> (%)			0.85 (0.64-1.12) <i>P</i> = 0.60
Yes	194 (59.2)	407 (57.4)	
No	134 (40.8)	302 (42.6)	
Adenoma detection, <i>n</i> (%)			0.99 (0.75-1.31) <i>P</i> = 0.65
Yes	133 (40.6)	298 (42.0)	
No	195 (59.4)	411 (58.0)	

can result in a higher than usual rate of missed polyps, which can lead to interval cancers^[11]. Studies have shown that endoscopists do not always follow guidelines and frequently recommend repeat colonoscopy at a shorter interval than suggested by those guidelines^[12,13]. This makes colonoscopy less cost-effective as a CRC screening modality. The reasons for such recommendations are not well known^[12], however the fear of missed lesions when bowel preparation is sub-optimal is probably a major factor^[14].

For all these reasons, a lot of attention has been paid in recent years towards improving the quality of bowel preparation, such as multiple studies comparing different types and brands of laxatives used for bowel preparation, as well as the recommended changes in the timing of those laxatives to "split dose"^[15].

However, there has not been much research to evaluate the effectiveness of AIPs in enhancing the adenoma detection rate, improving the quality of bowel preparation or decreasing the rate of procedures prematurely aborted and repeated due to inadequate bowel preparation. Our study supports the hypothesis that the use of AIPs during colonoscopy results in a significantly higher proportion of colonic preparation being rated as satisfactory with a corresponding decline in the odds of recommending a repeat procedure at a shorter than usual interval.

Our study results are in concurrence with other studies evaluating the relationship between quality of the bowel prep and the recommendation from the endoscopist about the timing of the repeat procedure^[16-18]. As colonoscopy is usually aborted when the bowel preparation is very poor and unlikely to be improved with any type of irrigation, manual or automated, there was no difference in the rate of procedures aborted for poor

preparation in our study.

Although studies have shown an increase in adenoma and polyp detection rate with improvement in the quality of bowel prep^[16,19-21], we did not find an increased rate of adenoma or polyp detection with the use of AIPs, despite the improvement in the quality of the bowel preparation. We believe this could possibly be from the heightened vigilance of the endoscopist when the use of AIPs was suspended for a limited period of time in our unit, and the results might have been different if the AIPs were introduced for the first time during the study.

The study has a few limitations. The retrospective design has some inherent limitations. The determination of the quality of preparation was based on each individual endoscopist's interpretation on the Aronchick scale. Withdrawal time was not routinely recorded in our endoscopy unit at the time of the study. The influence of cleaning using manual flushes or AIPs on total procedure as well as on withdrawal times, which might be different depending on the quality of the bowel preparation, could not be determined. The total volume of water used in either group was not recorded. Although the devices were routinely connected to the endoscope for every single case in the AIPs group, while they were not available in the other group, we could not determine if irrigation by either method was indeed used in every case. Some of the information that could influence adenoma detection rate such as lifestyle and dietary habits could not be evaluated. The sample in itself included both diagnostic and screening colonoscopies. We attempted to alleviate the bias by adjusting for indication of colonoscopy. In addition, our study population was from a Veterans Affairs medical center with a majority of African-American males. This

might limit the generalizability of the results of the study. The suspension of the use of AIPs for a period of time might by itself have led to results that could be different if AIPs were being introduced to an endoscopy unit for the first time. As we used the conventional bowel preparation regimen in our endoscopy unit at the time of the study, we could not evaluate the usefulness of AIPs with split dose bowel regimen.

In conclusion, our study provides evidence that AIPs improve the endoscopist assessment of the quality of the bowel preparation and reduce the number of repeat procedures due to sub-optimal preparation. This supports the widespread use of these devices in endoscopy units to improve the quality of colonoscopy.

COMMENTS

Background

Colonoscopy is used for screening to detect early cancer, and may also prevent colorectal cancer (CRC) by detection and removal of the CRC neoplastic precursor, the adenomatous polyp. Automated irrigation pumps (AIPs), which are operated by a foot pedal and connect to the auxiliary channel of newer generation endoscopes have largely replaced the manual irrigation method, as they are much more efficient and convenient. It is, however, not known whether the AIPs increase the detection of polyps during colonoscopy when compared to the manual method. Moreover, the efficacy of these AIPs in decreasing the rate of procedures prematurely repeated due to inadequate bowel preparation has also never been studied.

Research frontiers

AIPs, which are operated by a foot pedal and connect to the auxiliary channel of newer generation endoscopes have largely replaced the manual irrigation method, as they are much more efficient and convenient.

Innovations and breakthroughs

The aim of this study is to evaluate the effectiveness of AIPs in improving the quality of the bowel preparation, improving the yield of colonoscopy and decreasing the rate of repeat colonoscopy for inadequate bowel preparation.

Applications

This study provides evidence that AIPs improve the endoscopist assessment of the quality of the bowel preparation and reduce the number of repeat procedures due to sub-optimal preparation. This supports the widespread use of these devices in endoscopy units to improve the quality of colonoscopy.

Peer-review

This manuscript by Ravi *et al* describes a retrospective evaluation of patients receiving colonoscopy performed with manual irrigation or an automatic irrigation device. The manuscript is certainly relevant to modern endoscopic practices.

REFERENCES

- 1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71-96 [PMID: 18287387 DOI: 10.3322/CA.2007.0010]
- 2 American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society, 2014
- 3 Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Wayne JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]
- 4 Bokemeyer B, Bock H, Huppe D, Duffelmeyer M, Rambow A, Tacke W, Koop H. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. *Eur J Gastroenterol Hepatol* 2009; **21**: 650-655 [DOI: 10.1097/MEG.0b013e32830b8ac]
- 5 Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; **343**: 162-168 [PMID: 10900274]
- 6 Imperiale TF, Glowinski EA, Juliar BE, Azzouz F, Ransohoff DF. Variation in polyp detection rates at screening colonoscopy. *Gastrointest Endosc* 2009; **69**: 1288-1295 [PMID: 19481649 DOI: 10.1016/j.gie.2007.11.043]
- 7 Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005; **61**: 378-384 [PMID: 15758907]
- 8 Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003; **58**: 76-79 [PMID: 12838225]
- 9 Aronchick CLW, Wright S, DuFrane F, Bergman G. Validation of an instrument to assess colon cleansing. *AM J Gastroenterol* 1999; **94**: 2667
- 10 Maciosek MV, Solberg LI, Coffield AB, Edwards NM, Goodman MJ. Colorectal cancer screening: health impact and cost effectiveness. *Am J Prev Med* 2006; **31**: 80-89 [PMID: 16777546]
- 11 Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; **150**: 1-8 [PMID: 19075198]
- 12 Saini SD, Nayak RS, Kuhn L, Schoenfeld P. Why don't gastroenterologists follow colon polyp surveillance guidelines?: results of a national survey. *J Clin Gastroenterol* 2009; **43**: 554-558 [PMID: 19542818 DOI: 10.1097/MCG.0b013e31818242ad]
- 13 Mysliwiec PA, Brown ML, Klabunde CN, Ransohoff DF. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. *Ann Intern Med* 2004; **141**: 264-271 [PMID: 15313742]
- 14 Menees SB, Kim HM, Elliott EE, Mickevicius JL, Graustein BB, Schoenfeld PS. The impact of fair colonoscopy preparation on colonoscopy use and adenoma miss rates in patients undergoing outpatient colonoscopy. *Gastrointest Endosc* 2013; **78**: 510-516 [PMID: 23642491 DOI: 10.1016/j.gie.2013.03.1334]
- 15 Cohen B, Tang RS, Groessl E, Herrin A, Ho SB. Effectiveness of a simplified "patient friendly" split dose polyethylene glycol colonoscopy prep in Veterans Health Administration patients. *J Interv Gastroenterol* 2012; **2**: 177-182 [PMID: 23687605]
- 16 Lebwohl B, Kastrinos F, Glick M, Rosenbaum AJ, Wang T, Neugut AI. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest Endosc* 2011; **73**: 1207-1214 [PMID: 21481857 DOI: 10.1016/j.gie.2011.01.051]
- 17 Ben-Horin S, Bar-Meir S, Avidan B. The impact of colon cleanliness assessment on endoscopists' recommendations for follow-up colonoscopy. *Am J Gastroenterol* 2007; **102**: 2680-2685 [PMID: 17714555]
- 18 Menees SB, Elliott E, Govani S, Anastassiades C, Judd S, Urganus A, Boyce S, Schoenfeld P. The impact of bowel cleansing on follow-up recommendations in average-risk patients with a normal colonoscopy. *Am J Gastroenterol* 2014; **109**: 148-154 [PMID: 24496417 DOI: 10.1038/ajg.2013.243]
- 19 Adler A, Wegscheider K, Lieberman D, Aminalai A, Aschenbeck J, Drossel R, Mayr M, Mroß M, Scheel M, Schröder A, Gerber K, Stange G, Roll S, Gauger U, Wiedenmann B, Altenhofen L, Rosch T. Factors determining the quality of screening colonoscopy: a prospective study on adenoma detection rates, from 12,134 examinations (Berlin colonoscopy project 3, BECOP-3). *Gut* 2013; **62**: 236-241 [PMID: 22442161 DOI: 10.1136/gutjnl-2011-300167]
- 20 Chokshi RV, Hovis CE, Hollander T, Early DS, Wang JS. Prevalence of missed adenomas in patients with inadequate bowel

- preparation on screening colonoscopy. *Gastrointest Endosc* 2012; **75**: 1197-1203 [PMID: 22381531 DOI: 10.1016/j.gie.2012.01.005]
- 21 **Sherer EA**, Imler TD, Imperiale TF. The effect of colonoscopy

preparation quality on adenoma detection rates. *Gastrointest Endosc* 2012; **75**: 545-553 [PMID: 22138085 DOI: 10.1016/j.gie.2011.09.022]

P- Reviewer: Alberti LR, Chow WK, Kim BW, Pauli E
S- Editor: Song XX **L- Editor:** A **E- Editor:** Liu SQ



Retrospective Study

Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis

Yutaka Hirayama, Takafumi Ando, Yoshiki Hirooka, Osamu Watanabe, Ryoji Miyahara, Masanao Nakamura, Takeshi Yamamura, Hidemi Goto

Yutaka Hirayama, Takafumi Ando, Osamu Watanabe, Ryoji Miyahara, Masanao Nakamura, Hidemi Goto, Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

Yoshiki Hirooka, Takeshi Yamamura, Department of Endoscopy, Nagoya University Hospital, Nagoya 466-8550, Japan

Author contributions: Hirayama Y contributed to planning, data collection, clinical examination, statistical analysis, and drafting the manuscript; Ando T contributed to planning, data collection, statistical analysis, clinical examination, and drafting the manuscript; Miyahara R contributed to data collection and clinical examination; Watanabe O, Nakamura M and Yamamura T contributed to planning, data collection, and clinical examination; Hirooka Y contributed to clinical examination; Goto H contributed to manuscript direction, and critical review of the manuscript.

Institutional review board statement: The study protocol was reviewed and approved by the institutional review board of Nagoya University Graduate School of Medicine.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to examination, treatment, and data sharing by written consent.

Conflict-of-interest statement: No conflict of interest exists for any authors with regard to the content of this study.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

[licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)

Correspondence to: Takafumi Ando, MD, PhD, Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. takafumiando-gi@umin.ac.jp
Telephone: +81-52-7442144
Fax: +81-52-7442175

Received: June 20, 2015

Peer-review started: June 25, 2015

First decision: August 31, 2015

Revised: December 16, 2015

Accepted: January 16, 2016

Article in press: January 19, 2016

Published online: March 25, 2016

Abstract

AIM: To identify characteristic endoscopic findings and risk factors for cytomegalovirus (CMV)-associated colitis in patients with active ulcerative colitis (UC).

METHODS: A total of 149 UC patients admitted to the Department of Gastroenterology, Nagoya University Hospital, from January 2004 to December 2013 with exacerbation of UC symptoms were enrolled in this retrospective study. All medical records, including colonoscopy results, were reviewed. CMV infection was determined by the presence of CMV antigen, CMV inclusion bodies in biopsy specimens, or positive specific immunohistochemical staining for CMV. Multivariate analysis was used to identify independent risk factors for CMV colitis.

RESULTS: Multivariate analysis indicated independent associations with the extent of disease (pancolitis) and

use of > 400 mg corticosteroids for the previous 4 wk. In contrast, no association was seen with sex, age at UC diagnosis, immunomodulator use, or infliximab use. Punched-out ulceration was also significantly associated with CMV infection in patients with active UC (odds ratio = 12.672, 95%CI: 4.210-38.143).

CONCLUSION: Identification of a total corticosteroid dose > 400 mg for 4 wk, extensive colitis and a specific endoscopic finding of punched-out ulcer might facilitate the more rapid diagnosis and timely initiation of antiviral therapy for CMV-associated colitis in patients with active UC.

Key words: Colonoscopy; Risk factor; Ulcerative colitis; Antigenemia; Cytomegalovirus

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: It has been reported that cytomegalovirus (CMV) infection can be associated with steroid resistance and be an exacerbating factor in ulcerative colitis (UC). This paper provides important information regarding characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC. A total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis. In addition, punched-out ulceration appears predictive of CMV-associated colitis in active UC.

Hirayama Y, Ando T, Hirooka Y, Watanabe O, Miyahara R, Nakamura M, Yamamura T, Goto H. Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis. *World J Gastrointest Endosc* 2016; 8(6): 301-309 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i6/301.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i6.301>

INTRODUCTION

Cytomegalovirus (CMV), a member of the double-stranded DNA human herpes virus family, is reported to infect between 40% and 100% of the general population^[1]. Primary CMV infection is asymptomatic or minimally symptomatic, and is followed by a latent state, similar to other herpes virus infections^[2,3]. Most cases of symptomatic CMV infection are therefore caused by reactivation of latent virus^[1-3].

Although active CMV infection can occur in immunocompetent individuals, it occurs most frequently in immunocompromised patients, such as those with acquired immunodeficiency syndrome, leukemia patients during chemotherapy, and patients on high-dose immunosuppressants (e.g., recipients of solid organ or bone marrow transplants)^[1,4-7].

Powell *et al*^[8] reported that CMV infection in patients

with ulcerative colitis (UC) was associated with exacerbation of symptoms, while one early retrospective study reported the presence of CMV in surgical specimens of patients who underwent colectomy for the treatment of toxic megacolon or steroid-resistant UC^[9]. However, the significance of CMV infection in inflammatory bowel disease (IBD) is still controversial, and the pathogenic role of CMV infection in IBD is debated: Some authors believe that CMV is only an "innocent bystander" and does not significantly impact outcome, whereas many other studies have reported a significant association between CMV infection and IBD^[10-13].

Active CMV infection has been observed in UC patients receiving high-dose corticosteroid therapy^[13-17]. From 27% to 100% of patients with steroid-refractory UC have been found to harbor CMV, and steroid resistance is one of the central characteristics of CMV infection in UC patients^[9,16,18-21]. Moreover, multiple studies have concluded that CMV infection can be an exacerbating factor in UC patients and that UC prognosis is generally poor in patients with CMV if anti-viral therapy is not started at an early stage^[2,3,13-15,21-23].

Thus, CMV infection may exacerbate UC and may even cause death if appropriate treatment is not given. Although the development of ganciclovir (GCV) antiviral therapy has improved outcomes of CMV-associated colitis^[5,17,20], CMV infection must still be diagnosed early in corticosteroid-resistant UC patients so that antiviral therapy can be initiated as soon as possible. However, it is difficult to distinguish exacerbation of UC by CMV infection from exacerbation not associated with CMV on the basis of symptoms and signs alone. In such cases, UC symptoms, signs, and severity in patients at risk of CMV-associated colitis are routinely evaluated by endoscopy. While a few such studies have reported the absence of any characteristic endoscopic findings in patients with UC complicated by CMV infection^[24], others have reported characteristic endoscopic features, including the absence of large single ulcers and the presence of longitudinal ulcers, microerosions, deep ulcers, pseudotumors, punched-out ulcers, mucosal defects, geographic ulcers, and irregular ulcers^[1,25-30]. These studies have methodological differences, however, and no consensus on unique endoscopic features that can be used to facilitate early diagnosis of CMV-associated colitis in UC has yet been obtained.

Against this background, we conducted a retrospective review of all clinical and endoscopic findings in a large cohort of patients with moderate to severe UC with symptom exacerbation to identify risk factors and characteristic endoscopic findings of CMV-associated colitis.

MATERIALS AND METHODS

Patients

This study was a retrospective analysis of medical charts and endoscopic images obtained from patients diagnosed with moderate to severe (active) UC. From

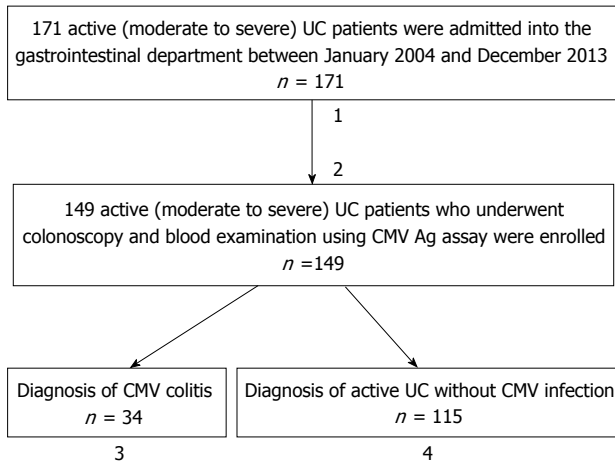


Figure 1 Clinical course of cytomegalovirus-associated colitis in patients with moderate to severe ulcerative colitis. Flow chart of the 171 patients admitted to our department with active UC. ¹Seven patients with a history of CMV-associated colitis or anti-CMV treatment were excluded; ²Fifteen patients who had not undergone colonoscopy and examination using the CMV antigenemia assay were also excluded; ³Out of 34 UC patients with CMV-associated colitis, 26 received GCV antiviral therapy. After GCV therapy, 13 patients achieved remission, but 13 required colectomy. Eight patients did not receive GCV antiviral therapy, 4 of whom underwent colectomy; ⁴The remaining 115 UC patients not diagnosed with CMV-associated colitis received treatment for active UC, of which 81 achieved remission. Of the remaining patients, some improved but did not fulfill remission criteria, while others required a second treatment, hospitalization, or colectomy. CMV: Cytomegalovirus; UC: Ulcerative colitis; Ag: Antigenemia; GCV: Ganciclovir.

January 2004 to December 2013, a total of 171 UC patients were admitted to the Department of Gastroenterology, Nagoya University Hospital, with exacerbation of UC symptoms (Figure 1). The diagnosis of UC was based on clinical, endoscopic, radiological, and pathological criteria, and the severity of UC was assessed according to Stange *et al.*^[31], Truelove *et al.*^[32] and Dignass *et al.*^[33]. We routinely examine CMV antigenemia in such patients, and almost all undergo colonoscopy or sigmoidoscopy at admission^[34-36]. Of the present 171 patients, we excluded 7 patients with a previous history of CMV-associated colitis or anti-CMV treatment, as well as 15 patients who had not undergone colonoscopy or examination using the antigenemia assay. Finally, 149 patients who received both a blood test for CMV antigenemia and endoscopic examination at admission were included in the analysis.

The following demographic and clinical data were obtained at the time of admission and classified according to the Montreal Classification^[31,33]: Age at admission, age at diagnosis, sex, familial or spontaneous disease (familial disease was considered when at least one first- or second-degree relative was diagnosed with IBD), and disease localization (proctitis, left sided colitis, or pancolitis) as revealed by colonoscopy.

Endoscopic findings

Disease severity was assessed by colonoscopy. If ulcers were present, the shape and depth were described, and biopsies were obtained at the margin and base

for histologic investigation. If no ulcers were detected, biopsies were obtained in the areas with the most severe inflammation. Colonic biopsy specimens were fixed, paraffinized, and stained with hematoxylin and eosin (HE) and specific immunohistochemical (IHC) staining with monoclonal antibody against CMV immediate early antigen^[6,37]. Specimens were also evaluated for the presence of characteristic CMV inclusion bodies by experienced pathologists.

Diagnosis of CMV infection/CMV-associated colitis

CMV infection was defined by a positive CMV antigenemia assay, the presence of inclusion bodies in HE stained sections, or positive specific IHC staining for CMV. Diagnosis of CMV-associated colitis in patients with active UC was determined by active UC complicated by CMV infection.

Ethical considerations

The study protocol was approved by the institutional review board of Nagoya University Graduate School of Medicine.

Statistical analysis

Data are presented as mean \pm SD or number (%) as appropriate. Categorical data were compared between groups using the χ^2 or Fisher's exact test. Continuous variables were compared using the Mann-Whitney *U* test. To identify candidate risk factors and characteristic endoscopic features for CMV-associated colitis, univariate analyses were conducted using Fisher's exact test. All factors which were significant on univariate analysis were entered into multivariate logistic regression models constructed to identify significant independent risk factors and characteristic endoscopic features of CMV-associated colitis. For continuous variables, we found the best cut-off value with plotting the area under the receiver operating characteristic curve. The results are expressed as odds ratios (ORs) with 95% CIs. *P*-values less than 0.05 were considered statistically significant for all tests. All statistical analyses were performed using SPSS Statistics 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

A total of 149 UC patients presenting with UC symptom exacerbation between January 2004 and December 2013 were included in the study. Of these, 34 (22.8%) tested positive on CMV antigenemia assay or had biopsy specimens with indicative of CMV infection. The clinical and demographical parameters of CMV-positive and CMV-negative patients are presented in Table 1. Univariate analysis revealed statistically significant group differences in age at UC diagnosis, age at admission, extent of disease (pancolitis), serum albumin level, systemic steroid dose on the day of admission, total systemic steroid dose for the week before admission, and total systemic steroid dose for 4 wk before admi-

Table 1 Clinical and demographic characteristics of patients with active ulcerative colitis (*n* = 149)

	CMV (+) <i>n</i> = 34	CMV (-) <i>n</i> = 115	<i>P</i> value
Sex (male/female)	19/15	64/51	0.981
Age at UC diagnosis (yr)	42.3 ± 14.4	29.0 ± 14.4	< 0.001
Age at admission (yr)	46.9 ± 18.1	35.0 ± 15.6	< 0.001
Disease duration (yr)	4.6 ± 4.9	6.0 ± 7.4	0.294
Clinical course			
Relapse	23 (67.6%)	79 (68.7%)	0.908
Chronic active	4 (11.8%)	11 (9.6%)	0.708
First attack	7 (20.6%)	25 (21.7%)	0.886
Disease extent			
Extensive UC (pancolitis)	28 (82%)	52 (45%)	< 0.001
Left-sided UC/proctitis	6 (18%)	63 (55%)	-
BMI at admission	19.5 ± 3.2	18.9 ± 3.1	0.384
Severity			
Severe	11 (32%)	27 (23%)	0.297
Moderate	23 (68%)	88 (77%)	-
Laboratory data at admission			
CRP (mg/dL)	3.4 ± 4.1	3.8 ± 5.4	0.685
WBC (× 10 ³ /μL)	8.7 ± 3.7	9.9 ± 4.2	0.132
Hemoglobin (g/dL)	11.4 ± 1.8	11.7 ± 1.2	0.387
Platelet (× 10 ³ /μL)	321.0 ± 118.9	349.9 ± 120.2	0.219
Total cholesterol (mg/dL)	155.3 ± 39.7	155.1 ± 44.3	0.979
Albumin (g/dL)	3.0 ± 0.54	3.4 ± 0.68	0.002
Medication			
Total lifetime systemic steroid dose before admission (g)	4.69 ± 5.80	4.86 ± 8.45	0.892
Total systemic steroid dose for 4 wk before admission (mg)	1083.4 ± 1113.5	245.5 ± 328.4	< 0.001
Total systemic steroid dose for 1 wk before admission (mg)	260.7 ± 103.9	92.3 ± 117.0	< 0.001
Systemic steroid dose on the day at admission (mg)	37.5 ± 15.0	13.9 ± 17.6	< 0.001
5-ASA	29 (85.3%)	82 (71.3%)	0.100
SASP	1 (2.9%)	10 (8.7%)	0.260
Cytapheresis	5 (15%)	11 (9.6%)	0.395
Immunomodulator use	8 (24%)	20 (17%)	0.421
AZA	4 (12%)	16 (14%)	0.747
6-MP	2 (5.9%)	2 (1.7%)	0.177
Tacrolimus	2 (5.9%)	2 (1.7%)	0.177
Infliximab use	5 (15%)	7 (6.1%)	0.105
Family history of IBD	1 (2.9%)	1 (0.87%)	0.356
PSC	0	2 (1.7%)	-
Outcome			
Ganciclovir use	26 (76%)	0	-
Colectomy	17 (50%)	37 (32%)	0.058
Colectomy for cancer or dysplasia	0	4 (3.5%)	-

Values presented as mean ± SD or number (%) as appropriate. CMV: Cytomegalovirus; CRP: C-reactive protein; WBC: White blood count; BMI: Body mass index; 5-ASA: 5-aminosalicylate acid; SASP: Salicylazosulfapyridine; AZA: Azathioprine; 6-MP: 6-mercaptopurine; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis.

Table 2 Risk factors for cytomegalovirus-associated colitis among the 149 patients with active ulcerative colitis (multivariate analysis)

	Odds ratio	95%CI	<i>P</i> value
Age at UC diagnosis > 30 yr	2.764	0.581-13.152	0.202
Age at admission > 35 yr	1.433	0.295-6.951	0.655
Pancolitis	3.419	1.077-10.856	0.037
Albumin < 3.0 g/dL	1.402	0.480-4.098	0.537
Total systemic steroid dose for 4 wk before admission > 400 mg	26.697	5.848-121.868	< 0.001

UC: Ulcerative colitis; CMV: Cytomegalovirus.

ssion. There were no significant group differences in sex ratio, disease duration, clinical course, total lifetime systemic steroid dose, immunomodulator use, infliximab

use, or laboratory data at admission other than serum albumin level.

For multivariate analysis, we selected a total systemic steroid dose for 4 wk before admission as the most important factor among factors regarding steroid dose. This multivariate analysis using a logistic regression model identified pancolitis and a total systemic steroid dose > 400 mg for 4 wk before admission as significant independent risk factors for CMV infection (Table 2). Patients treated with more than 400 mg corticosteroid for UC exacerbation over the 4 wk prior to admission had a 27-fold greater risk of CMV-associated colitis and patients with extensive UC (pancolitis) had about a 3-fold greater risk. The other factors tested (age at UC diagnosis, age at admission, and serum albumin) were not significant risk factors by multivariate analysis.

Table 3 Endoscopic findings in patients with active ulcerative colitis (*n* = 149)

	CMV (+) <i>n</i> = 34	CMV (-) <i>n</i> = 115	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	<i>P</i> value
Deep ulcer	17 (50.0%)	14 (12.2%)	79.2	50.0	87.8	54.8	85.6	< 0.001
Punched-out ulcer	20 (58.8%)	8 (7.0%)	85.2	58.8	93.0	71.4	88.4	< 0.001
Geographical ulcer	14 (41.2%)	25 (21.7%)	76.5	41.2	78.2	35.9	81.8	0.024
Longitudinal ulcer	11 (32.4%)	24 (20.9%)	68.5	32.4	79.1	31.4	79.8	0.165
Mucosal defect	6 (17.6%)	10 (8.7%)	74.5	17.6	91.3	37.5	78.9	0.139
Mucopurulent exudate	24 (70.6%)	66 (57.4%)	49.0	70.6	42.6	26.7	83.1	0.167
Spontaneous bleeding	14 (41.2%)	19 (16.5%)	73.8	41.2	83.5	42.4	82.8	0.002
Cobblestone-like appearance	5 (14.7%)	7 (6.1%)	75.8	14.7	93.9	41.7	78.8	0.105
Post inflammatory polyp	9 (26.5%)	21 (18.3%)	75.8	26.5	81.7	30.0	79.0	0.294

PPV: Positive predictive value; NPV: Negative predictive value; CMV: Cytomegalovirus.

Table 4 Characteristic endoscopic findings for cytomegalovirus-associated colitis in patients with active ulcerative colitis (multivariate analysis)

	Odds ratio	95%CI	<i>P</i> value
Deep ulcer	2.128	0.678-6.680	0.196
Punched-out ulcer	12.672	4.210-38.143	< 0.001
Geographical ulcer	1.919	0.664-5.542	0.229
Spontaneous bleeding	2.106	0.735-6.036	0.166

Endoscopic findings

To identify endoscopic findings characteristic of CMV-associated colitis in patients with active UC, we analyzed ulcerative features (*e.g.*, deep ulcer, punched-out ulcer, geographical ulcer, longitudinal ulcer, and mucosal defect) and mucosal features (*e.g.*, mucopurulent exudate, spontaneous bleeding, cobblestone-like appearance, and post inflammatory polyp). Characteristic colonoscopic features of CMV-associated colitis included deep ulcer, punched-out ulcer, geographical ulcer, longitudinal ulcer, and mucosal defect (Figure 2). We defined endoscopic findings according to published reports^[28,38]. Deep ulcer was defined as deep excavated ulceration near or beyond muscularis propria with or without slightly raised edges. Punched-out ulcer was defined as ulceration with an almost round shape and clear demarcation. Geographical ulcer was defined as ulceration with an irregular pattern and a branched shape. Longitudinal ulcer was defined as ulceration with a longitudinal spread along the lumen of the colon. Mucosal defect was defined as a wide area of defect with a longitudinal and/or transverse spread, indicating that more than one-fourth of the mucosa in the endoscopic field was defective. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for each of these features were determined. Univariate analysis revealed that deep ulcer, punched-out ulcer, geographical ulcer, and spontaneous bleeding were more frequent in CMV-positive patients than in CMV-negative patients (Table 3).

Multivariate analysis showed that only punched-out ulcer was a significant independent predictor of CMV colitis (OR = 12.672, 95%CI: 4.210-38.143) (Table 4).

Patient outcomes

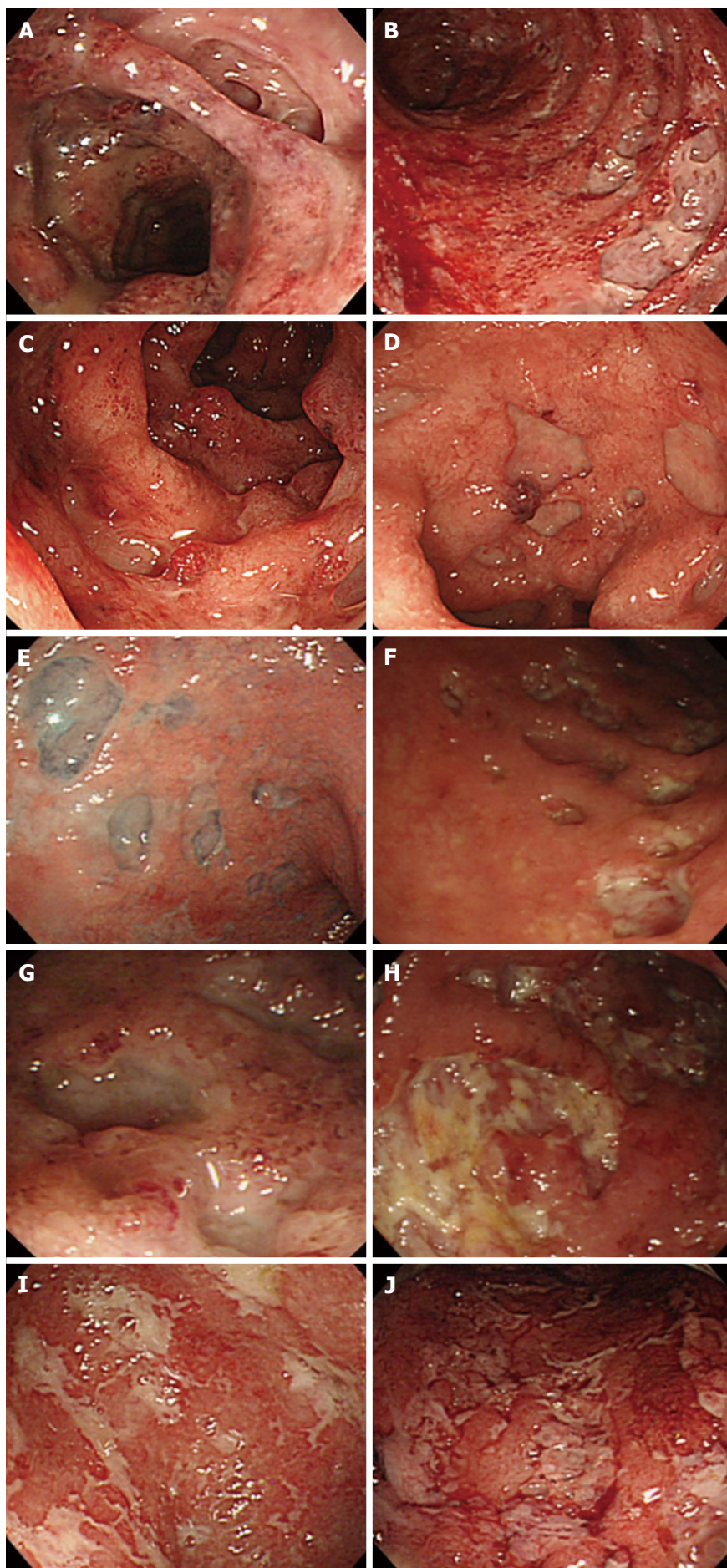
In the CMV-positive (CMV-associated colitis) group, 26 of the 34 patients (76.5%) received antiviral therapy with GCV. After GCV therapy, 13 of these patients achieved remission, while 13 required colectomy because of severe and refractory UC. Of the remaining 8 patients who did not receive GCV antiviral therapy, 4 underwent colectomy because of severe UC.

Among the CMV-negative group, 81 patients (70.4%) achieved remission with anti-inflammatory therapy (including relapse cases), while 37 (32.2%) eventually underwent colectomy during the course of follow-up. Among these 37 patients, 4 underwent colectomy for cancer or dysplasia.

DISCUSSION

In this retrospective study of 149 UC patients presenting with exacerbation of symptoms, we identified extensive UC (pancolitis) and 4 wk of high-dose steroid treatment as independent risk factors for CMV-associated colitis in active UC. The only endoscopic finding indicative of CMV-associated colitis by multivariate analysis was punched-out ulcer. To our knowledge, this is the first study to identify both risk factors and characteristic endoscopic findings for CMV-associated colitis in patients with moderate to severe UC. These factors may help facilitate both the timely diagnosis and treatment of UC complicated by CMV infection.

We evaluated total systemic steroid dose over the patient's lifetime, as well as dose over the 4 wk before admission, over the previous week before admission, and on the day of admission. Between CMV-positive and CMV-negative patients, total systemic steroid dose over the 4 wk prior to admission (total dose > 400 mg) was an independent risk factor for CMV-associated colitis in active UC patients. Furthermore, neither immunomodulator nor infliximab use was associated with CMV-associated colitis. However, this study included only a few cases treated by immunomodulators or infliximab, and additional studies are required to confirm these results. Nonetheless, the finding that immunomodulator and infliximab use did not alter the risk of CMV-associated colitis is important, because it suggests an alternative



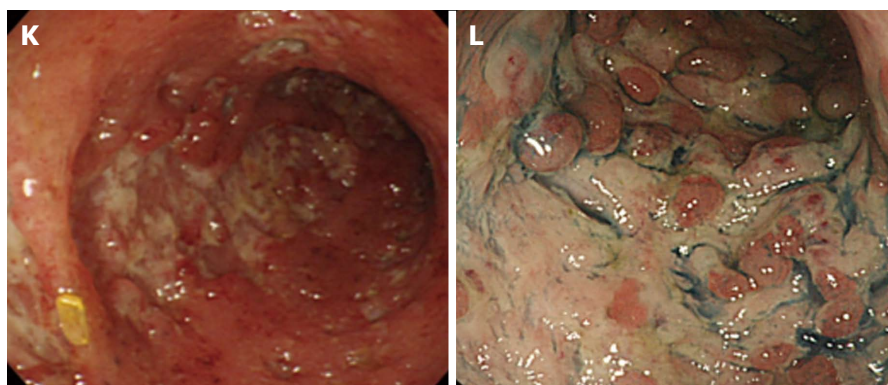


Figure 2 Endoscopic images of cytomegalovirus-associated colitis in patients with active ulcerative colitis. A-C: Deep ulcer; D-G: Punched-out ulcer; H-J: Geographical ulcer; K: Longitudinal ulcer; L: Mucosal defect.

treatment regimen for patients with moderate to severe UC rather than using high-dose corticosteroids for corticosteroid-refractory cases or corticosteroid-resistant cases. Given that tumor necrosis factor (TNF)- α from monocytes and dendritic cells plays an important role in the reactivation of CMV and that infliximab is a potent blocker of TNF- α , we consider that this combination therapy may be particularly effective^[7,39]. However, the efficacy of infliximab for UC patients with concomitant CMV infection remains controversial, as there have been few case reports and no controlled clinical trials.

Pancolitis was significantly associated with CMV infection in active UC, consistent with the theory that CMV is prone to proliferate in granulation tissue^[9]. Some studies reported that CMV was readily found in granulation tissue and tissue from deep ulcers, suggesting that CMV can penetrate inflamed mucosa *via* mononuclear cells and then proliferate in the mucosa^[2,9,40,41]. It is thus possible that a more extensive UC lesion may lead to wider CMV infection.

In general, there is no clear consensus on the diagnostic criteria for CMV infection in active UC. There are several methods of detecting CMV infection, including histology with IHC, serology, CMV culture, polymerase chain reaction (PCR) detection of the CMV genome, and CMV antigenemia^[6,34-37,42]. Each method offers advantages and disadvantages in the precise diagnosis of CMV infection. For example, histological examination is a relatively easy method, but its sensitivity is lower (10%-87%) than PCR. In contrast, PCR for CMV genes is highly sensitive, but the method is time-consuming and its selectivity is low given the ubiquity of CMV infection. CMV culture is too slow. In contrast, CMV antigenemia is relatively sensitive (60%-100%) and easy to measure within a short period, and has also been used to monitor CMV infection in heart transplant recipients and for the early diagnosis of CMV infection in renal transplant recipients^[43]. Moreover, results of CMV antigenemia are good indication for antiviral therapy^[44,45].

Accordingly, we adopted CMV antigenemia and histology, including IHC for CMV, to detect CMV infection in our analysis. Results showed that 33 of the 34 CMV-associated colitis patients (97.1%) were positive for CMV

antigenemia. Histology including IHC is considered the objective standard for the diagnosis of CMV infection. In our study, however, among the 34 patients with CMV-associated colitis whose biopsy specimens were stained with HE and a CMV antibody, only 8 patients were positive by histology. Only 7 were positive by both CMV antigenemia and histology. We therefore suggest that our combination of CMV antigenemia and histology including IHC for CMV is an appropriate strategy for diagnosis of CMV infection/CMV-associated colitis in active UC patients.

Colonoscopy is usually performed in patients with exacerbation of UC symptoms because direct observation of the colonic mucosa provides detailed information on disease status and is useful for judging disease severity and treatment efficacy. The rapid and accurate diagnosis of CMV-associated colitis in UC patients is critical, because its treatment strategy differs markedly from that for UC exacerbation not associated with CMV infection. A few reports have documented the endoscopic findings of CMV-associated colitis, but several failed to find features able to rapidly distinguish CMV-associated colitis from unrelated active UC. Endoscopic findings of UC concomitant with CMV infection can range from normal appearing mucosa to mucosal erosion or ulceration, which can be difficult to distinguish from active UC unrelated to CMV infection. In our study, punched-out ulceration was significantly more frequent in UC patients with CMV infection, consistent with reports that CMV tends to localize to the colon mucosa and granulation tissue in deep ulcers^[2,9,40,41]. Regardless of etiology, we suggest that a finding of punched-out ulceration may facilitate the rapid and accurate diagnosis of CMV-associated colitis in UC patients.

The limitations of this study include its retrospective nature and evaluation of patients at a single institution. This study also involved a relatively small number of patients, which limits its statistical power.

In conclusion, this study suggests that a total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis in patients with moderate to severe UC. In addition, punched-out ulceration appears predictive of

CMV-associated colitis associated with UC. These clinical predictors and specific endoscopic findings may facilitate rapid diagnosis and antiviral treatment.

COMMENTS

Background

Although it has been reported that cytomegalovirus (CMV) infection can be associated with steroid resistance and be an exacerbating factor in ulcerative colitis (UC), the relationship between CMV and UC is not well studied.

Research frontiers

The aim of this study was to identify characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC.

Innovations and breakthroughs

This is one of a few retrospective studies focused on important information regarding characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC.

Applications

This study suggests that a total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis in patients with moderate to severe UC. In addition, punched-out ulceration appears predictive of CMV-associated colitis associated with UC. These clinical predictors and specific endoscopic findings may facilitate rapid diagnosis and antiviral treatment.

Peer-review

An interesting article dealing with clinically relevant subject of risk factors in ulcerative colitis. There is a solid number of patients and good experimental and clinical design. Data are good and discussion is a good representation of the problem.

REFERENCES

- Goodgame RW. Gastrointestinal cytomegalovirus disease. *Ann Intern Med* 1993; **119**: 924-935 [PMID: 8215005 DOI: 10.7326/0003-4819-119-9-199311010-00010]
- Hommes DW, Sterringa G, van Deventer SJ, Tytgat GN, Weel J. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. *Inflamm Bowel Dis* 2004; **10**: 245-250 [PMID: 15290919 DOI: 10.1097/00054725-200405000-00011]
- Surawicz CM, Myerson D. Self-limited cytomegalovirus colitis in immunocompetent individuals. *Gastroenterology* 1988; **94**: 194-199 [PMID: 2826283]
- Dieterich DT, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr* 1991; **4** Suppl 1: S29-S35 [PMID: 1848619]
- Papadakis KA, Tung JK, Binder SW, Kam LY, Abreu MT, Targan SR, Vasiliauskas EA. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 2137-2142 [PMID: 11467645 DOI: 10.1111/j.1572-0241.2001.03949.x]
- de la Hoz RE, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. *J Clin Virol* 2002; **25** Suppl 2: S1-12 [PMID: 12361752 DOI: 10.1016/S1386-6532(02)00091-4]
- Pereyra F, Rubin RH. Prevention and treatment of cytomegalovirus infection in solid organ transplant recipients. *Curr Opin Infect Dis* 2004; **17**: 357-361 [PMID: 15241082 DOI: 10.1097/01.qco.0000136933.67920.dd]
- Powell RD, Warner NE, Levine RS, Kirsner JB. Cytomegalic inclusion disease and ulcerative colitis; report of a case in a young adult. *Am J Med* 1961; **30**: 334-340 [PMID: 13737621 DOI: 10.1016/0002-9343(61)90105-X]
- Cooper HS, Raffensperger EC, Jonas L, Fitts WT. Cytomegalovirus inclusions in patients with ulcerative colitis and toxic dilation requiring colonic resection. *Gastroenterology* 1977; **72**: 1253-1256 [PMID: 192627]
- Orvar K, Murray J, Carmen G, Conklin J. Cytomegalovirus infection associated with onset of inflammatory bowel disease. *Dig Dis Sci* 1993; **38**: 2307-2310 [PMID: 8261839 DOI: 10.1007/BF01299914]
- Matsuoka K, Iwao Y, Mori T, Sakuraba A, Yajima T, Hisamatsu T, Okamoto S, Morohoshi Y, Izumiya M, Ichikawa H, Sato T, Inoue N, Ogata H, Hibi T. Cytomegalovirus is frequently reactivated and disappears without antiviral agents in ulcerative colitis patients. *Am J Gastroenterol* 2007; **102**: 331-337 [PMID: 17156136 DOI: 10.1111/j.1572-0241.2006.00989.x]
- Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis* 2010; **16**: 1620-1627 [PMID: 20232408 DOI: 10.1002/ibd.21275]
- Cottone M, Pietrosi G, Martorana G, Casà A, Pecoraro G, Oliva L, Orlando A, Rosselli M, Rizzo A, Pagliaro L. Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis. *Am J Gastroenterol* 2001; **96**: 773-775 [PMID: 11280549 DOI: 10.1111/j.1572-0241.2001.03620.x]
- Kaufman HS, Kahn AC, Iacobuzio-Donahue C, Talamini MA, Lillemo KD, Hamilton SR. Cytomegaloviral enterocolitis: clinical associations and outcome. *Dis Colon Rectum* 1999; **42**: 24-30 [PMID: 10211516 DOI: 10.1007/BF02235178]
- Berk T, Gordon SJ, Choi HY, Cooper HS. Cytomegalovirus infection of the colon: a possible role in exacerbations of inflammatory bowel disease. *Am J Gastroenterol* 1985; **80**: 355-360 [PMID: 2859801]
- Wada Y, Matsui T, Mataka H, Sakurai T, Yamamoto J, Kikuchi Y, Yorioka M, Tsuda S, Yao T, Yao S, Haraoka S, Iwashita A. Intractable ulcerative colitis caused by cytomegalovirus infection: a prospective study on prevalence, diagnosis, and treatment. *Dis Colon Rectum* 2003; **46**: S59-S65 [PMID: 14530660]
- Kambham N, Vij R, Cartwright CA, Longacre T. Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. *Am J Surg Pathol* 2004; **28**: 365-373 [PMID: 15104299 DOI: 10.1097/00000478-200403000-00009]
- Kuwabara A, Okamoto H, Suda T, Ajioka Y, Hatakeyama K. Clinicopathologic characteristics of clinically relevant cytomegalovirus infection in inflammatory bowel disease. *J Gastroenterol* 2007; **42**: 823-829 [PMID: 17940835 DOI: 10.1007/s00535-007-2103-3]
- Domènech E, Vega R, Ojanguren I, Hernández A, Garcia-Planella E, Bernal I, Rosinach M, Boix J, Cabré E, Gassull MA. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. *Inflamm Bowel Dis* 2008; **14**: 1373-1379 [PMID: 18452205 DOI: 10.1002/ibd.20498]
- Roblin X, Pillet S, Oussalah A, Berthelot P, Del Tedesco E, Phelip JM, Chambonnière ML, Garraud O, Peyrin-Biroulet L, Pozzetto B. Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. *Am J Gastroenterol* 2011; **106**: 2001-2008 [PMID: 2178989 DOI: 10.1038/ajg.2011.202]
- Kojima T, Watanabe T, Hata K, Shinozaki M, Yokoyama T, Nagawa H. Cytomegalovirus infection in ulcerative colitis. *Scand J Gastroenterol* 2006; **41**: 706-711 [PMID: 16716970 DOI: 10.1080/00365520500408584]
- Nakase H, Matsumura K, Yoshino T, Chiba T. Systematic review: cytomegalovirus infection in inflammatory bowel disease. *J Gastroenterol* 2008; **43**: 735-740 [PMID: 18958541 DOI: 10.1007/s00535-008-2246-x]
- Nakase H, Yoshino T, Ueno S, Uza N, Mikami S, Matsuura M, Chiba T. Importance of early detection of cytomegalovirus infection in refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 364 [PMID: 17206718 DOI: 10.1002/ibd.20033]
- Franzin G, Muolo A, Griminelli T. Cytomegalovirus inclusions in

- the gastroduodenal mucosa of patients after renal transplantation. *Gut* 1981; **22**: 698-701 [PMID: 6271652 DOI: 10.1136/gut.22.9.698]
- 25 **Battaglini MP**, Rockey DC. Cytomegalovirus colitis presenting with the endoscopic appearance of pseudomembranous colitis. *Gastrointest Endosc* 1999; **50**: 697-700 [PMID: 10536332 DOI: 10.1016/S0016-5107(99)80025-X]
 - 26 **Nishimoto Y**, Matsumoto T, Suekane H, Shimizu M, Mikami Y, Iida M. Cytomegalovirus infection in a patient with ulcerative colitis: colonoscopic findings. *Gastrointest Endosc* 2001; **53**: 816-818 [PMID: 11375602 DOI: 10.1067/mge.2001.114955]
 - 27 **Falagas ME**, Griffiths J, Prekezes J, Worthington M. Cytomegalovirus colitis mimicking colon carcinoma in an HIV-negative patient with chronic renal failure. *Am J Gastroenterol* 1996; **91**: 168-169 [PMID: 8561127]
 - 28 **Suzuki H**, Kato J, Kuriyama M, Hiraoka S, Kuwaki K, Yamamoto K. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection. *World J Gastroenterol* 2010; **16**: 1245-1251 [PMID: 20222169 DOI: 10.3748/wjg.v16.i10.1245]
 - 29 **Omiya M**, Matsushita M, Tanaka T, Kawamata S, Okazaki K. The absence of large ulcer predicts latent cytomegalovirus infection in ulcerative colitis with positive mucosal viral assay. *Intern Med* 2010; **49**: 2277-2282 [PMID: 21048360 DOI: 10.2169/internalmedicine.49.3657]
 - 30 **Iida T**, Ikeya K, Watanabe F, Abe J, Maruyama Y, Ohata A, Teruyuki S, Sugimoto K, Hanai H. Looking for endoscopic features of cytomegalovirus colitis: a study of 187 patients with active ulcerative colitis, positive and negative for cytomegalovirus. *Inflamm Bowel Dis* 2013; **19**: 1156-1163 [PMID: 23619714 DOI: 10.1097/MIB.0b013e31828075ce]
 - 31 **Stange EF**, Travis SP, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, Feakins R, Fléjou JF, Herfarth H, Hommes DW, Kupcinskis L, Lakatos PL, Mantzaris GJ, Schreiber S, Villanacci V, Warren BF. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. *J Crohns Colitis* 2008; **2**: 1-23 [PMID: 21172194 DOI: 10.1016/j.crohns.2007.11.001]
 - 32 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: 13260656 DOI: 10.1136/bmj.2.4947.1041]
 - 33 **Dignass A**, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part I: definitions and diagnosis. *J Crohns Colitis* 2012; **6**: 965-990 [PMID: 23040452 DOI: 10.1016/j.crohns.2012.09.003]
 - 34 **Mazzulli T**, Drew LW, Yen-Lieberman B, Jekic-McMullen D, Kohn DJ, Isada C, Moussa G, Chua R, Walmsley S. Multicenter comparison of the digene hybrid capture CMV DNA assay (version 2.0), the pp65 antigenemia assay, and cell culture for detection of cytomegalovirus viremia. *J Clin Microbiol* 1999; **37**: 958-963 [PMID: 10074509]
 - 35 **Mori T**, Mori S, Kanda Y, Yakushiji K, Mineishi S, Takaue Y, Gondo H, Harada M, Sakamaki H, Yajima T, Iwao Y, Hibi T, Okamoto S. Clinical significance of cytomegalovirus (CMV) antigenemia in the prediction and diagnosis of CMV gastrointestinal disease after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004; **33**: 431-434 [PMID: 14676775 DOI: 10.1038/sj.bmt.1704369]
 - 36 **Nagata N**, Kobayakawa M, Shimbo T, Hoshimoto K, Yada T, Gotoda T, Akiyama J, Oka S, Uemura N. Diagnostic value of antigenemia assay for cytomegalovirus gastrointestinal disease in immunocompromised patients. *World J Gastroenterol* 2011; **17**: 1185-1191 [PMID: 21448424 DOI: 10.3748/wjg.v17.i9.1185]
 - 37 **Beaugerie L**, Cywiner-Golenzer C, Monfort L, Girard PM, Carbonnel F, Ngô Y, Cosnes J, Rozenbaum W, Nicolas JC, Châtelet FP, Gendre JP. Definition and diagnosis of cytomegalovirus colitis in patients infected by human immunodeficiency virus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **14**: 423-429 [PMID: 9170416 DOI: 10.1097/00042560-199704150-00005]
 - 38 **Annese V**, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kiefflich R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R; European Crohn's and Colitis Organisation. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: 982-1018 [PMID: 24184171 DOI: 10.1016/j.crohns.2013.09.016]
 - 39 **Nakase H**, Chiba T. TNF-alpha is an important pathogenic factor contributing to reactivation of cytomegalovirus in inflamed mucosa of colon in patients with ulcerative colitis: lesson from clinical experience. *Inflamm Bowel Dis* 2010; **16**: 550-551 [PMID: 19637380 DOI: 10.1002/ibd.210]
 - 40 **Yoshino T**, Nakase H, Ueno S, Uza N, Inoue S, Mikami S, Matsuura M, Ohmori K, Sakurai T, Nagayama S, Hasegawa S, Sakai Y, Chiba T. Usefulness of quantitative real-time PCR assay for early detection of cytomegalovirus infection in patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm Bowel Dis* 2007; **13**: 1516-1521 [PMID: 17828781 DOI: 10.1002/ibd.20253]
 - 41 **Pfau P**, Kochman ML, Furth EE, Lichtenstein GR. Cytomegalovirus colitis complicating ulcerative colitis in the steroid-naïve patient. *Am J Gastroenterol* 2001; **96**: 895-899 [PMID: 11280572 DOI: 10.1111/j.1572-0241.2001.03672.x]
 - 42 **Kishore J**, Ghoshal U, Ghoshal UC, Krishnani N, Kumar S, Singh M, Ayyagari A. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. *J Med Microbiol* 2004; **53**: 1155-1160 [PMID: 15496396 DOI: 10.1099/jmm.0.45629-0]
 - 43 **Bernabeu-Wittel M**, Pachón-Ibáñez J, Cisneros JM, Cañas E, Sánchez M, Gómez MA, Gentil MA, Pachón J. Quantitative pp65 antigenemia in the diagnosis of cytomegalovirus disease: prospective assessment in a cohort of solid organ transplant recipients. *J Infect* 2005; **51**: 188-194 [PMID: 16230214 DOI: 10.1016/j.jinf.2004.10.014]
 - 44 **Manteiga R**, Martino R, Sureda A, Labeaga R, Brunet S, Sierra J, Rabella N. Cytomegalovirus pp65 antigenemia-guided pre-emptive treatment with ganciclovir after allogeneic stem transplantation: a single-center experience. *Bone Marrow Transplant* 1998; **22**: 899-904 [PMID: 9827819 DOI: 10.1038/sj.bmt.1701439]
 - 45 **Boeckh M**, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. *Blood* 1996; **88**: 4063-4071 [PMID: 8916975]

P-Reviewer: Landsman MJ, Ma XP, Vetvicka V

S-Editor: Song XX **L-Editor:** A **E-Editor:** Liu SQ



Systematic review comparing endoscopic, percutaneous and surgical pancreatic pseudocyst drainage

Anthony Yuen Bun Teoh, Vinay Dhir, Zhen-Dong Jin, Mitsuhiro Kida, Dong Wan Seo, Khék Yu Ho

Anthony Yuen Bun Teoh, Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

Vinay Dhir, Baldota Institute of Digestive Sciences, Maharashtra 400012, Mumbai, India

Zhen-Dong Jin, Department of Gastroenterology, Changhai Hospital, Shanghai 200433, China

Mitsuhiro Kida, Department of Gastroenterology, Kitasato University East Hospital, Kitasato 252-0380, Japan

Dong Wan Seo, Department of Gastroenterology, Asan Medical Centre, Seoul 138-050, South Korea

Khék Yu Ho, Department of Medicine, National University of Singapore, Singapore 119077, Singapore

Author contributions: Teoh AYB design, literature review, quality assessment, and writing up of the manuscript; Dhir V design, literature review and quality assessment; Jin ZD and Kida M important intellectual input, final approval of the article; Seo DW designed, important intellectual input and final approval of the article; Ho KY concept, important intellectual input, final approval of the article.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at anthonyteoh@surgery.cuhk.edu.hk. Consent was not obtained but the presented data are anonymized and risk of identification is low.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Anthony Yuen Bun Teoh, Professor, Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China. anthonyteoh@surgery.cuhk.edu.hk
Telephone: +852-26322627
Fax: +852-26377974

Received: November 24, 2015
Peer-review started: November 25, 2015
First decision: December 22, 2015
Revised: January 2, 2016
Accepted: January 29, 2016
Article in press: January 31, 2016
Published online: March 25, 2016

Abstract

AIM: To perform a systematic review comparing the outcomes of endoscopic, percutaneous and surgical pancreatic pseudocyst drainage.

METHODS: Comparative studies published between January 1980 and May 2014 were identified on PubMed, Embase and the Cochrane controlled trials register and assessed for suitability of inclusion. The primary outcome was the treatment success rate. Secondary outcomes included were the recurrence rates, re-interventions, length of hospital stay, adverse events and mortalities.

RESULTS: Ten comparative studies were identified and 3 were randomized controlled trials. Four studies reported on the outcomes of percutaneous and surgical drainage. Based on a large-scale national study, surgical drainage appeared to reduce mortality and adverse events rate as compared to the percutaneous approach. Three studies reported on the outcomes of endoscopic ultrasound (EUS) and surgical drainage. Clinical success and adverse events rates appeared to be comparable but the EUS approach reduced hospital stay, cost and improved quality of life. Three other studies compared

EUS and esophagogastroduodenoscopy-guided drainage. Both approaches were feasible for pseudocyst drainage but the success rate of the EUS approach was better for non-bulging cyst and the approach conferred additional safety benefits.

CONCLUSION: In patients with unfavorable anatomy, surgical cystojejunostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

Key words: Interventional endosonography; Endoscopic ultrasound; Pancreatic pseudocyst; Cystogastrostomy; Cystojejunostomy; Pseudocyst drainage

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Pancreatic pseudocysts are traditionally managed by open surgical internal drainage. With continued improvements in medical technology, the uses of percutaneous, endoscopic and laparoscopic drainage were increasingly reported. Nevertheless, trials comparing these different approaches are lacking. In this systematic review, endoscopic ultrasound-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystojejunostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

Teoh AYB, Dhir V, Jin ZD, Kida M, Seo DW, Ho KY. Systematic review comparing endoscopic, percutaneous and surgical pancreatic pseudocyst drainage. *World J Gastrointest Endosc* 2016; 8(6): 310-318 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i6/310.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i6.310>

INTRODUCTION

Pancreatic pseudocysts are amylase rich fluid collections in the peri-pancreatic tissues surrounded by a well-defined wall^[1]. There should be absence of necrosis or solid component in the collections. The relative proportion of acute and chronic pseudocyst varies between reports and depends on how the pseudocysts are being defined^[2]. The incidence is higher in patients suffering from chronic pancreatitis. Pancreatic pseudocysts are traditionally managed by open surgical internal drainage. With continued improvements in medical technology, less invasive options including percutaneous, endoscopic and laparoscopic drainage were increasingly reported. Nevertheless, trials comparing these different approaches

are lacking and there is an absence in consensus on the best approach for management of this condition. Thus, the aim of the current systematic review was to evaluate the outcomes of comparative studies on endoscopic, percutaneous and surgical pancreatic pseudocyst drainage and to summarize the findings of available data.

MATERIALS AND METHODS

Inclusion criteria

Eligible studies were comparative studies on endoscopic, percutaneous or surgical methods of pancreatic pseudocyst drainage. The definition of pseudocyst was according to the revised Atlanta's classification^[1] (Table 1). In brief, pseudocyst referred to a fluid collection in the peri-pancreatic tissues persisting for more than 4 wk on computed tomography, surrounded by a well-defined wall and contained no solid material. Studies describing the results of pancreatic necrosis or abscesses were excluded. The indications for treatment of pancreatic pseudocyst was if they persisted for more than 4 to 6 wk and are ≥ 6 cm in size, causing symptoms or complications^[3,4].

Search strategy and trial identification

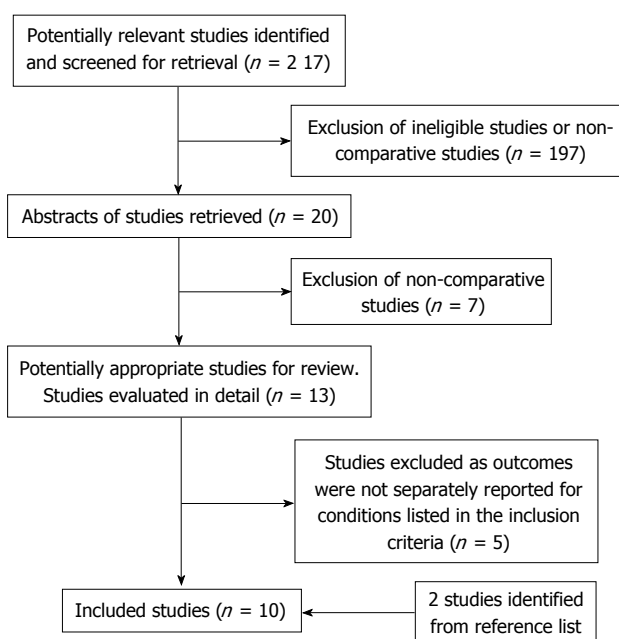
A computerized systematic literature review from January 1980 to May 2014 on PubMed, Embase and the Cochrane controlled trials register was performed. Articles were selected using MeSH headings and text words related to pancreatic pseudocyst, pseudocyst drainage, cystogastrostomy, cystojejunostomy, transmural pseudocyst drainage, transpapillary pseudocyst drainage and percutaneous pseudocyst drainage. Only English comparative studies involving the concerned treatment approaches were included. Reference lists from eligible trials were checked to locate missing publications. The titles of the articles and abstracts located were evaluated (Anthony Yuen Bun, TEOH1 and Vinay DHIR2). Where the article fulfilled the selection criterion, a copy of the full manuscript was obtained. Full manuscripts were then reviewed and a final decision was made about the inclusion. Studies published only in abstract form, conference abstracts, symposium proceedings and case reports were not eligible for inclusion. Any disagreements were resolved by consensus.

Data extraction and outcomes

Data were extracted using a standard extraction form. Parameters included were study methodology (including randomization and blinding), inclusion criteria, demographics, the indications of treatment and types of pancreatic fluid collection. Procedural data including the technical approaches, methods of anastomosis, catheters and stents used were also recorded. The primary outcome was the treatment success rate. Secondary outcomes included were the recurrence rates, re-interventions, lengths of hospital stay, adverse events and mortalities. Treatment success was defined

Table 1 Definition of peri-pancreatic fluid collections according to the revised Atlanta's classification

Name of the collection	Definition
Onset < 4 wk after initial attack	
Acute peripancreatic fluid collection	Fluid collections that develop in the early phase of pancreatitis. They do not have a well-defined wall, are homogeneous, are confined by normal fascial planes in the retroperitoneum
Acute necrotic collection	A collection containing variable amounts of fluid and necrotic tissue without a well-defined wall
Onset ≥ 4 wk after initial attack	
Pancreatic pseudocyst	A collection of fluid in the peripancreatic tissues surrounded by a well-defined wall and contains no solid material
Walled-off pancreatic necrosis	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis and has a well-defined inflammatory
Any time after initial attack	
Infected necrosis	Presence of superimposed infection of the necrotic pancreas. May be indicated by presence of gas in the collection

**Figure 1** Flow chart showing selection of included studies.

as radiographic cyst resolution after the index intervention. Re-intervention was defined as the need for repeat interventions owing to persistent symptoms in association with a residual pseudocyst. Adverse events were defined according to the individual study criteria.

Assessment of methodological quality and risk of bias of the included studies. Assessment of risk of bias were performed by AT and VD according to principles of the Cochrane Handbook for systemic reviews of interventions version 5.1^[5]. For randomized trials, the assessment focused on sequence generation, allocation concealment, blinding, incomplete outcome data, follow-up losses, intention to treat method of analysis and selective reporting. For non-randomized comparative trials, quality assessments were according to the Newcastle-Ottawa scale and the studies were scored on 3 domains including: Case selection, comparability of cases and controls and outcome assessments^[6]. The results of this study were reported according to the PRISMA guidelines^[7].

RESULTS

The search identified 217 potentially relevant publications and 20 articles were selected for reviewing of the abstracts. Seven studies were rejected as they were not comparative studies and the full manuscripts of the remaining 13 publications were reviewed. Two studies were further excluded as the outcomes for pseudocyst drainage were not separately reported and in 3 studies the outcomes of the different techniques were not reported individually. Two further articles were identified from the reference list of the included studies (Figure 1)^[8-17]. Since there was significant heterogeneity amongst the study interventions, recruitment and outcome measurements, statistical pooling of the results was not performed.

Description of the techniques

Surgical drainage procedures: Cystogastrostomy, cystoduodenostomy and cystojejunostomy:

Surgical drainage of pseudocysts is traditionally performed by the open approach^[18,19]. However in recent years, laparoscopic pseudocyst drainage is increasingly reported^[9,20]. For the open approach, midline or bilateral subcostal incisions were employed. The type of surgical drainage depended on the location of the cysts and whether it was adherent to the stomach or duodenum. When adhered to the posterior wall of the stomach, a cystogastrostomy were performed. If the cyst were not adhered to the stomach or duodenum, then a Roux-en Y cystojejunostomy would be fashioned. It is acknowledged that resectional procedures are sometimes required for patients with concomitant pancreatic ductal pathologies or complicated pseudocyst. However, resectional procedures do not have comparable endoscopic counterparts and these are not considered in this review.

In laparoscopic drainage procedures, various techniques have been described to replicate their open equivalents^[9,20]. These include intragastric, transgastric or exogastric approaches and they differ in the method of accessing the posterior wall of the stomach to create a cystogastrostomy. The anastomosis is usually created with a laparoscopic stapler and the enterostomy closed

by laparoscopic suturing. Laparoscopic cystojejunostomy is also possible for pseudocysts that protrude into the infracolic compartment and this is usually drained by a Roux-en Y jejunal loop.

Percutaneous drainage

Percutaneous drainage can be performed by ultrasound or computed tomography (CT) guidance and this can be achieved by the retroperitoneal route or transperitoneally^[15-17]. The appropriate drainage site is first identified, followed by progressive track dilation and insertion of a 7 to 12 Fr drainage catheter into the pseudocyst. In patients that received transperitoneal drainage, a transgastric needle puncture can be performed and the passage through the stomach could allow subsequent exchange of a double pigtail stent and internalization into the stomach. In patients with retroperitoneal drainage, the pigtail stents would be connected to an external bag for free drainage.

Endoscopic drainage

Endoscopic drainage can be performed transpapillary or transmurally^[21]. Transpapillary drainage can be performed if the pseudocyst communicates with the pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP) and a transpapillary stent is passed through the pancreatic duct into the pseudocyst. In patients with pancreatic ductal leak or ductal stricture, the stent may also serve to bridge the leak or stricture site^[22].

Endoscopic transmural drainage can be performed with or without endoscopic ultrasound (EUS) guidance^[11-13]. A prerequisite is that the pseudocyst is in direct apposition with the gastric or duodenal wall. When performed under esophagogastroduodenoscopy (EGD) guidance, the location of the pseudocyst is usually identified by the presence of bulging on the stomach wall. This is then confirmed by needle puncture, aspiration of the fluid and injection of contrast. A catheter and guide-wire is then passed into the pseudocyst. The fistula track is dilated with a balloon catheter and 1 or 2 plastic stents would be inserted. When performed under EUS guidance, the puncture site of the pseudocyst is chosen away from intervening vessels or structures. The pseudocyst is then punctured with a 19-gauge needle and a guide-wire passed to form 2 or more loops. The needle tract is dilated and plastic stents would be inserted. Recently, the use of metallic stents for draining pseudocyst has also been described but results from comparative studies are lacking^[23,24]. All the studies included in the current review used plastic stents.

Description of the studies

The identified studies covered a heterogeneous group of patients and mostly included small numbers from a single center (Table 2). In only one study, the outcomes of percutaneous drainage were compared to surgical drainage on a national level. Amongst the 10 included

studies, 3 were randomized controlled trials^[8,10,12]. One compared EUS drainage with open cystogastrostomy and 2 compared EGD vs EUS guided-drainage. The remaining seven studies were non-randomized trials, 1 compared laparoscopic, endoscopic and open cystogastrostomies^[9], 1 study compared EUS drainage with open cystogastrostomy^[10], 1 study compared EGD and EUS-guided drainage and 4 studies compared percutaneous and open surgical drainage^[13-17]. The definition of pseudocyst was clearly stated in all the randomized studies and in 6 out of 7 non-randomized studies. The indications for intervention were defined in all the randomized studies and 2 non-randomized studies.

Assessment of risk of bias of the included studies

The risks of bias in the randomized trials were assessed according to the principles of the Cochrane Handbook for systemic reviews of interventions (Table 3). None of the studies blinded the assessor of the outcomes. In one study comparing EGD versus EUS drainage^[11], the patients randomized to the EGD arm also received EUS when the pseudocyst could not be located. This resulted in a hybrid technique and may contaminate the data in the EGD arm resulting in contamination bias. The risks of bias in non-randomized trials were assessed using the Newcastle-Ottawa scale (Table 4). Most studies were of moderate quality and scored between 4 to 7 stars out of 10.

Assessment of outcomes by the different approaches of pseudocyst drainage

Percutaneous vs surgical drainage: Four retrospective studies were included (Table 5). The largest United States study included more than 14000 patients (Percutaneous: 8121 and surgical: 6409) that were identified using a US national database^[14]. Significant differences in background demographics between the groups were noted, including the cause of pseudocyst, the percentage of patients that received CT or ERCP and the proportion of patients that were treated in a teaching hospital. After adjusting for these confounding variables, a reduction in mortality was still observed in the surgical drainage arm (OR = 1.37, 95%CI: 1.12-1.68). Both emergency admission and acute pancreatitis increased the odds of in-patient mortality (OR = 2.45, 95%CI: 1.87-2.30 and OR = 2.36, 95%CI: 1.89-2.96, respectively) and the use of ERCP yielded a protective effect (OR = 0.68, 95%CI: 0.51-0.9). This study was the largest and most statistically robust amongst all the included studies. Yet, there is also a risk of selection biases, as the patients who were poor candidates for surgery tended to receive percutaneous drainage.

Heider *et al.*^[15] compared the results of expectant treatment with percutaneous and open surgical drainage. No statistical analysis of the results was performed (no *P*-values given). The patients that were treated by percutaneous drainage had a re-intervention rate of

Table 2 Characteristics of the included studies

Ref.	Design	Study duration	Follow-up duration ¹	Interventions	Sample size	Pseudocyst defined	Inclusion criteria or indications for intervention
Varadarajulu <i>et al</i> ^[8] (United States)	Single center RCT	Jan 2009-Dec 2009	24	EUS <i>vs</i> open cystogastrostomy	20:20	Yes	Pseudocyst > 6 cm and adjacent to stomach History of acute or chronic pancreatitis Persistent pain Complications of pseudocyst Symptomatic pseudocyst
Melman <i>et al</i> ^[9] (United States)	Single center retrospective	Mar 1999-Aug 2007	9.5	EUS <i>vs</i> laparoscopic <i>vs</i> open cystogastrostomy	45:16:22	Yes	NA
Varadarajulu <i>et al</i> ^[10] (United States)	Single center retrospective	Jul 2005-Jun 2007	24	EUS <i>vs</i> Open cystogastrostomy	20:10	Yes	NA
Park <i>et al</i> ^[11] (South Korea)	Single center RCT	Jan 2004-Dec 2007	25 - 27	EGD \pm R-EUS <i>vs</i> EUS	29:31	Yes	Symptomatic pseudocyst > 4 wk
Varadarajulu <i>et al</i> ^[12] (United States)	Single center RCT	May 2007-Oct 2007	NA	EGD <i>vs</i> EUS	15:15	Yes	Symptomatic pseudocyst > 4 wk
Kahaleh <i>et al</i> ^[13] (United States)	Single center retrospective	2000-2005	11	EGD <i>vs</i> EUS	53:46	Yes	NA
Morton <i>et al</i> ^[14] (United States)	National multicenter retrospective	Jan 1997-Dec 2001	NA	Percutaneous <i>vs</i> Surgical drainage	8121:6409	Yes	NA
Heider <i>et al</i> ^[15] (United States)	Single center retrospective	1984-1995	NA	Percutaneous <i>vs</i> Surgical drainage	66:66	Yes	NA
Adams <i>et al</i> ^[16] (United States)	Single center retrospective	1965-1991	NA	Percutaneous <i>vs</i> Surgical drainage	52:42	No	Percutaneous drainage: Symptomatic pseudocyst > 5 cm without PD dilation Wall thickness < 3 mm
Lang <i>et al</i> ^[17] (United States)	Single center retrospective	Jan 1978-Jun 1988	NA	Percutaneous <i>vs</i> Surgical drainage	12:14	Yes	Wall thickness < 3 mm

¹Mean duration of follow-up shown in months. RCT: Randomized controlled trial; NA: Not available; R-EUS: Radial echoendoscope; PD: Pancreatic duct; EGD: Esophagogastroduodenoscopy.

Table 3 Methodological summary of the risk of bias of the included randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Other bias
Varadarajulu <i>et al</i> ^[8]	Low risk	Low risk	High risk	Low risk	Unclear risk
Park <i>et al</i> ^[11]	Low risk	Unclear risk	High risk	Low risk	High risk
Varadarajulu <i>et al</i> ^[12]	Low risk	Unclear risk	High risk	Low risk	Low risk

Assessment of the risk of bias was according to principles of the Cochrane Handbook for systemic reviews of interventions version 5.1.

Table 4 Methodological summary of the risk of bias of the included non-randomized comparative studies

	Selection (+ + + +)	Comparability (+ +)	Outcomes (+ + + +)
Melman <i>et al</i> ^[9]	++		++
Varadarajulu <i>et al</i> ^[12]	++	+	+++
Kahaleh <i>et al</i> ^[13]	++		+++
Morton <i>et al</i> ^[14]	++	++	+++
Heider <i>et al</i> ^[15]	++	+	++
Adams <i>et al</i> ^[16]	++		++
Lang <i>et al</i> ^[17]	++		++

Quality assessment was according to the Newcastle-Ottawa scale for non-randomized trials. +: High quality of the studies.

50%, adverse events rate of 67% and mortality rate of 9.1% and the results were worse than surgery. On the contrary, two smaller studies favored the percutaneous

approach. Adams noted higher risk of mortalities, morbidities and re-interventions in patients that were treated with surgical drainage^[16]. Whilst in another study, similar risks of mortalities and adverse events were observed in both groups but the patients that underwent surgery required more subsequent re-interventions^[17].

It is worthwhile to note that the definition of pseudocyst in some of the older studies may not be according to the Atlanta's classification and thus, the study population could include some patients with pancreatic necrosis and the results of these may need to be interpreted with caution. Based on the results of the national study, surgical drainage appeared to reduce mortality and adverse events risk as compared to the percutaneous approach. The lack of an external catheter also reduced risk developing pancreatic fistula and wound site infection. However, the validity of these results in the current era needs to be confirmed by a

Table 5 Percutaneous vs surgical drainage of pancreatic pseudocysts

Ref.	Sample size	Size (cm) ¹	Clinical success	Hospital stay (d) ¹	Reintervention	Mortalities	Adverse events	Bleeding	Intra-abdominal infection
Morton <i>et al</i> ^[14]	Perc: 8121	-	-	21 (22) ²		5.9% ²	-	9.64% ²	6.8% ²
	Surg: 6409	-	-	15 (15)		2.8%	-	8.96%	4.54%
Heider <i>et al</i> ^[15]	Perc: 66	8.2 (1.1)	42%	45 (5)	50%	9.1%	64% ²	9.1%	45.5%
	Surg: 66	7.4 (1.3)	88%	18 (2)	12%	0	27%	4.5%	15.2%
Adams <i>et al</i> ^[16]	Perc: 52	-	-	36.7	9.5%	2	7.7%	1.9%	1.9%
	Surg: 42	-	-	39.8	19.2%	7.1%	16.7%	4.8%	4.8%
Lang <i>et al</i> ^[17]	Perc: 26	-	76.9%	-	11.5%	3.8%	3.8%	3.8%	0
	Surg: 26	-	73.1%	-	23.1%	3.8%	0	0	0

¹Values in mean \pm SD except otherwise indicated; ²Indicates significant differences between the 2 groups. Perc: Percutaneous drainage; Surg: Surgical drainage.

Table 6 Endoscopic ultrasound vs surgical drainage of pancreatic pseudocysts

Ref.	Sample size	Size (cm)	Clinical success	Hospital stay (d)	Reintervention	Mortalities	Adverse events	Bleeding	Intra-abdominal infection
Varadarajulu <i>et al</i> ^[8]	EUS: 20	10.5 (9-14.9) ¹	95%	2 (1-4) ^{1,3}	5%	0	0	0	0
	Open: 20	11 (8.4-14.5) ¹	100%	6 (5-9) ¹	5%	0	2%	1	0
Melman <i>et al</i> ^[9]	EUS: 45	9.1 (0.4)	51.1% ²	3.9 (0-25) ²	-	0	15.6%	2.2%	0
	Lap: 16	10.4 (0.5)	87.5%	6.9 (3-23) ²	-	0	25%	12.5%	0
Varadarajulu <i>et al</i> ^[10]	Open: 22	9.5 (0.8)	81.2%	10.8 (4-82) ²	-	0	22.7%	0	0
	EUS: 20	9.8	95%	2.6 (1-11) ^{2,3}	0	0	0	0	0
	Open: 10	8.9	100%	6.5 (4-20) ²	10%	0	0	0	0

¹Values in mean \pm interquartile range; ²Values in mean (range) except otherwise indicated; ³Indicates significant differences between the 2 groups. EUS: Endoscopic ultrasound drainage; Lap: Laparoscopic drainage; Open: Open drainage.

modernized randomized trial with updated definitions.

EUS vs surgical drainage: One randomized trial and two retrospective studies were included (Table 6). Varadarajulu *et al*^[10] first published a retrospective case-matched study comparing EUS and open cystogastrostomy. No differences in treatment success, adverse events or re-interventions were noted between the groups. The same author then followed-up with the first randomized study, comparing 20 patients that received EUS drainage with an equal number receiving open cystogastrostomy^[8]. The time to pseudocyst recurrence was used as the main outcome measurement. However, none of the patients in the EUS group developed recurrence, thus raising the issue of an underpowered study. Nevertheless, similar rates of clinical success, mortalities and morbidities were observed between the two groups. In addition, the EUS group was associated with significantly lower hospital costs (mean difference of -\$8040 USD) and better quality of life scores (physical component scores and mental component scores). Hence, favoring the EUS approach over open cystogastrostomy.

In another study comparing EUS, laparoscopic and open cystogastrostomy, a significantly higher rate of clinical success was observed in the surgery arm. However, the rate of clinical success in the EUS group was unusually low at 51.1% and grade 2 or above complications occurred in up to 15.6% of the patients. Three patients required urgent laparotomy and 2 experienced a gastric perforation. These results reflect that

the endoscopist performing the procedures may still be overcoming their learning curves and the difference in outcomes may not be truly representative of the techniques. Nevertheless, this study was the only comparative study that incorporated the results of laparoscopic cystogastrostomy.

EUS vs EGD drainage: Two randomized trials and 1 retrospective comparison were included (Table 7)^[11-13]. Kahaleh performed a retrospective comparison of patients that underwent EUS or EGD drainage^[13]. Those with bulging pseudocyst underwent EGD drainage whilst patients with non-bulging cyst or those at risk of bleeding underwent EUS drainage. No difference in clinical success and adverse event rates were observed between the two groups. In a Korean randomized study, EUS was compared to a modified EGD approach^[11]. In patients with bulging cyst, a blind EGD puncture was performed. Whilst in patients with the absence of bulging, radial EUS was employed to mark the site of puncture. This resulted in hybrid EUS-EGD approach in some of the patients. The trial found a significant difference in technical success rates in favor of the EUS approach (94% vs 72%, $P = 0.039$). The patients with failed EGD approach then crossed over to EUS drainage and this was successful in all patients. No differences in adverse events were observed in both arms. The third study was also a randomized study comparing EUS with pure EGD drainage of pseudocyst^[12]. The EUS approach was shown to have significantly higher success rate as compared to the pure EGD technique (100% vs 33.3%,

Table 7 Endoscopic ultrasound vs esophagogastroduodenoscopy drainage of pancreatic pseudocysts

Ref.	Sample size	Size (cm) ¹	Clinical success	Hospital stay (d)	Reintervention	Mortalities	Adverse events	Bleeding	Intra-abdominal infection
Park <i>et al</i> ^[11]	EUS: 31	8.2 (3.8)	89%	-	6.5%	0	7%	3.2%	-
	EGD: 29	7.4 (4)	86%	-	6.5%	0	10%	6.9%	-
Varadarajulu <i>et al</i> ^[12]	EUS: 15	6.5 (5-12) ²	100% ⁵	2 (1-9) ²	-	0	0	0	-
	EGD: 15	7 (4.2-13) ²	33% ⁴	1 (1-8) ²	-	6.7%	13.3%	13.3%	-
Kahaleh <i>et al</i> ^[13]	EUS: 46	8.6 (4-20) ³	84%	-	10.9%	0	19.6%	4.3%	8.7%
	EGD: 53	9.5 (3-20) ³	91%	-	9.4%	0	18.9%	1.9%	7.5%

¹Values in mean \pm SD; ²Values in mean (interquartile range); ³Values in mean (range); ⁴Values in median (range) except otherwise indicated; ⁵Indicates significant differences between the 2 groups. EUS: Endoscopic ultrasound drainage; EGD: Esophagogastroduodenoscopy drainage.

$P < 0.001$) and all patients with failed EGD drainage were successfully drained with the EUS technique. However, of more concern was that 2 patients in the EGD arm suffered from severe bleeding after drainage. One patient died within 4 h after the procedure due to massive bleeding into the cyst and another required endoscopic hemostasis and blood transfusion.

Hence, the results of these studies suggest that although a blind EGD pseudocyst drainage is technically feasible, it may result in life-threatening adverse events. The success rate of the EUS approach was better for non-bulging cyst and the approach conferred additional safety benefits by allowing visualization of extraluminal structures.

DISCUSSION

Although the current review has established a strict criterion for inclusion, the included studies incorporated a heterogeneous group of patients that were treated with a number of different approaches. Thus, the results were not directly comparable and statistical analysis in a form of meta-analysis was inappropriate. Nevertheless, a number of conclusions could still be made. EUS-guided drainage has similar efficacy to surgery but the EUS approach may reduce hospital stay, costs of the procedure and improve quality of life. EGD and EUS-guided drainages are both feasible but the success rate of the EUS approach is better for non-bulging cyst and it may offer additional safety benefit. Whether surgical internal drainage of pancreatic pseudocyst is preferred over percutaneous drainage needs to be validated, as no results from a modern study are available. However, surgical cystogastrostomy may still be preferred it avoids the need of an external catheter and reduces the risk developing an external pancreatic fistula. Consequently, the EUS approach is preferred when anatomy of the pseudocyst allows for direct drainage into the stomach or duodenum. However, if the pseudocyst is located away from the stomach or duodenum, surgical cystojejunostomy or percutaneous drainage could be considered. In addition, it is acknowledged that laparoscopic drainage is the modern minimally invasive approach for surgical drainage. However, results from comparative studies were lacking and the long-term outcomes of the treatment approaches could not be made.

The current study is the only systematic review comparing percutaneous, endoscopic and surgical drainage of pseudocyst. A prior systematic review compared endoscopic and laparoscopic internal drainage by summarizing the results from cohort studies without direct statistical comparison^[20]. No randomized or comparative studies were available. The review concluded that both approaches were safe and the laparoscopic approach appeared to have a higher success rate, lower morbidity and recurrence. In a meta-analysis comparing EGD and EUS-guided drainage, 2 randomized studies and 2 prospective studies were included^[25]. Technical success was higher for EUS drainage (RR = 12.38, 95%CI: 1.39-110.22) and adverse events were similar between the two techniques. The review concluded that for bulging pseudocysts, both approaches could be selected whereas for non-bulging pseudocyst, portal hypertension or coagulopathy, EUS drainage is the preferred modality.

There were some limitations to the current study. Firstly, the numbers of high quality comparative studies assessing the 3 approaches were lacking. Hence, the robustness of the results generated in this review is limited by the quality of the original studies. Furthermore, with regards to the available randomized trials, all were single center studies with small sample sizes and they were not designed to detect differences in recurrence rates or adverse event rates between the modalities. Thus, the results were prone to type II error. In addition, the literature search failed to identify any comparative studies involving endoscopic transpapillary drainage and laparoscopic internal drainage. Therefore, conclusions regarding these approaches could not be made. Furthermore, it was observed that many of the studies did not report on the follow-up time or only reported a very short follow-up period. This may not be adequate to detect longer-term recurrence. Lastly, the definitions of pseudocyst has changed over time and may be different for each study, thus of the patients included in the current review may not be suffering from the modern definition of pseudocyst and the outcomes of treatment may be affected by the definition.

Currently, there is a lack of consensus in the best practice for pseudocyst drainage. A number of professional bodies have attempted to establish guidelines regarding the management of complications of acute pancreatitis including infected pseudocyst and pancreatic

necrosis^[26]. However, none of these guidelines have received widespread acceptance. In a systemic review of 16 guidelines published by profession bodies, it was observed that the guidelines lacked consensus and few were graded according to the strength of evidence. In addition, there were wide variations in the recommendations regarding the role of percutaneous and endoscopic drainage of pancreatic fluid collections. For infected pseudocyst, percutaneous drainage was recommended by 6 guidelines, 1 did not recommend its use and for endoscopic drainage, the approach was recommended by 7 guidelines. A recent guideline published by the International Association of Pancreatology and the American Association of Pancreateology, represented the best evidenced-based recommendations concerning key aspects the management of acute pancreatitis^[27]. However, the optimal management of pseudocysts were not discussed and there is still a pressing need for more randomized studies to establish the best approach for management of this condition.

In conclusion, significant heterogeneity was present in the included studies and a clear conclusion could not be made. However, EUS-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystogastrostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

ACKNOWLEDGMENTS

The authors would like to extend the deepest gratitude to all Asian EUS group members for their support to the group. We would also like to thank Mr. Steven Chan and his team in their excellent support during all AEG related activities.

COMMENTS

Background

Pancreatic pseudocysts are traditionally managed by open surgical internal drainage. With continued improvements in medical technology, the uses of percutaneous, endoscopic and laparoscopic drainage were increasingly reported. Nevertheless, trials comparing these different approaches are lacking. Thus, the aim of this study is to perform a systematic review comparing the outcomes of endoscopic, percutaneous and surgical pancreatic pseudocyst drainage.

Research frontiers

Currently, there is a lack of consensus in the best practice for pseudocyst drainage. A number of professional bodies have attempted to establish guidelines regarding the management of complications of acute pancreatitis including infected pseudocyst and pancreatic necrosis. However, the guidelines lacked consensus and few were graded according to the strength of evidence.

Innovations and breakthroughs

Endoscopic ultrasound (EUS)-guided pseudocyst drainage is an endoscopic approach for establishing internal transmural drainage of a pseudocyst. The approach allows visualization of extra-mural structures to allow precise

placement of internal stents.

Applications

In the current study, the authors conclude that EUS-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystojejunostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

Terminology

Pseudocyst are fluid collections in the peri-pancreatic tissues persisting for more than 4 wk on computed tomography, surrounded by a well-defined wall and contained no solid material after an attack of pancreatitis.

Peer-review

The manuscript gives an overview of publications on outcome of endoscopic drainage of pancreatic pseudocysts, compared with percutaneous and/or surgical drainage.

REFERENCES

- 1 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]
- 2 **Aghdassi AA**, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM. Pancreatic pseudocysts--when and how to treat? *HPB (Oxford)* 2006; **8**: 432-441 [PMID: 18333098 DOI: 10.1080/13651820600748012]
- 3 **Yeo CJ**, Bastidas JA, Lynch-Nyhan A, Fishman EK, Zinner MJ, Cameron JL. The natural history of pancreatic pseudocysts documented by computed tomography. *Surg Gynecol Obstet* 1990; **170**: 411-417 [PMID: 2326721]
- 4 **Bradley EL**, Clements JL, Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. *Am J Surg* 1979; **137**: 135-141 [PMID: 758840 DOI: 10.1016/0002-9610(79)90024-2]
- 5 **Higgins JPT**, Green S. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. The Cochrane Collaboration, 2011 [DOI: 10.1002/9780470712184]
- 6 **Wells GA**, Shea B, O'Connell D, Peterson J, Welch WV, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Accessed 2014 May]. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
- 7 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]
- 8 **Varadarajulu S**, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583-90.e1 [PMID: 23732774 DOI: 10.1053/j.gastro.2013.05.046]
- 9 **Melman L**, Azar R, Beddow K, Brunt LM, Halpin VJ, Eagon JC, Frisella MM, Edmundowicz S, Jonnalagadda S, Matthews BD. Primary and overall success rates for clinical outcomes after laparoscopic, endoscopic, and open pancreatic cystgastrostomy for pancreatic pseudocysts. *Surg Endosc* 2009; **23**: 267-271 [PMID: 19037696 DOI: 10.1007/s00464-008-0196-2]
- 10 **Varadarajulu S**, Lopes TL, Wilcox CM, Drelichman ER, Kilgore ML, Christein JD. EUS versus surgical cyst-gastrostomy for management of pancreatic pseudocysts. *Gastrointest Endosc* 2008; **68**: 649-655 [PMID: 18547566 DOI: 10.1016/j.gie.2008.02.057]

- 11 **Park DH**, Lee SS, Moon SH, Choi SY, Jung SW, Seo DW, Lee SK, Kim MH. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. *Endoscopy* 2009; **41**: 842-848 [PMID: 19798610 DOI: 10.1055/s-0029-1215133]
- 12 **Varadarajulu S**, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111 [PMID: 18640677 DOI: 10.1016/j.gie.2008.04.028]
- 13 **Kahaleh M**, Shami VM, Conaway MR, Tokar J, Rockoff T, De La Rue SA, de Lange E, Bassignani M, Gay S, Adams RB, Yeaton P. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. *Endoscopy* 2006; **38**: 355-359 [PMID: 16680634 DOI: 10.1055/s-2006-925249]
- 14 **Morton JM**, Brown A, Galanko JA, Norton JA, Grimm IS, Behrns KE. A national comparison of surgical versus percutaneous drainage of pancreatic pseudocysts: 1997-2001. *J Gastrointest Surg* 2005; **9**: 15-20; discussion 20-21 [PMID: 15623440 DOI: 10.1016/j.gassur.2004.10.005]
- 15 **Heider R**, Meyer AA, Galanko JA, Behrns KE. Percutaneous drainage of pancreatic pseudocysts is associated with a higher failure rate than surgical treatment in unselected patients. *Ann Surg* 1999; **229**: 781-787; discussion 787-789 [PMID: 10363891 DOI: 10.1097/00000658-199906000-00004]
- 16 **Adams DB**, Anderson MC. Percutaneous catheter drainage compared with internal drainage in the management of pancreatic pseudocyst. *Ann Surg* 1992; **215**: 571-576; discussion 576-578 [PMID: 1632678 DOI: 10.1097/00000658-199206000-00003]
- 17 **Lang EK**, Paolini RM, Pottmeyer A. The efficacy of palliative and definitive percutaneous versus surgical drainage of pancreatic abscesses and pseudocysts: a prospective study of 85 patients. *South Med J* 1991; **84**: 55-64 [PMID: 1702557 DOI: 10.1097/00007611-199101000-00014]
- 18 **Frey CF**. Pancreatic pseudocyst--operative strategy. *Ann Surg* 1978; **188**: 652-662 [PMID: 309751 DOI: 10.1097/00000658-197811000-00012]
- 19 **Aranha GV**, Prinz RA, Freeark RJ, Kruss DM, Greenlee HB. Evaluation of therapeutic options for pancreatic pseudocysts. *Arch Surg* 1982; **117**: 717-721 [PMID: 7073495 DOI: 10.1001/archsurg.1982.01380290163029]
- 20 **Aljarabah M**, Ammori BJ. Laparoscopic and endoscopic approaches for drainage of pancreatic pseudocysts: a systematic review of published series. *Surg Endosc* 2007; **21**: 1936-1944 [PMID: 17717626 DOI: 10.1007/s00464-007-9515-2]
- 21 **Binmoeller KF**, Seifert H, Walter A, Soehendra N. Transpapillary and transmural drainage of pancreatic pseudocysts. *Gastrointest Endosc* 1995; **42**: 219-224 [PMID: 7498686 DOI: 10.1016/S0016-5107(95)70095-1]
- 22 **Varadarajulu S**, Noone TC, Tutuian R, Hawes RH, Cotton PB. Predictors of outcome in pancreatic duct disruption managed by endoscopic transpapillary stent placement. *Gastrointest Endosc* 2005; **61**: 568-575 [PMID: 15812410 DOI: 10.1016/S0016-5107(04)02832-9]
- 23 **Weilert F**, Binmoeller KF, Shah JN, Bhat YM, Kane S. Endoscopic ultrasound-guided drainage of pancreatic fluid collections with indeterminate adherence using temporary covered metal stents. *Endoscopy* 2012; **44**: 780-783 [PMID: 22791588 DOI: 10.1055/s-0032-1309839]
- 24 **Itoi T**, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). *Gastrointest Endosc* 2012; **75**: 870-876 [PMID: 22301347 DOI: 10.1016/j.gie.2011.10.020]
- 25 **Panamonta N**, Ngamruengphong S, Kijirichareanchai K, Nugent K, Rakvit A. Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. *Eur J Gastroenterol Hepatol* 2012; **24**: 1355-1362 [PMID: 23114741 DOI: 10.1097/MEG.0b013e32835871eb]
- 26 **Loveday BP**, Mittal A, Phillips A, Windsor JA. Minimally invasive management of pancreatic abscess, pseudocyst, and necrosis: a systematic review of current guidelines. *World J Surg* 2008; **32**: 2383-2394 [PMID: 18670801 DOI: 10.1007/s00268-008-9701-y]
- 27 **Working Group IAP/APA Acute Pancreatitis Guidelines**. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol* 2013; **13**: e1-15 [PMID: 24054878 DOI: 10.1016/j.pan.2013.07.063]

P- Reviewer: Boulay B, Buanes TA, De Palma GD, Osawa S, Thomopoulos KC, Wilcox CM

S- Editor: Qi Y **L- Editor:** A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 April 10; 8(7): 319-356





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Izuru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

REVIEW

- 319 What are the current and potential future roles for endoscopic ultrasound in the treatment of pancreatic cancer?

Oh SY, Irani S, Kozarek RA

ORIGINAL ARTICLE

Retrospective Cohort Study

- 330 Risk factors for local recurrence after *en bloc* endoscopic submucosal dissection for early gastric cancer

Lee JY, Cho KB, Kim ES, Park KS, Lee YJ, Lee YS, Jang BK, Chung WJ, Hwang JS

Retrospective Study

- 338 Stent type used does not impact complication rate or placement time but can decrease treatment cost for benign and malignant esophageal lesions

McGaw C, Alkaddour A, Vega KJ, Munoz JC

- 344 What is the impact of capsule endoscopy in the long term period?

Ormeci A, Akyuz F, Baran B, Gokturk S, Ormeci T, Pinarbasi B, Soyer OM, Evirgen S, Akyuz U, Karaca C, Demir K, Kaymakoglu S, Besisik F

- 349 Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics

Shindo Y, Matsumoto S, Miyatani H, Yoshida Y, Mashima H

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 7 April 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Bo Yu, MD, Professor, Department of General Surgery, Beijing Military Command General Hospital, Beijing 100700, China

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Su-Qing Liu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
April 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

What are the current and potential future roles for endoscopic ultrasound in the treatment of pancreatic cancer?

Stephen Y Oh, Shayan Irani, Richard A Kozarek

Stephen Y Oh, Shayan Irani, Richard A Kozarek, the Digestive Disease Institute at Virginia Mason Medical Center, Seattle, WA 98101, United States

Author contributions: Oh SY wrote the manuscript; Irani S provided images and edited the manuscript; Kozarek RA received a solicitation to publish a review article from *WJGE* and edited the manuscript.

Conflict-of-interest statement: Dr. Stephen Y Oh has no conflicts of interest. Dr. Richard A Kozarek is an investigator for Boston Scientific and has been on the Speakers Bureau x 1 for Cook. All funds accrue to the clinic. Dr. Kozarek has owned Glaxo stock since 1983. Dr. Shayan Irani is a consultant for Boston Scientific (remittances to clinic); also provided Gore educational talk.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Richard A Kozarek, MD, the Digestive Disease Institute at Virginia Mason Medical Center, 1100 9th Avenue, MS: C3-GAS, Seattle, WA 98101, United States. richard.kozarek@virginiamason.org
Telephone: +1-206-2232319
Fax: +1-206-2236379

Received: October 20, 2015
Peer-review started: October 27, 2015
First decision: November 27, 2015
Revised: January 19, 2016
Accepted: February 14, 2016
Article in press: February 16, 2016
Published online: April 10, 2016

Abstract

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States. Due to the aggressive tumor biology and late manifestations of the disease, long-term survival is extremely uncommon and the current 5-year survival rate is 7%. Over the last two decades, endoscopic ultrasound (EUS) has evolved from a diagnostic modality to a minimally invasive therapeutic alternative to radiologic procedures and surgery for pancreatic diseases. EUS-guided celiac plexus intervention is a useful adjunct to conventional analgesia for patients with pancreatic cancer. EUS-guided biliary drainage has emerged as a viable option in patients who have failed endoscopic retrograde cholangiopancreatography. Recently, the use of lumen-apposing metal stent to create gastrojejunal anastomosis under EUS and fluoroscopic guidance in patients with malignant gastric outlet obstruction has been reported. On the other hand, anti-tumor therapies delivered by EUS, such as the injection of anti-tumor agents, brachytherapy and ablations are still in the experimental stage without clear survival benefit. In this article, we provide updates on well-established EUS-guided interventions as well as novel techniques relevant to pancreatic cancer.

Key words: Endoscopic ultrasound; Pancreatic cancer; Palliation; Endoscopic ultrasound-guided celiac plexus neurolysis and block; Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided gastrojejunal anastomosis; Endoscopic ultrasound-guided anti-tumor therapy; Endoscopic ultrasound-guided fiducial placement; Endoscopic ultrasound-guided ablation

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic ultrasound (EUS) is an indis-

pensable tool in pancreatic cancer not only for tissue diagnosis and disease staging but also for therapeutic purposes. Although some EUS-guided therapies such as celiac plexus interventions and biliary drainage in the setting of unsuccessful endoscopic retrograde cholangiopancreatography (in expert tertiary referral centers) have become widely accepted interventions for patients with pancreatic cancer, other techniques have yet to evolve. Given the lack of effective systemic treatment for pancreatic cancer at present, further research in therapeutic EUS is warranted.

Oh SY, Irani S, Kozarek RA. What are the current and potential future roles for endoscopic ultrasound in the treatment of pancreatic cancer? *World J Gastrointest Endosc* 2016; 8(7): 319-329 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i7/319.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i7.319>

INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States^[1]. Only 20% of patients at diagnosis are amenable to surgical resection^[2], which offers the best chance of long-term survival. As a result, the majority of patients are treated with palliative chemotherapy or best supportive care. From a histological standpoint, one of the defining features of pancreatic ductal adenocarcinoma is extensive desmoplastic stroma with fibrotic reaction around the tumor. The fibrotic stroma promotes tumor growth^[3], induces resistance to chemotherapy and radiotherapy^[4], and constitutes a barrier to the delivery of therapeutic agents^[5]. Due to the aggressive tumor biology and late manifestations of the disease, long-term survival is extremely uncommon and the current 5-year survival rate is 7%^[6].

Over the last two decades, endoscopic ultrasound (EUS) has evolved from a diagnostic modality to a minimally invasive therapeutic alternative to radiologic procedures and surgery for pancreatic diseases. EUS-guided celiac plexus neurolysis (CPN)/block are widely accepted techniques for pain management in patients with pancreatic cancer. Recently, EUS-guided biliary access in both malignant and non-malignant biliary obstruction has been increasingly utilized. As EUS offers dynamic images, unparalleled access to the pancreas and Doppler to avoid vascular structures, it has a theoretical advantage of targeting the tumor directly through the desmoplastic stroma while minimizing complications. This, coupled with the lack of effective systemic chemotherapies for pancreatic cancer, has prompted researchers to investigate local EUS-guided delivery of anti-tumor agents and ablative therapies over the last decade.

In this article, we provide updates on well-established EUS-guided interventions as well as novel techniques that are in the development for the treat-

ment of pancreatic cancer.

PALLIATIVE/SYMPTOMATIC THERAPIES

EUS-guided celiac plexus interventions

CPN refers to permanent chemical ablation of the celiac plexus and is performed by injecting alcohol or phenol into or around the celiac plexus or ganglion. Celiac plexus block denotes inhibition of pain transmission *via* the celiac plexus by injecting a combination of a corticosteroid and a long acting local anesthetic. Injections can be delivered *via* a percutaneous, surgical or EUS-guided approach. EUS provides access to the celiac plexus which is located adjacent to the proximal gastric wall. The main advantage of this route over a percutaneous one is the ability to avoid vessels with Doppler, in addition to being able to undertake concomitantly at the time of another intervention such as an endoscopic retrograde cholangiopancreatography (ERCP) or fine needle aspiration of the primary mass.

Since the first report of EUS-CPN in 30 patients with intra-abdominal malignancy (25 with pancreatic cancer) showing significant improvement in pain scores^[7], multiple randomized controlled and meta-analyses^[8-12] have demonstrated that EUS-CPN provided effective pain relief in patients with pancreatic cancer compared with conventional analgesia. There is also evidence that CPN reduces analgesia use. Two meta-analyses showed that CPN (either EUS or percutaneous approach) was associated with a significant reduction in narcotic use^[8,11]. Additionally, a randomized controlled trial involving 96 patients with advanced pancreatic cancer reported that morphine consumption was lower at 3 mo in the EUS-CPN group compared to placebo^[11]. Nonetheless, approximately 15% of patients may see no reduction in their use of narcotics, and in this group, a repeat EUS-CPN has not been shown to be effective. A study of 24 patients with pancreatic cancer undergoing repeat EUS-CPN showed that repeat CPN was not as effective as index procedure in pain control (67% after the initial CPN vs 29% at 1 mo follow-up)^[13].

EUS-guided injection can be given centrally into the space between the aorta and the origin of the coeliac trunk, or bilaterally on either side of the coeliac axis. To date, one randomized trial comparing the two techniques demonstrated no difference in the duration of pain relief (11 wk vs 14 wk), complete pain relief (2/29 patients vs 2/21 patients) or reduction in pain medication (9/29 patients vs 7/21 patients)^[14]. The decision to inject centrally or bilaterally often depends on the personal preference and experience of an endosonographer and further prospective studies are needed to determine which approach is superior. On the other hand, a Japanese group investigated the efficacy of broad plexus neurolysis (BPN) extending over the superior mesenteric artery with the aim of delivering a larger amount of neurolytic agents^[15]. The study found that EUS-BPN patients had significantly greater reductions at days 7 and 30 on the visual analog pain



Figure 1 Endoscopic ultrasound-guided injection into the celiac ganglion. A: Celiac ganglion visualized by linear endoscopic ultrasound as a hypoechoic structure anterior to the aorta (arrow); B: 19-gauge needle puncture into the celiac ganglia for neurolysis.

scale scores compared with EUS-CPN group. This technique, however, is yet to be validated in a large, prospective trial.

There has been an interest in direct celiac ganglia injection to improve the efficacy of CPN (Figure 1). Celiac ganglia appear as an oval, hypo to isoechoic structures around the celiac axis and are visible in upwards of 80% of the general population^[16,17]. A recent study randomized 34 patients to EUS-ceeliac ganglia neurolysis vs EUS-CPN showed that celiac ganglion neurolysis was associated with more effective pain relief compared with CPN (73.5% vs 45.5%, respectively; $P = 0.026$) with a smaller volume of alcohol needed for the ablation^[18].

Contraindications to celiac plexus interventions include coagulopathy (international normalized ratio > 1.5), thrombocytopenia (platelets $< 50000/L$), and hemodynamic or respiratory instability prohibiting adequate sedation. Otherwise, EUS-guided celiac plexus intervention is generally safe. Diarrhea, abdominal pain and hypotension due to the disruption of the autonomic nervous system are usually self-limiting. A paradoxical increase in pain has been shown to occur in 9% of cases but generally resolves spontaneously^[19]. Serious adverse events including paralysis from anterior spinal cord infection^[20,21], necrotic gastric perforation^[22], and celiac artery thrombosis causing infarction^[23,24] are rare.

EUS-guided biliary drainage

ERCP for biliary access and drainage is successful in 90% to 95% of cases and is the preferred method of stenting the bile duct in obstructive jaundice from pancreatic cancer. In cases of unsuccessful ERCP due to difficult cannulation or altered anatomy, the alternatives have been precut papillotomy, percutaneous transhepatic biliary drainage (PTBD) and surgical bypass. Recently, EUS-guided biliary drainage has emerged as an alternative to these options. EUS-guided approach spares patients the discomfort of an external drain, and can be performed at the time of an unsuccessful ERCP, reducing the need for additional percutaneous interventions.

Three main approaches for EUS-guided biliary

drainage have been described. Rendezvous technique is where a guidewire is placed into the intra or extrahepatic bile duct and passed through the papilla for retrieval by duodenoscopy for retrograde biliary intervention. Direct transgastric (hepaticogastrostomy) or transduodenal (choledochoduodenostomy) route involves the dilation of the tract followed by stenting for transmural biliary drainage (Figure 2). This obviates biliary access *via* the papilla. A third, less frequently performed intervention, involves the antegrade placement of a stent across the papilla *via* a transduodenal approach^[25,26]. The transduodenal approach requires at least an intact duodenal bulb^[27] and can sometimes be performed after placement of a duodenal stent for gastric outlet obstruction. In patients with obstruction at the level of the pylorus, the transgastric approach almost always requires a dilated intrahepatic biliary system^[28].

Available evidence suggests excellent technical and clinical success with EUS-guided biliary drainage in 87% of cases, however, adverse events up to 10%-20% have been reported^[29-40]. One of the major shortcomings of the rendezvous technique is a failure rate of 25%, and this can be associated with prolonged procedure times and higher risk of bile leak^[31,36,37,40,41]. In contrast, transluminal stenting can be complicated by stent migration or occlusion, bile leak and biliary peritonitis, cholangitis, hemobilia and pneumoperitoneum^[27,33-35].

Alternatively, EUS-guided gallbladder drainage may be an option when the previously mentioned approaches are not feasible. As the gallbladder presents a large target in close proximity to the gastric antrum and duodenal bulb, this technique can be performed more easily. However, it would not be beneficial in a non-dilated gallbladder suggesting cystic duct invasion by tumor^[42]. Excellent technical success, clinical success and safety profiles with EUS-guided gallbladder drainage in patients with acute cholecystitis have been demonstrated in a randomized controlled trial^[43] and its use in the setting of malignancy has been described in case reports and small series^[44,45].

At present, experts recommend that EUS-guided biliary drainage should be performed by an advanced

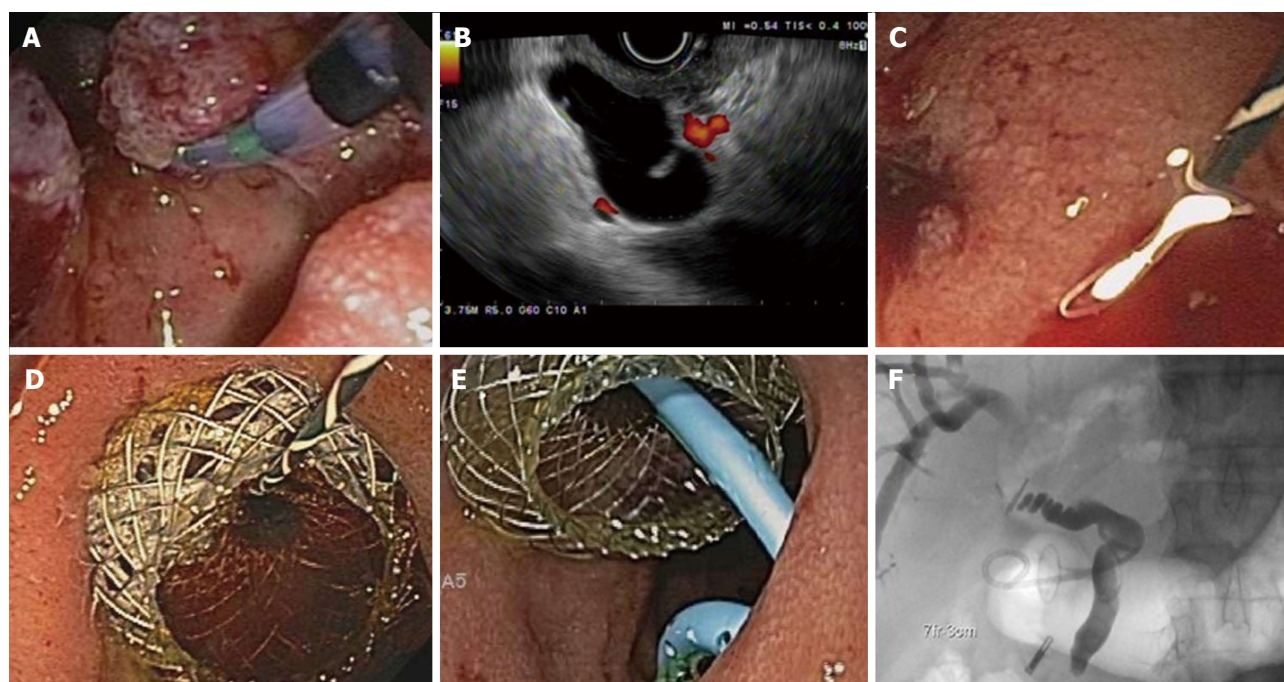


Figure 2 A 84 years old male with duodenal adenocarcinoma causing biliary obstruction underwent endoscopic ultrasound-guided choledochoduodenostomy following unsuccessful endoscopic retrograde cholangiopancreatography. A: Tumor involving the major papilla; B: Endoscopic ultrasound-guided puncture of the common bile duct through the duodenum with a 19-gauge needle; C: Guidewire insertion and balloon dilation of a choledochoduodenal fistula; D: Followed by the placement of a 10 mm × 10 mm lumen-apposing metal stent to create a choledochoduodenostomy; E and F: Endoscopic (E) and fluoroscopic (F) view after the placement of a 7 Fr × 3 cm double pigtail stent into the common hepatic duct.

endoscopist with expertise in both ERCP and EUS in a tertiary center, where surgery and radiology unit can provide support to manage adverse events if they arise^[46,47].

EUS-guided anastomosis

Gastric outlet obstruction is a common late manifestation of cancer in the head of the pancreas. When endoscopic gastroduodenal stent placement is unsuccessful in relieving obstruction, bypass surgery can be performed to accomplish the anastomosis between the stomach and jejunum. However, in poor surgical candidates, the EUS-guided approach may offer a minimally invasive means of establishing an anastomosis. In this technique, a gastrojejunal fistula is created by obtaining an access to the jejunum *via* EUS-guided needle, placing a guidewire through the needle and dilating the tract over the wire using a dilator catheter, balloon and/or electrical cautery needle. Subsequently, a lumen-apposing stent is placed across the fistula (Figure 3). This has been described in 2 recent case reports^[48,49]. EUS-guided gastrojejunostomy using a double-balloon enteric tube to distend the jejunum between the two balloons at the EUS-guided needle puncture has also been reported^[50,51].

The use of magnetic compression devices through oral, percutaneous, and surgical introduction of magnets to create gastroenterostomy and cholecystoenteric anastomosis in animal models has been reported^[52,53] (Figure 4). Encouraged by the favorable outcomes of the experimental studies, two human trials of endoscopic gastroenteric anastomosis have been performed. The

first study evaluated 15 patients with malignant obstruction undergoing gastroenteric anastomosis using magnetic compression devices and a yoyo stent and found that the procedure was successful in 13 (87%) patients^[54]. One perforation occurred and was attributed to manipulation of the recently formed fistula. Three stents migrated (2 distal and 1 proximal) and no mortality was reported. Subsequently, a prospective multicenter study evaluated 18 patients who had gastroenteric anastomosis using magnetic compression device and self-expandable stent^[55]. The procedure was successful in 12 (67%) patients but the study was terminated after inclusion of 18 patients due to a fatal perforation in 1 patient. Three (25%) patients experienced stent migration. This technique is usually performed by forward-viewing endoscope but can also be performed under the guidance of EUS combined with fluoroscopy. Creation of magnetic biliary anastomoses using endoscopic and radiologic techniques has also been described in case reports^[56,57] but there are no large trials to date.

Through-the-scope device for EUS-guided suturing and tissue approximation between two organs has been tested in porcine models^[58,59]. A suturing device was developed for suturing under EUS guidance to the desired depth. The device allowed multiple sutures to be placed without withdrawing the echoendoscope. Stitching, knot tying, and thread cutting were achieved through an accessory channel in the echoendoscope. Traction for the insertion of stents and other devices was provided through the lumen of both organs. With-

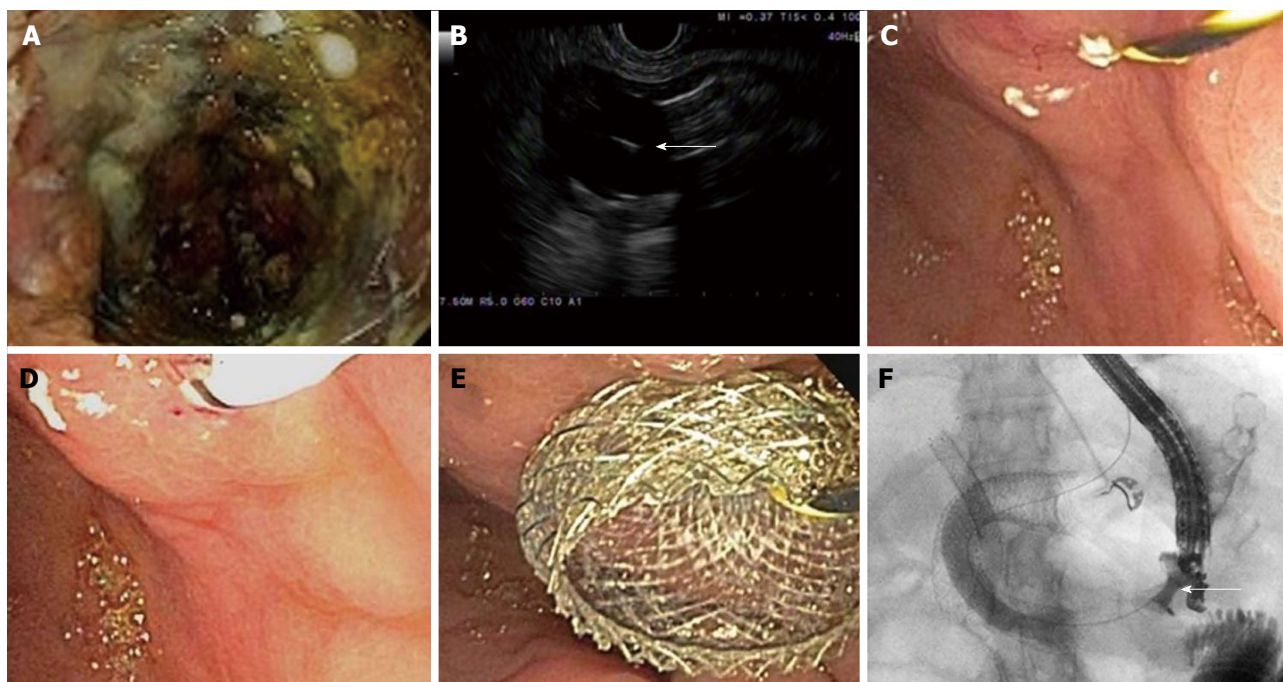


Figure 3 A 66 years old female with metastatic cholangiocarcinoma and gastric outlet obstruction undergoing endoscopic ultrasound-guided gastrojejunostomy. A: Tumor ingrowth into two previously placed duodenal stents; B: Endoscopic ultrasound visualization of a 20 mm balloon inflated in the proximal jejunum followed by a 19-gauge needle puncture (arrow); C and D: Balloon dilation of the gastrojejunal fistula over a 0.035 inch guidewire; E and F: Endoscopic (E) and fluoroscopic (F) demonstration of contrast flow across 10 mm × 15 mm lumen-apposing metal stent (arrow) into the jejunum.

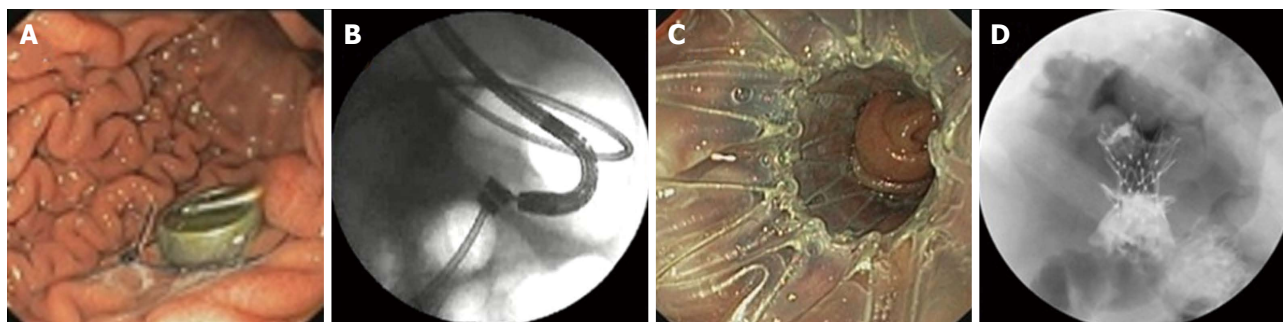


Figure 4 Magnetic anastomosis device to create endoscopic gastrojejunostomy (Images courtesy of Cook Medical). A: Gastric magnet marked with an endoscopy clip; B: Mating of gastric and proximal jejunal magnets under fluoroscopic guidance to create a gastrojejunal fistula; C: Placement of a fully covered stent within the fistula with a proximal flanged edge positioned in the gastric lumen; D: The stent within the fistula functions as a gastrojejunostomy.

in 4 to 7 d, anastomoses had formed between the small intestine and the stomach, and between the gallbladder and the stomach. The initial diameter of the anastomoses ranged from 3 to 9 mm, and no adverse events were reported.

ANTI-TUMOR THERAPIES

EUS-fine needle injection of anti-tumor agents

Cytoimplant: An allogenic mixed lymphocyte culture (Cytoimplant) induces cytokine production and activates the host immune effector mechanism. EUS-fine needle injection (EUS-FNI) of Cytoimplant was examined in a phase I trial of 8 patients with advanced pancreatic cancer^[60]. The median survival was 13.2 mo, with 2 partial responses (> 50% reduction in tumor size

measured on imaging) and 1 minor response (tumor size reduction of < 50%). The technique was feasible and no major complications were seen.

Immunotherapy/dendritic cells: Immature dendritic cells can stimulate primary T-cell response against tumor antigens. To date, 2 pilot trials have been conducted on EUS-FNI of dendritics for the treatment of unresectable pancreatic cancer. The use of EUS-FNI of immature dendritic cells was reported in a study of 7 patients with advanced pancreatic cancer who previously failed gemcitabine. Injections of 10 billion or more dendritic cells at two to three sites were performed. There was 1 complete response, 3 partial responses and 2 patients had stable disease with a median survival of 9.9 mo. No adverse events were seen^[61]. Later, the

use of combined systemic gemcitabine and EUS-FNI of OK432-pulsed dendritic cells, followed by intravenous lymphokine-activated killer cells was reported in 5 patients with unresectable pancreatic cancer. One patient showed a partial response and 2 patients had stable disease over 6 mo^[62].

Tumor necrosis factor erade: Tumor necrosis factor (TNF)erade is a replication-deficient adenovirus vector that expresses human TNF- α gene regulated by promoter Egr-1, which is inducible by chemotherapy and radiation. Preliminary results from a phase I / II trial of intratumoral TNFerade injection (either EUS or percutaneous approach) in combination with systemic 5-fluorouracil and radiotherapy in 50 patients with locally advanced pancreatic cancer demonstrated encouraging results^[63]. One complete response, 3 partial responses and 12 stable disease with a median survival of 297 d was noted. Interestingly, seven patients had surgical resection, 6 with negative margins, 1 with complete pathologic response and 3 surviving more than 2 years. However, a subsequent large randomized multicenter trial involving 304 patients with locally advanced pancreatic cancer showed no survival benefit of combining intratumoral TNFerade injection with 5-fluorouracil and radiotherapy compared with chemoradiation alone^[64]. In addition, the study used either EUS-guided or a percutaneous approach for the injection of TNFerade and found that EUS-FNI was associated with inferior progression-free survival. This was thought to be the operator-dependent nature of EUS-FNI.

ONYX-015: ONYX-015 is a modified adenovirus (deletion in the E1B gene) which preferentially replicates in tumor cells leading to cell death. In a phase I / II trial using EUS-FNI of ONYX-015 in 21 patients with locally advanced pancreatic cancer, patients received 8 injections and the last injection was administered with systemic gemcitabine^[65]. The mean survival was 7.5 mo. Serious adverse events included duodenal perforations and sepsis in 2 patients each, raising concerns over its safety.

BC-819: BC-819 is a DNA plasmid that targets the expression of diphtheria-toxin gene under the control of H19 regulatory sequences and has the potential to treat pancreatic cancer that overexpresses the *H19* gene. In a phase I / II a trial, EUS or computed tomography (CT)-guided FNI of BC-819 was performed in 9 patients with advanced pancreatic cancer treated with concurrent chemoradiation^[66]. Three patients achieved partial response and 2 were successfully downstaged for surgery. No serious adverse events were reported.

Radiotherapy and EUS

EUS-guided brachytherapy: Brachytherapy involves the insertion of a radioactive seed directly into the tumor for local destruction. Iodine-125 (125I) is the most common radioactive seed used and has a half-life of

59.7 d and tissue penetration of 1.7 cm^[67]. EUS-guided implantation of 125I into pancreatic tumor was first reported in a pilot study of 15 patients with unresectable pancreatic cancer^[68]. The study showed partial response in 27%, minimal response in 20% and stable disease in 33%. Reduction in pain was noted in 30% but the effect was short-lived. Two further studies examined the efficacy of combined EUS-brachytherapy and systemic gemcitabine-based chemotherapy in patients with advanced pancreatic cancer, both demonstrating no significant survival benefit but improvement in pain was again noted^[69,70].

Stereotactic body radiotherapy and fiducial placement: The main benefit of stereotactic body radiotherapy (SBRT) is that it limits the field of radiation to the organ of interest thereby minimizing irradiation of adjacent normal tissue^[71]. One prospective^[71] and two retrospective studies^[72,73] showed that local tumor control and overall survival following SBRT were comparable with the outcomes of external beam radiotherapy.

Placement of fiducial markers prior to SBRT acts as a landmark and enables precise tumor targeting. Fiducial markers are available in different forms, including radiopaque spheres, coils or seeds and were traditionally placed in or near the tumor using surgical or radiological techniques (Figure 5^[74]). However, two recent prospective studies have demonstrated that EUS-guided placement of fiducial markers in pancreatic tumors had excellent technical success rates (88% to 90%) and safety^[74,75]. EUS-guided placement is performed by passing fiducials through a 19G or 22G needle and deploying them by using stylet or injecting sterile water into the needle after the needle is punctured to the desired depth^[76]. Different types of fiducial markers have also been studied. Khashab *et al*^[77] evaluated the EUS-placement of traditional vs coiled fiducials in a study of 39 patients with locally advanced pancreatic cancer. Visibility score was significantly better for traditional compared with coil fiducials but no difference in migration rate, number of fiducials placed, technical success or complication rate were seen. The authors recommended the placement of traditional fiducials whenever possible.

EUS-guided ablative techniques

Radiofrequency ablation: Radiofrequency ablation (RFA) works by passing electrical current in the range of radio waves between a needle electrode positioned in the tumor, and grounding pads placed on the patient's skin. Radiofrequency current produces a high level of heat within the tumor leading to protein desaturation and loss of fluids (coagulative necrosis)^[78]. Several studies have demonstrated the feasibility of RFA *via* open, percutaneous and laparoscopic approaches in patients with locally advanced pancreatic cancer^[79,80].

The application of EUS-guided RFA in porcine models was shown to be effective in destroying pancreatic tissue^[78,81,82]. Complications included pancreatitis^[81], intestinal wall adhesion^[82], and retroperitoneal fibrosis

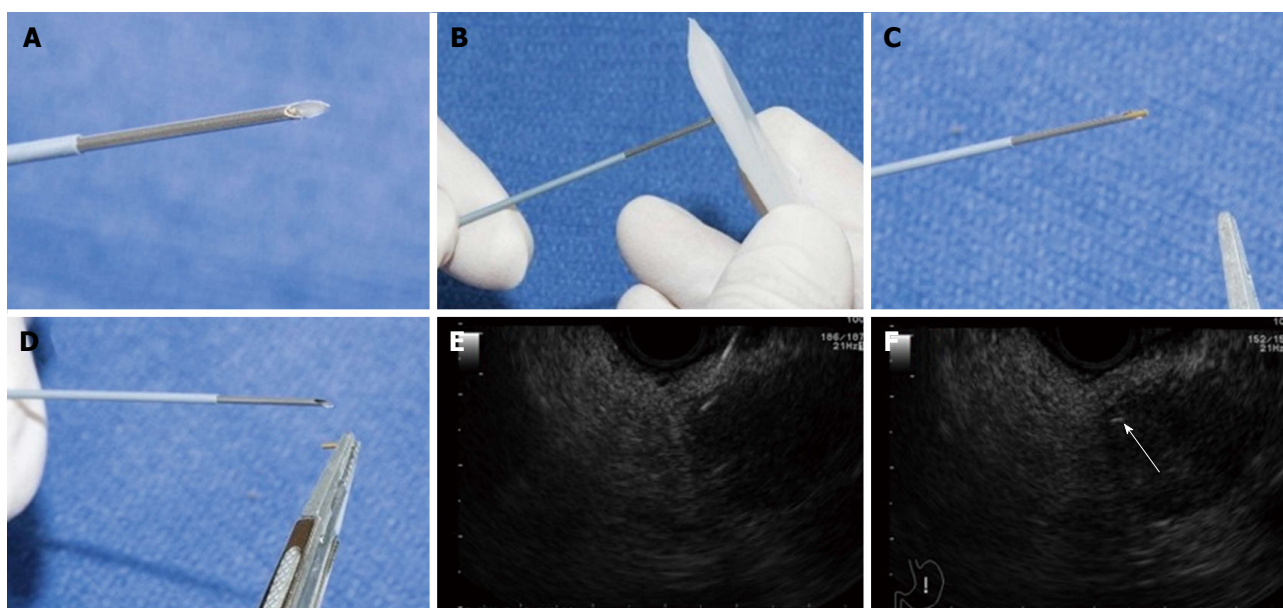


Figure 5 Images courtesy of Sanders *et al*^[74]. A: Fiducial loaded into 19-gauge needle with sterile forceps; B: Fiducial within tip of needle; C: Sealing fiducial with sterile bonewax; D: Loaded fiducial ready for advancement down operating channel; E and F: Needle delivering fiducial into pancreatic mass (arrow).

in an adjacent organ^[83]. To date, there is only one study that reported the use of EUS-RFA in humans. The study used a cryothermal probe which is a large bore flexible bipolar device that combines radiofrequency with cryogenic cooling in the same session. The probe was successfully applied under EUS guidance in 73% (16/22) of patients with locally advanced pancreatic cancer and the procedure was well tolerated in all patients. In 6/16 patients, reduction in tumor size was noted on follow-up CT^[83].

Photodynamic therapy: Photodynamic therapy (PDT) is a technique where a specific wavelength of light is delivered *via* optical fibers threaded through a needle placed in the target tissue^[84]. Wavelength light is then activated by a photosensitizing agent which is usually administered intravenously. Photosensitizer is also present in pancreatic cancer at a sevenfold greater concentration compared with normal tissue^[85]. The combination of a photosensitizing agent and wavelength light in the presence of oxygen leads to the generation of reactive oxygen species that can damage cellular constituents leading to cell death^[86]. Unlike RFA, PDT is collagen sparing and preserves normal tissue architecture^[87].

Promising results of PDT on cholangiocarcinoma have been reported including survival benefit^[88-94] however its use in pancreatic cancer is still at an experimental stage. Three pilot trials of PDT in patients with locally advanced pancreatic cancer have demonstrated its feasibility and safety^[86,95,96].

CONCLUSION

EUS-guided celiac plexus intervention is a useful adjunct

to conventional analgesia for pain management in patients with pancreatic cancer. Direct injection into the celiac ganglia may result in a better response.

EUS-guided biliary drainage has emerged as a viable alternative to PTBD in patients who have failed ERCP. However, it should be performed by an interventional endoscopist with expertise in both ERCP and EUS at a tertiary center where surgery and radiology can provide support in case of adverse events.

EUS-guided anastomosis is in the preliminary stage of development and the majority of studies are limited to animal models. Major advancements in technique and prospective human trials are needed before it becomes a feasible alternative to surgery in patients at high risk of operative complications.

Results of trials with EUS-guided anti-tumor injection therapy have been disappointing. The lack of effective anti-tumor agents is a significant barrier to the development in this field.

EUS-guided brachytherapy and fiducial placement can be performed safely and easily. However, there is no available data to suggest clear survival benefit, although clinical benefit from pain relief has been noted in some studies.

The use of EUS-guided ablative therapies is still at an experimental stage. Further human trials are needed to determine its clinical benefit.

To summarize, EUS is an indispensable tool in pancreatic cancer not only for tissue diagnosis and disease staging but also for therapeutic purposes. Although some EUS-guided therapies have become widely accepted interventions for patients with pancreatic cancer, others have yet to evolve. Given the lack of effective systemic treatment for pancreatic cancer at present, further research in this field is warranted.

REFERENCES

- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300 [PMID: 20610543 DOI: 10.3322/caac.20073]
- Yeo TP, Hruban RH, Leach SD, Wilentz RE, Sohn TA, Kern SE, Iacobuzio-Donahue CA, Maitra A, Goggins M, Canto MI, Abrams RA, Laheru D, Jaffee EM, Hidalgo M, Yeo CJ. Pancreatic cancer. *Curr Probl Cancer* 2002; **26**: 176-275 [PMID: 12399802]
- Vonlaufen A, Joshi S, Qu C, Phillips PA, Xu Z, Parker NR, Toi CS, Pirola RC, Wilson JS, Goldstein D, Apte MV. Pancreatic stellate cells: partners in crime with pancreatic cancer cells. *Cancer Res* 2008; **68**: 2085-2093 [PMID: 18381413 DOI: 10.1158/0008-5472.CAN-07-2477]
- Hwang RF, Moore T, Arumugam T, Ramachandran V, Amos KD, Rivera A, Ji B, Evans DB, Logsdon CD. Cancer-associated stromal fibroblasts promote pancreatic tumor progression. *Cancer Res* 2008; **68**: 918-926 [PMID: 18245495 DOI: 10.1158/0008-5472.CAN-07-5714]
- Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Rückert F, Grützmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457-1461 [PMID: 19460966 DOI: 10.1126/science.1171362]
- Sun H, Ma H, Hong G, Sun H, Wang J. Survival improvement in patients with pancreatic cancer by decade: a period analysis of the SEER database, 1981-2010. *Sci Rep* 2014; **4**: 6747 [PMID: 25339498 DOI: 10.1038/srep06747]
- Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. *Gastrointest Endosc* 1996; **44**: 656-662 [PMID: 8979053]
- Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. *Am J Gastroenterol* 2007; **102**: 430-438 [PMID: 17100960]
- Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci* 2009; **54**: 2330-2337 [PMID: 19137428 DOI: 10.1007/s10620-008-0651-x]
- Kaufman M, Singh G, Das S, Concha-Parra R, Erber J, Micames C, Gress F. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. *J Clin Gastroenterol* 2010; **44**: 127-134 [PMID: 19826273 DOI: 10.1097/MCG.0b013e3181bb854d]
- Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. *Cochrane Database Syst Rev* 2011; **(3)**: CD007519 [PMID: 21412903 DOI: 10.1002/14651858.CD007519.pub2]
- Wyse JM, Carone M, Paquin SC, Usatii M, Sahai AV. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol* 2011; **29**: 3541-3546 [PMID: 21844506 DOI: 10.1200/JCO.2010.32.2750]
- McGreevy K, Hurley RW, Erdek MA, Aner MM, Li S, Cohen SP. The effectiveness of repeat celiac plexus neurolysis for pancreatic cancer: a pilot study. *Pain Pract* 2013; **13**: 89-95 [PMID: 22568823 DOI: 10.1111/j.1533-2500.2012.00557.x]
- LeBlanc JK, Al-Haddad M, McHenry L, Sherman S, Juan M, McGreevy K, Johnson C, Howard TJ, Lillemoe KD, DeWitt J. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? *Gastrointest Endosc* 2011; **74**: 1300-1307 [PMID: 22000795 DOI: 10.1016/j.gie.2011.07.073]
- Sakamoto H, Kitano M, Kamata K, Komaki T, Imai H, Chikugo T, Takeyama Y, Kudo M. EUS-guided broad plexus neurolysis over the superior mesenteric artery using a 25-gauge needle. *Am J Gastroenterol* 2010; **105**: 2599-2606 [PMID: 20823834 DOI: 10.1038/ajg.2010.339]
- Ascunce G, Ribeiro A, Reis I, Rocha-Lima C, Sleeman D, Merchan J, Levi J. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). *Gastrointest Endosc* 2011; **73**: 267-274 [PMID: 21295640 DOI: 10.1016/j.gie.2010.10.029]
- Gleeson FC, Levy MJ, Papachristou GI, Pelaez-Luna M, Rajan E, Clain JE, Topazian MD. Frequency of visualization of presumed celiac ganglia by endoscopic ultrasound. *Endoscopy* 2007; **39**: 620-624 [PMID: 17549662]
- Doi S, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, Mukai T, Katanuma A, Kubota K, Ohnishi T, Ryozaawa S, Hara K, Itoi T, Hanada K, Yamao K. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. *Endoscopy* 2013; **45**: 362-369 [PMID: 23616126 DOI: 10.1055/s-0032-1326225]
- Gunarathnam NT, Sarma AV, Norton ID, Wiersema MJ. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. *Gastrointest Endosc* 2001; **54**: 316-324 [PMID: 11522971]
- Fujii L, Clain JE, Morris JM, Levy MJ. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. *Endoscopy* 2012; **44** Suppl 2 UCTN: E265-E266 [PMID: 22814912 DOI: 10.1055/s-0032-1309708]
- Mittal MK, Rabinstein AA, Wijdicks EF. Pearls & pyrrhic victories: Acute spinal cord infarction following endoscopic ultrasound-guided celiac plexus neurolysis. *Neurology* 2012; **78**: e57-e59 [PMID: 22371417]
- Loeve US, Mortensen MB. Lethal necrosis and perforation of the stomach and the aorta after multiple EUS-guided celiac plexus neurolysis procedures in a patient with chronic pancreatitis. *Gastrointest Endosc* 2013; **77**: 151-152 [PMID: 22624792 DOI: 10.1016/j.gie.2012.03.005]
- Gimeno-García AZ, Elwassief A, Paquin SC, Sahai AV. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. *Endoscopy* 2012; **44** Suppl 2 UCTN: E267 [PMID: 22814913 DOI: 10.1055/s-0032-1309709]
- Jang HY, Cha SW, Lee BH, Jung HE, Choo JW, Cho YJ, Ju HY, Cho YD. Hepatic and splenic infarction and bowel ischemia following endoscopic ultrasound-guided celiac plexus neurolysis. *Clin Endosc* 2013; **46**: 306-309 [PMID: 23767046 DOI: 10.5946/ce.2013.46.3.306]
- Nguyen-Tang T, Binmoeller KF, Sanchez-Yague A, Shah JN. Endoscopic ultrasound (EUS)-guided transhepatic antegrade self-expandable metal stent (SEMS) placement across malignant biliary obstruction. *Endoscopy* 2010; **42**: 232-236 [PMID: 20119894 DOI: 10.1055/s-0029-1243858]
- Artifon EL, Safatle-Ribeiro AV, Ferreira FC, Poli-de-Figueiredo L, Rasslan S, Carnevale F, Otoch JP, Sakai P, Kahaleh M. EUS-guided antegrade transhepatic placement of a self-expandable metal stent in hepatico-jejunal anastomosis. *JOP* 2011; **12**: 610-613 [PMID: 22072253]
- Itoi T, Yamao K. EUS 2008 Working Group document: evaluation of EUS-guided choledochoduodenostomy (with video). *Gastrointest Endosc* 2009; **69**: S8-12 [PMID: 19179177 DOI: 10.1016/j.gie.2008.11.003]
- Savides TJ, Varadarajulu S, Palazzo L. EUS 2008 Working Group document: evaluation of EUS-guided hepaticogastrostomy. *Gastrointest Endosc* 2009; **69**: S3-S7 [PMID: 19179166 DOI: 10.1016/j.gie.2008.10.060]
- Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. *Gastrointest Endosc* 2006; **64**: 52-59 [PMID: 16813803]
- Maranki J, Hernandez AJ, Arslan B, Jaffan AA, Angle JF, Shami VM, Kahaleh M. Interventional endoscopic ultrasound-guided

- cholangiography: long-term experience of an emerging alternative to percutaneous transhepatic cholangiography. *Endoscopy* 2009; **41**: 532-538 [PMID: 19533558 DOI: 10.1055/s-0029-1214712]
- 31 **Kim YS**, Gupta K, Mallery S, Li R, Kinney T, Freeman ML. Endoscopic ultrasound rendezvous for bile duct access using a transduodenal approach: cumulative experience at a single center. A case series. *Endoscopy* 2010; **42**: 496-502 [PMID: 20419625 DOI: 10.1055/s-0029-1244082]
 - 32 **Fabbri C**, Luigiano C, Fuccio L, Polifemo AM, Ferrara F, Ghersi S, Bassi M, Billi P, Maimone A, Cennamo V, Masetti M, Jovine E, D'Imperio N. EUS-guided biliary drainage with placement of a new partially covered biliary stent for palliation of malignant biliary obstruction: a case series. *Endoscopy* 2011; **43**: 438-441 [PMID: 21271507 DOI: 10.1055/s-0030-1256097]
 - 33 **Komaki T**, Kitano M, Sakamoto H, Kudo M. Endoscopic ultrasonography-guided biliary drainage: evaluation of a choledochoduodenostomy technique. *Pancreatol* 2011; **11** Suppl 2: 47-51 [PMID: 21464587 DOI: 10.1159/000323508]
 - 34 **Park do H**, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. *Gastrointest Endosc* 2011; **74**: 1276-1284 [PMID: 21963067 DOI: 10.1016/j.gie.2011.07.054]
 - 35 **Hara K**, Yamao K, Niwa Y, Sawaki A, Mizuno N, Hijioka S, Tajika M, Kawai H, Kondo S, Kobayashi Y, Matumoto K, Bhatia V, Shimizu Y, Ito A, Hirooka Y, Goto H. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. *Am J Gastroenterol* 2011; **106**: 1239-1245 [PMID: 21448148 DOI: 10.1038/ajg.2011.84]
 - 36 **Iwashita T**, Lee JG, Shinoura S, Nakai Y, Park DH, Muthusamy VR, Chang KJ. Endoscopic ultrasound-guided rendezvous for biliary access after failed cannulation. *Endoscopy* 2012; **44**: 60-65 [PMID: 22127960 DOI: 10.1055/s-0030-1256871]
 - 37 **Shah JN**, Marson F, Weilert F, Bhat YM, Nguyen-Tang T, Shaw RE, Binmoeller KF. Single-operator, single-session EUS-guided antegrade cholangiopancreatography in failed ERCP or inaccessible papilla. *Gastrointest Endosc* 2012; **75**: 56-64 [PMID: 22018554 DOI: 10.1016/j.gie.2011.08.032]
 - 38 **Dhir V**, Bhandari S, Bapat M, Maydeo A. Comparison of EUS-guided rendezvous and precut papillotomy techniques for biliary access (with videos). *Gastrointest Endosc* 2012; **75**: 354-359 [PMID: 22248603 DOI: 10.1016/j.gie.2011.07.075]
 - 39 **Park do H**, Jeong SU, Lee BU, Lee SS, Seo DW, Lee SK, Kim MH. Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video). *Gastrointest Endosc* 2013; **78**: 91-101 [PMID: 23523301 DOI: 10.1016/j.gie.2013.01.042]
 - 40 **Khashab MA**, Dewitt J. EUS-guided biliary drainage: is it ready for prime time? Yes! *Gastrointest Endosc* 2013; **78**: 102-105 [PMID: 23820411 DOI: 10.1016/j.gie.2013.03.004]
 - 41 **Artifon EL**, Aparicio D, Paione JB, Lo SK, Bordini A, Rabello C, Otoch JP, Gupta K. Biliary drainage in patients with unresectable, malignant obstruction where ERCP fails: endoscopic ultrasonography-guided choledochoduodenostomy versus percutaneous drainage. *J Clin Gastroenterol* 2012; **46**: 768-774 [PMID: 22810111 DOI: 10.1097/MCG.0b013e31825f264c]
 - 42 **Ogura T**, Higuchi K. Does endoscopic ultrasound-guided biliary drainage really have clinical impact? *World J Gastroenterol* 2015; **21**: 1049-1052 [PMID: 25632176 DOI: 10.3748/wjg.v21.i4.1049]
 - 43 **Jang JW**, Lee SS, Song TJ, Hyun YS, Park do H, Seo DW, Lee SK, Kim MH, Yun SC. Endoscopic ultrasound-guided transmural and percutaneous transhepatic gallbladder drainage are comparable for acute cholecystitis. *Gastroenterology* 2012; **142**: 805-811 [PMID: 22245666 DOI: 10.1053/j.gastro.2011.12.051]
 - 44 **Itoi T**, Binmoeller K, Itokawa F, Umeda J, Tanaka R. Endoscopic ultrasonography-guided cholecystogastrostomy using a lumen-apposing metal stent as an alternative to extrahepatic bile duct drainage in pancreatic cancer with duodenal invasion. *Dig Endosc* 2013; **25** Suppl 2: 137-141 [PMID: 23617665 DOI: 10.1111/den.12084]
 - 45 **Widmer J**, Alvarez P, Gaidhane M, Paddu N, Umrana H, Sharaiha R, Kahaleh M. Endoscopic ultrasonography-guided cholecystogastrostomy in patients with unresectable pancreatic cancer using anti-migratory metal stents: a new approach. *Dig Endosc* 2014; **26**: 599-602 [PMID: 24102709 DOI: 10.1111/den.12163]
 - 46 **Luz LP**, Al-Haddad MA, Sey MS, DeWitt JM. Applications of endoscopic ultrasound in pancreatic cancer. *World J Gastroenterol* 2014; **20**: 7808-7818 [PMID: 24976719 DOI: 10.3748/wjg.v20.i24.7808]
 - 47 **Gavini H**, Lee JH. Endoscopic ultrasound-guided endotherapy. *J Clin Gastroenterol* 2015; **49**: 185-193 [PMID: 25551210 DOI: 10.1097/MCG.0000000000000276]
 - 48 **Tyberg A**, Kumta N, Karia K, Zerbo S, Sharaiha RZ, Kahaleh M. EUS-guided gastrojejunostomy after failed enteral stenting. *Gastrointest Endosc* 2015; **81**: 1011-1012 [PMID: 25680897 DOI: 10.1016/j.gie.2014.10.018]
 - 49 **Ikeuchi N**, Itoi T, Tsuchiya T, Nagakawa Y, Tsuchida A. One-step EUS-guided gastrojejunostomy with use of lumen-apposing metal stent for afferent loop syndrome treatment. *Gastrointest Endosc* 2015; **82**: 166 [PMID: 25887724 DOI: 10.1016/j.gie.2015.01.010]
 - 50 **Itoi T**, Itokawa F, Uraoka T, Gotoda T, Horii J, Goto O, Moriyasu F, Moon JH, Kitagawa Y, Yahagi N. Novel EUS-guided gastrojejunostomy technique using a new double-balloon enteric tube and lumen-apposing metal stent (with videos). *Gastrointest Endosc* 2013; **78**: 934-939 [PMID: 24237949 DOI: 10.1016/j.gie.2013.09.025]
 - 51 **Itoi T**, Ishii K, Tanaka R, Umeda J, Tonozuka R. Current status and perspective of endoscopic ultrasonography-guided gastrojejunostomy: endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy (with videos). *J Hepatobiliary Pancreat Sci* 2015; **22**: 3-11 [PMID: 25155270 DOI: 10.1002/jhbp.148]
 - 52 **Cope C**. Evaluation of compression cholecystogastric and cholecystojejunal anastomoses in swine after peroral and surgical introduction of magnets. *J Vasc Interv Radiol* 1995; **6**: 546-552 [PMID: 7579862]
 - 53 **Cope C**. Creation of compression gastroenterostomy by means of the oral, percutaneous, or surgical introduction of magnets: feasibility study in swine. *J Vasc Interv Radiol* 1995; **6**: 539-545 [PMID: 7579861]
 - 54 **Chopita N**, Vaillaverde A, Cope C, Bernedo A, Martinez H, Landoni N, Jmelnitzky A, Burgos H. Endoscopic gastroenteric anastomosis using magnets. *Endoscopy* 2005; **37**: 313-317 [PMID: 15824939]
 - 55 **van Hooft JE**, Vleggaar FP, Le Moine O, Bizzotto A, Voermans RP, Costamagna G, Deviere J, Siersema PD, Fockens P. Endoscopic magnetic gastroenteric anastomosis for palliation of malignant gastric outlet obstruction: a prospective multicenter study. *Gastrointest Endosc* 2010; **72**: 530-535 [PMID: 20656288 DOI: 10.1016/j.gie.2010.05.025]
 - 56 **Mimuro A**, Tsuchida A, Yamanouchi E, Itoi T, Ozawa T, Ikeda T, Nakamura R, Koyanagi Y, Nakamura K. A novel technique of magnetic compression anastomosis for severe biliary stenosis. *Gastrointest Endosc* 2003; **58**: 283-287 [PMID: 12872106]
 - 57 **Itoi T**, Yamanouchi E, Ikeda T, Sofuni A, Kurihara T, Tsuchiya T, Tsuchida A, Kasuya K, Moriyasu F. Magnetic compression anastomosis: a novel technique for canalization of severe hilar bile duct strictures. *Endoscopy* 2005; **37**: 1248-1251 [PMID: 16329026]
 - 58 **Fritscher-Ravens A**, Mosse CA, Mills TN, Mukherjee D, Park PO, Swain P. A through-the-scope device for suturing and tissue approximation under EUS control. *Gastrointest Endosc* 2002; **56**: 737-742 [PMID: 12397289]
 - 59 **Fritscher-Ravens A**, Mosse CA, Mukherjee D, Mills T, Park PO, Swain CP. Transluminal endosurgery: single lumen access anastomotic device for flexible endoscopy. *Gastrointest Endosc* 2003; **58**: 585-591 [PMID: 14520300]
 - 60 **Chang KJ**, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, Granger GA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced

- pancreatic carcinoma. *Cancer* 2000; **88**: 1325-1335 [PMID: 10717613]
- 61 **Irisawa A**, Takagi T, Kanazawa M, Ogata T, Sato Y, Takenoshita S, Ohto H, Ohira H. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine: a pilot study. *Pancreas* 2007; **35**: 189-190 [PMID: 17632329]
 - 62 **Hirooka Y**, Itoh A, Kawashima H, Hara K, Nonogaki K, Kasugai T, Ohno E, Ishikawa T, Matsubara H, Ishigami M, Katano Y, Ohmiya N, Niwa Y, Yamamoto K, Kaneko T, Nieda M, Yokokawa K, Goto H. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. *Pancreas* 2009; **38**: e69-e74 [PMID: 19276867 DOI: 10.1097/MPA.0b013e318197a9e3]
 - 63 **Hecht JR**, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, Hanna N, Chang KJ, Javle M, Posner M, Waxman I, Reid A, Erickson R, Canto M, Chak A, Blatner G, Kovacevic M, Thornton M. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. *Gastrointest Endosc* 2012; **75**: 332-338 [PMID: 22248601 DOI: 10.1016/j.gie.2011.10.007]
 - 64 **Herman JM**, Wild AT, Wang H, Tran PT, Chang KJ, Taylor GE, Donehower RC, Pawlik TM, Ziegler MA, Cai H, Savage DT, Canto MI, Klapman J, Reid T, Shah RJ, Hoffe SE, Rosemurgy A, Wolfgang CL, Laheru DA. Randomized phase III multi-institutional study of TNFerade biologic with fluorouracil and radiotherapy for locally advanced pancreatic cancer: final results. *J Clin Oncol* 2013; **31**: 886-894 [PMID: 23341531 DOI: 10.1200/JCO.2012.44.7516]
 - 65 **Hecht JR**, Bedford R, Abbruzzese JL, Lahoti S, Reid TR, Soetikno RM, Kirn DH, Freeman SM. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003; **9**: 555-561 [PMID: 12576418]
 - 66 **Hanna N**, Ohana P, Konikoff FM, Leichtmann G, Hubert A, Appelbaum L, Kopelman Y, Czerniak A, Hochberg A. Phase 1/2a, dose-escalation, safety, pharmacokinetic and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic cancer. *Cancer Gene Ther* 2012; **19**: 374-381 [PMID: 22498722 DOI: 10.1038/cgt.2012.10]
 - 67 **Jin Z**, Chang KJ. Endoscopic ultrasound-guided fiducial markers and brachytherapy. *Gastrointest Endosc Clin N Am* 2012; **22**: 325-331, x [PMID: 22632954 DOI: 10.1016/j.giec.2012.04.012]
 - 68 **Sun S**, Xu H, Xin J, Liu J, Guo Q, Li S. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. *Endoscopy* 2006; **38**: 399-403 [PMID: 16680642]
 - 69 **Jin Z**, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy* 2008; **40**: 314-320 [PMID: 18283622 DOI: 10.1055/s-2007-995476]
 - 70 **Du Y**, Jin Z, Jin H, Meng H, Zou D, Chen J, Liu Y, Zhan X, Wang D, Liao Z, Li Z. Long-term effect of gemcitabine-combined endoscopic ultrasonography-guided brachytherapy in pancreatic cancer. *J Interv Gastroenterol* 2013; **3**: 18-24
 - 71 **Koong AC**, Christofferson E, Le QT, Goodman KA, Ho A, Kuo T, Ford JM, Fisher GA, Greco R, Norton J, Yang GP. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005; **63**: 320-323 [PMID: 16168826]
 - 72 **Didolkar MS**, Coleman CW, Brenner MJ, Chu KU, Olexa N, Stanwyck E, Yu A, Neerchal N, Rabinowitz S. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J Gastrointest Surg* 2010; **14**: 1547-1559 [PMID: 20839073 DOI: 10.1007/s11605-010-1323-7]
 - 73 **Rwigema JC**, Parikh SD, Heron DE, Howell M, Zeh H, Moser AJ, Bahary N, Quinn A, Burton SA. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. *Am J Clin Oncol* 2011; **34**: 63-69 [PMID: 20308870 DOI: 10.1097/COC.0b013e3181d270b4]
 - 74 **Sanders MK**, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, Burton S, McGrath K. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. *Gastrointest Endosc* 2010; **71**: 1178-1184 [PMID: 20362284 DOI: 10.1016/j.gie.2009.12.020]
 - 75 **Park WG**, Yan BM, Schellenberg D, Kim J, Chang DT, Koong A, Patalano C, Van Dam J. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. *Gastrointest Endosc* 2010; **71**: 513-518 [PMID: 20189509 DOI: 10.1016/j.gie.2009.10.030]
 - 76 **Pishvaian AC**, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc* 2006; **64**: 412-417 [PMID: 16923491]
 - 77 **Khashab MA**, Kim KJ, Tryggestad EJ, Wild AT, Roland T, Singh VK, Lennon AM, Shin EJ, Ziegler MA, Sharaiha RZ, Canto MI, Herman JM. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. *Gastrointest Endosc* 2012; **76**: 962-971 [PMID: 23078921 DOI: 10.1016/j.gie.2012.07.006]
 - 78 **Carrara S**, Arcidiacono PG, Albarello L, Addis A, Enderle MD, Boemo C, Campagnol M, Ambrosi A, Doglioni C, Testoni PA. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. *Endoscopy* 2008; **40**: 321-326 [PMID: 18389449 DOI: 10.1055/s-2007-995595]
 - 79 **Wu Y**, Tang Z, Fang H, Gao S, Chen J, Wang Y, Yan H. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. *J Surg Oncol* 2006; **94**: 392-395 [PMID: 16967436]
 - 80 **Spiliotis JD**, Datsis AC, Michalopoulos NV, Kekelos SP, Vaxevanidou A, Rogdakis AG, Christopoulou AN. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. *J Surg Oncol* 2007; **96**: 89-90 [PMID: 17345594]
 - 81 **Goldberg SN**, Mallery S, Gazelle GS, Brugge WR. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. *Gastrointest Endosc* 1999; **50**: 392-401 [PMID: 10462663]
 - 82 **Kim HJ**, Seo DW, Hassanuddin A, Kim SH, Chae HJ, Jang JW, Park do H, Lee SS, Lee SK, Kim MH. EUS-guided radiofrequency ablation of the porcine pancreas. *Gastrointest Endosc* 2012; **76**: 1039-1043 [PMID: 23078928 DOI: 10.1016/j.gie.2012.07.015]
 - 83 **Arcidiacono PG**, Carrara S, Reni M, Petrone MC, Cappio S, Balzano G, Boemo C, Cereda S, Nicoletti R, Enderle MD, Neugebauer A, von Renteln D, Eickhoff A, Testoni PA. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. *Gastrointest Endosc* 2012; **76**: 1142-1151 [PMID: 23021160 DOI: 10.1016/j.gie.2012.08.006]
 - 84 **Vesper BJ**, Colvard MD. Photodynamic therapy (PDT): an evolving therapeutic technique in head and neck cancer treatment. In: Radosevich JA, editor. *Head & Neck Cancer: Current Perspectives, Advances, and Challenges*. Springer Netherlands, 2013: 649-676
 - 85 **Chatlani PT**, Nuutinen PJ, Toda N, Barr H, MacRobert AJ, Bedwell J, Bown SG. Selective necrosis in hamster pancreatic tumours using photodynamic therapy with phthalocyanine photosensitization. *Br J Surg* 1992; **79**: 786-790 [PMID: 1393474]
 - 86 **Bown SG**, Rogowska AZ, Whitelaw DE, Lees WR, Lovat LB, Ripley P, Jones L, Wyld P, Gillams A, Hatfield AW. Photodynamic therapy for cancer of the pancreas. *Gut* 2002; **50**: 549-557 [PMID: 11889078]
 - 87 **Fan BG**, Andrén-Sandberg A. Photodynamic therapy for pancreatic cancer. *Pancreas* 2007; **34**: 385-389 [PMID: 17446835]
 - 88 **McCaughan JS**, Mertens BF, Cho C, Barabash RD, Payton HW. Photodynamic therapy to treat tumors of the extrahepatic biliary ducts. A case report. *Arch Surg* 1991; **126**: 111-113 [PMID: 1824676]

- 89 **Ortner MA**, Liebetruth J, Schreiber S, Hanft M, Wruck U, Fusco V, Müller JM, Hörtnagl H, Lochs H. Photodynamic therapy of nonresectable cholangiocarcinoma. *Gastroenterology* 1998; **114**: 536-542 [PMID: 9496944]
- 90 **Ortner ME**, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, Voderholzer W, Schachschal G, Mössner J, Lochs H. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003; **125**: 1355-1363 [PMID: 14598251]
- 91 **Witzigmann H**, Berr F, Ringel U, Caca K, Uhlmann D, Schoppmeyer K, Tannapfel A, Wittekind C, Mossner J, Hauss J, Wiedmann M. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. *Ann Surg* 2006; **244**: 230-239 [PMID: 16858185]
- 92 **Zoepf T**, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 2005; **100**: 2426-2430 [PMID: 16279895]
- 93 **Pereira SP**, Ayaru L, Rogowska A, Mosse A, Hatfield AR, Bown SG. Photodynamic therapy of malignant biliary strictures using meso-tetrahydroxyphenylchlorin. *Eur J Gastroenterol Hepatol* 2007; **19**: 479-485 [PMID: 17489058]
- 94 **Wolfsen HC**. Uses of photodynamic therapy in premalignant and malignant lesions of the gastrointestinal tract beyond the esophagus. *J Clin Gastroenterol* 2005; **39**: 653-664 [PMID: 16082272]
- 95 **Chan HH**, Nishioka NS, Mino M, Lauwers GY, Puricelli WP, Collier KN, Brugge WR. EUS-guided photodynamic therapy of the pancreas: a pilot study. *Gastrointest Endosc* 2004; **59**: 95-99 [PMID: 14722560]
- 96 **Huggett MT**, Jermyn M, Gillams A, Illing R, Mosse S, Novelli M, Kent E, Bown SG, Hasan T, Pogue BW, Pereira SP. Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. *Br J Cancer* 2014; **110**: 1698-1704 [PMID: 24569464 DOI: 10.1038/bjc.2014.95]

P- Reviewer: Buanes TA, Kitano M, Sadik R **S- Editor:** Ji FF

L- Editor: A **E- Editor:** Liu SQ



Retrospective Cohort Study

Risk factors for local recurrence after *en bloc* endoscopic submucosal dissection for early gastric cancer

Ju Yup Lee, Kwang Bum Cho, Eun Soo Kim, Kyung Sik Park, Yoo Jin Lee, Yoon Suk Lee, Byoung Kuk Jang, Woo Jin Chung, Jae Seok Hwang

Ju Yup Lee, Kwang Bum Cho, Eun Soo Kim, Kyung Sik Park, Yoo Jin Lee, Yoon Suk Lee, Byoung Kuk Jang, Woo Jin Chung, Jae Seok Hwang, Department of Internal Medicine, Keimyung University School of Medicine, Daegu 41931, South Korea

Author contributions: Lee JY reviewed the literature and drafted the manuscript; Cho KB designed and supervised research; Kim ES and Park KS designed and advised research; Lee YJ and Lee YS performed data collection and statistical analysis; Jang BK, Chung WJ and Hwang JS reviewed manuscript and advised.

Institutional review board statement: This study was approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center, South Korea (DSMC 2015-10-047).

Informed consent statement: The institutional review board waived the requirement for informed consent because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment.

Conflict-of-interest statement: The authors have no competing interests.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Kwang Bum Cho, MD, PhD, Department of Internal Medicine, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, South Korea. chokb@dsmc.or.kr
Telephone: +82-53-2507088
Fax: +82-53-2507442

Received: November 9, 2015
Peer-review started: November 10, 2015
First decision: December 18, 2015
Revised: January 1, 2016
Accepted: January 29, 2016
Article in press: January 31, 2016
Published online: April 10, 2016

Abstract

AIM: To investigate factors related to recurrence following *en bloc* resection using endoscopic submucosal dissection (ESD) in patients with early gastric cancer (EGC).

METHODS: A total of 1121 patients (1215 lesions) who had undergone ESD for gastric neoplasia between April 2003 and May 2010 were retrospectively reviewed. Data from 401 patients (415 lesions) were analyzed, following the exclusion of those who underwent piecemeal resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions.

RESULTS: Local recurrence after *en bloc* ESD was found in 36 cases (8.7%). Unclear resection margins, long procedure times, and narrow safety margins were identified as risk factors for recurrence. Lesions located in the upper third of the stomach showed a higher rate of recurrence than those located in the lower third of the stomach (OR = 2.9, $P = 0.03$). The probability of no recurrence for up to 24 mo was 79.9% in those with a safety resection margin ≤ 1 mm and 89.5% in those with a margin > 1 mm (log-rank test, $P = 0.03$).

CONCLUSION: Even in cases in which *en bloc* ESD is performed for EGC, local recurrence still occurs. To reduce local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases

in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important.

Key words: Early gastric cancer; Endoscopic mucosal resection; Recurrence; *En bloc* resection; Endoscopic submucosal dissection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Unclear resection margins, long procedure times, and narrow safety margins were identified as risk factors for recurrence following *en bloc* endoscopic submucosal dissection (ESD) for early gastric cancer. Lesions located in the upper third of the stomach demonstrated more recurrences than those located in the lower third of the stomach. To reduce local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important.

Lee JY, Cho KB, Kim ES, Park KS, Lee YJ, Lee YS, Jang BK, Chung WJ, Hwang JS. Risk factors for local recurrence after *en bloc* endoscopic submucosal dissection for early gastric cancer. *World J Gastrointest Endosc* 2016; 8(7): 330-337 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i7/330.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i7.330>

INTRODUCTION

As regular national gastric cancer screening *via* endoscopy is being implemented in South Korea with an increased interest in health, findings of early gastric cancer (EGC) and precancerous lesions are increasing rapidly^[1,2]. In addition, due to advances in the development of endoscopy-related tools and equipment and improvements in the procedural skills of doctors, performing endoscopic treatment for EGC is getting easier^[3]. As a result, existing endoscopic mucosal resection (EMR) has led to significant progress in endoscopic submucosal dissection (ESD), in terms of resection techniques, and regardless of the size of the lesions, *en bloc* resection has become possible^[4].

The classic EMR method is a simple procedure, but it has limitations in that the ratio of *en bloc* resection to complete resection decreases depending on the size of the lesion^[5,6]. In the contrast, the ESD method is a relatively complex procedure with a high level of difficulty, but it has a higher rate of *en bloc* resection than the EMR method, with the capacity to perform accurate post-resection pathological assessment, and it has recently become widely available as a treatment

for EGC^[5-8]. In endoscopic resection, accomplishing reconstruction of dissected tissues when the resection is performed in a piecemeal fashion and determining whether complete resection of the lesion has been achieved is difficult, and this results in higher rates of local recurrence. Therefore, *en bloc* resection is being suggested as the standard method of ESD as it increases the accuracy of pathological assessment of complete resection and lowers the rate of local recurrence^[9]. Incomplete resection procedures have been identified as an independent factor that increases the risk of local recurrence^[10], but although *en bloc* resection has been practiced, there have been very few studies on the risk factors associated with local recurrence after *en bloc* resection. To that end, the aim of the current study was to investigate factors related to local recurrence in patients with EGC who underwent *en bloc* resection *via* ESD.

MATERIALS AND METHODS

Study subjects

The medical records of 1121 patients (1215 lesions) who had undergone ESD for the treatment of gastric neoplasia between April 2003 and May 2010 at Keimyung University Dongsan Hospital (Daegu, South Korea) were retrospectively reviewed. Because we aimed to evaluate the risk factors for local recurrence after *en bloc* resection only and to analyze the risk factors depending on the safety resection margin, patients who underwent partial resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions were excluded. Finally, data from 401 patients (415 lesions) were analyzed (Figure 1). Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center, South Korea (DSMC 2015-10-047).

ESD methods

The ESD procedure was performed following a standard method. First the boundaries of the lesions were clarified using a solution of indigo carmine diluted to 10 times its volume, and the margins were marked with a 5 mm space from the boundaries of the lesions using an argon plasma laser connected to an ERBE VIO 300D electrosurgical unit (ERBE United States, Marietta, GA, United States). For submucosal injection, a solution was used consisting of hypertonic saline solution 100 mL, 1:1000 epinephrine 1 mL, and indigo carmine 1 mL. The incision knife was connected to the ERBE VIO 300D electrosurgical unit, a flex knife (Olympus, Tokyo, Japan) was used in mucosal incision, and the IT-2 knife (Olympus, Tokyo, Japan) was used for most submucosal dissection, but in some cases, a hook knife (Olympus, Tokyo, Japan) was used as well. Most procedures were carried out in Endocut I mode (Effect 2), and in some portions containing blood vessels, forced coagulation

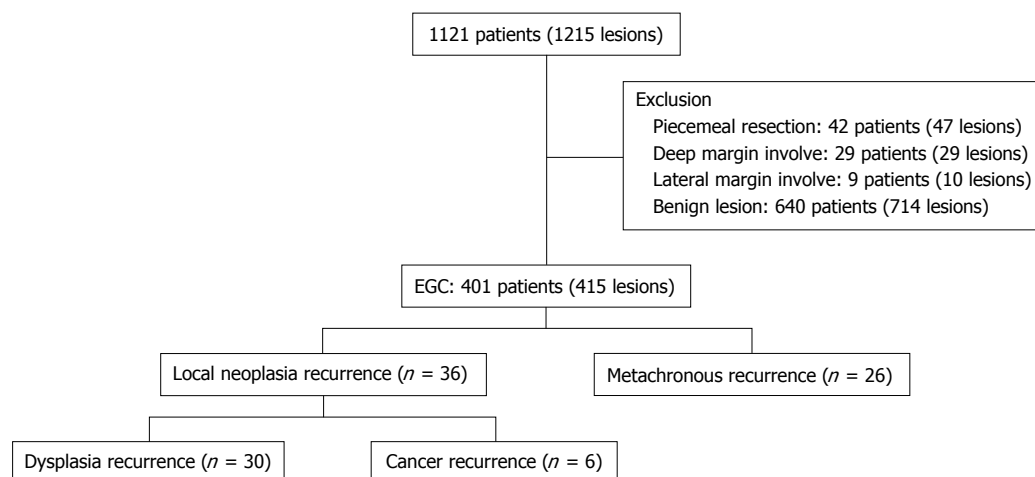


Figure 1 Flow chart of the patients. EGC: Early gastric cancer.

mode (Effect 1) was utilized.

Histopathological evaluation

For histopathological examination, resected specimens were sectioned perpendicularly at 2-mm intervals. The EGC location was classified into upper third, middle third, and lower third according to the location of the center point. The gross type of EGC was classified into type I (protruded type), type II (superficial type), and type III (excavated type) in accordance with the classification methods of the Japan Gastroenterological Endoscopy Society, and type II was subdivided again into type IIa (superficial elevated), type IIb (flat type), and type IIc (superficial depressed type)^[11]. In cases in which various shapes were mixed in one lesion, it was recorded as the mixed type. Based on the histological findings, tissues of the lesion were classified into differentiated type adenocarcinoma (well or moderately differentiated adenocarcinoma) and undifferentiated type adenocarcinoma (poorly differentiated or signet ring cell adenocarcinoma). Tumor involvement in the lateral and deep margins, lymphatic and vascular involvement, and the presence of submucosal invasion was assessed. In cases of submucosal infiltration, invasion depth was measured and quantified.

Evaluation of outcomes

The following clinical variables were investigated: Patient age, sex, gross tumor type, *en bloc* resection rate, location, size, histology, procedure time, safety margin, local neoplasia recurrence rate, and local cancer recurrence rate.

En bloc resection was defined as a resection in a single piece, whereas piecemeal resection was conducted in multiple pieces. Complete resection was defined as complete reconstruction of the lesion with negative deep and lateral margins with no lymphovascular involvement. The sizes of lesions were categorized into less than 20 mm, 21–30 mm, 31–40 mm, and over 40 mm. When malignant cells were found from the resection site within

3 mo after endoscopic removal of gastric carcinoma, the case was defined as incomplete resection, and when malignant cells or dysplastic cells (low grade, high grade) were found from the resection site during follow-up examinations after 3 mo, the case was defined as local recurrence of neoplasia. When only malignant cells were found from the resection site, the case was defined as local cancer recurrence. In addition, when neoplasia (dysplasia or malignant) was found from a site other than the resection site during follow-up observation, the case was defined as metachronous recurrence. Procedure time was defined as the time from the start of marking to complete removal of the tumor. Safety margins were defined as the distance between the lesion and the edges of the cuts around the resected specimen.

Follow-up observation

Patients were followed up with endoscopic examinations and biopsy at 3, 6, 12 and 24 mo after ESD. To detect local recurrence or metachronous cancer, biopsy was performed at the treatment-related scar in the case of any suspicious abnormalities. The cumulative neoplasia recurrence-free rate was estimated.

Statistical analysis

SPSS software version 18.0 for Windows (SPSS, Inc., Chicago, IL, United States) was used for statistical analysis. For comparison of continuous variables between two groups, the independent samples t-test was used, while for comparison of frequency variables, the χ^2 test was used through cross analysis. Continuous variables were presented as means \pm SD, and count variables were presented in the forms of frequency and percentage. Multivariate analysis was performed using binary logistic regression methods. Cumulative recurrence rates and recurrence times were calculated by the Kaplan-Meier method, and they were compared with each other using a log-rank test. A *P* value less than 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Lee YJ and Lee YS.

Table 1 Clinicopathologic feature of the 415 lesions treated with endoscopic submucosal dissection

	No. of lesions <i>n</i> = 415
Age, yr (mean ± SD)	64.2 ± 9.8
Sex, <i>n</i> (%)	
Male	291 (70.1)
Female	124 (29.9)
Gross type of tumor, <i>n</i> (%)	
Protruded (I)	29 (7.0)
Superficial elevated (II a)	146 (35.2)
Flat (II b)	76 (18.3)
Superficial depressed (II c)	134 (32.3)
Excavated (III)	2 (0.5)
Mixed	28 (6.7)
<i>En bloc</i> resection, <i>n</i> (%)	415 (100)
Piecemeal resection, <i>n</i> (%)	0 (0)
Tumor location, <i>n</i> (%)	
Upper	15 (3.6)
Mid	129 (30.9)
Lower	271 (65.0)
Tumor size, <i>n</i> (%)	
≤ 20 mm	116 (28.0)
21-30 mm	77 (18.8)
31-40 mm	122 (29.4)
> 40 mm	100 (24.1)
Histology, <i>n</i> (%)	
Well differentiated	195 (47.0)
Moderate differentiated	180 (43.4)
Poorly differentiated	30 (7.2)
Signet ring cell	10 (2.4)
Follow-up period, mo (mean ± SD)	19.7 ± 17.5

RESULTS

Characteristics of patients and lesions

The mean age of patients was 64.2 ± 9.8 years and 291 (70.1) patients were men. For the gross type of tumor, 146 (35.2%) cases were type II a and this was the most frequent type. Regarding the location of lesions, 271 (65.0%) patients had lesions in the lower third of the stomach, representing the highest frequency, followed by 129 (30.9%) patients with lesions in the mid-third of the stomach, and 15 (3.6%) patients with lesions in the upper third of stomach. Regarding the size of tumors removed by ESD, tumors ≤ 20 mm were found in 110 (28.0%) cases, tumors 21-30 mm were found in 77 (18.8%) cases, tumors 31-40 mm were found in 122 (29.4%) cases, and tumors over 40 mm were found in 100 (24.1%) cases. Histologically, well differentiated adenocarcinoma and moderately differentiated adenocarcinoma were observed in 195 (47.0%) and 180 (43.4%) cases, respectively, constituting ≥ 90%. The mean follow-up period for these patients was 19.7 mo (Table 1).

Comparison of the recurrence group and the non-recurrence group

Local neoplasia recurrence was observed in 36 (8.7%) cases, but there was no significant difference in age at the time of diagnosis, sex, tumor size, location, or degree of differentiation when compared to the non-

recurrence group (Table 2). However, there were many recurrences in cases in which tumors had ill-defined margins (33.3% vs 17.4%, $P = 0.02$), long procedure times (63.5 min vs 48.8 min, $P = 0.02$), and narrow safety resection margins (3.1 mm vs 4.2 mm, $P = 0.03$) (Table 2). The performance of multivariate analysis revealed that ill-defined tumor margin was the element factor that related to local neoplasia recurrence ($P = 0.03$) (Table 2).

Factors related to sufficient safety resection margins

When 1 mm was used as the reference value, 63 (15.2%) cases were found to have safety resection margins ≤ 1 mm. There was no difference in age at the time of diagnosis, sex, tumor size, location, or degree of differentiation between the two groups. Nevertheless, the group with safety resection margins ≤ 1 mm was found to have more lesions located in the upper third and mid-third of the stomach ($P < 0.0001$) and had longer operation times ($P = 0.04$) (Table 3). Multivariate analysis revealed that the patients with lesions located in the upper third of the stomach demonstrated more recurrences than those with lesions located in the lower third of the stomach (OR = 2.900, 95%CI: 1.110-7.579, $P = 0.03$) (Table 4). Designating 1 mm as the safety resection margin, there was no difference in recurrence of neoplasia, but there was more frequent recurrence of cancer ($P = 0.006$) (Table 5).

Follow-up observation and cumulative local recurrence rate

During the entire follow-up observation period, 6 cases (6/415, 1.4%) were observed of the recurrence of malignancy at the same site, and 26 cases (26/415, 6.3%) were observed of metachronous gastric carcinoma (Figure 1). In addition, the probability of no recurrence for up to 24 mo was 79.9% in those with safety resection margin ≤ 1 mm and 89.5% in those with margins that exceeded 1 mm, indicating that the local recurrence of neoplasia was observed more frequently in those with safety resection margins ≤ 1 mm, and the difference between the two groups was significant ($P = 0.03$) (Figure 2).

DISCUSSION

In cases of lesions larger than 20 mm, ESD offers far superior *en bloc* resection rates and very low local recurrence rates when compared with EMR^[12]. In general, the results of ESD for lesions larger than 20 mm have demonstrated an *en bloc* resection rate of over 90% with little local recurrence, while EMR has demonstrated very low *en bloc* resection rates of about 60% in cases of lesions sized about 10 mm and 14%-40% for lesions sized about 20-30 mm, and the local recurrence rate is about 10%^[13,14]. Regarding the *en bloc* resection rate, following the resection, determining complete resection with histological accuracy and thereby significantly reducing the occurrence of any situations that require

Table 2 Risk factor associated with neoplasia recurrence

	Recurrence <i>n</i> = 36	No recurrence <i>n</i> = 379	Univariate <i>P</i> value	Multivariate <i>P</i> value
Age, yr (mean ± SD)	66.7 ± 9.0	64.0 ± 9.9	0.11	
Male/female	25/11	266/113	0.93	
Tumor margin, <i>n</i> (%)			0.02	0.03
Well-defined	24 (66.7)	313 (82.6)		
Ill-defined	12 (33.3)	66 (17.4)		
Tumor size, <i>n</i> (%)			0.62	
≤ 20 mm	9 (25.0)	107 (28.2)		
21-30 mm	6 (16.7)	71 (18.7)		
31-40 mm	14 (38.9)	108 (28.5)		
> 40 mm	7 (19.4)	93 (24.5)		
Tumor location, <i>n</i> (%)			0.05	
Upper	3 (8.3)	12 (3.2)		
Mid	14 (38.9)	115 (30.3)		
Lower	19 (52.8)	252 (66.5)		
Histology, <i>n</i> (%)			0.7	
Well differentiated	17 (47.2)	178 (47.0)		
Moderate differentiated	13 (36.1)	167 (44.1)		
Poorly differentiated	6 (16.7)	24 (6.3)		
Signet ring cell	0 (0.0)	10 (2.6)		
Procedure time, min (mean ± SD)	63.5 ± 56.9	48.8 ± 34.3	0.02	0.06
Safety margin, mm (mean ± SD)	3.1 ± 2.1	4.2 ± 2.9	0.03	0.05

Table 3 Factors associated with sufficient safety margin after endoscopic submucosal dissection (Univariate)

	Safety margin ≤ 1 mm <i>n</i> = 63	Safety margin > 1 mm <i>n</i> = 352	<i>P</i> value
Age, yr (mean ± SD)	65.9 ± 11.1	63.9 ± 9.5	0.14
Male/female	38/25	253/99	0.12
Tumor margin, <i>n</i> (%)			0.52
Well-defined	53 (84.1)	284 (80.7)	
Ill-defined	10 (15.9)	68 (19.3)	
Tumor size, <i>n</i> (%)			0.55
≤ 20 mm	21 (33.3)	95 (27.0)	
21-30 mm	12 (19.0)	65 (18.5)	
31-40 mm	14 (22.2)	108 (30.7)	
> 40 mm	16 (25.4)	84 (23.9)	
Tumor location, <i>n</i> (%)			< 0.0001
Upper	7 (11.1)	8 (2.3)	
Mid	31 (49.2)	98 (27.8)	
Lower	25 (39.7)	246 (69.9)	
Histology, <i>n</i> (%)			0.85
Well differentiated	32 (50.8)	163 (46.3)	
Moderate differentiated	24 (38.1)	156 (44.3)	
Poorly differentiated	3 (4.8)	27 (7.7)	
Signet ring cell	4 (6.3)	6 (1.7)	
Procedure time, min (mean ± SD)	58.9 ± 43.8	48.5 ± 35.4	0.04

Table 4 Factors associated with sufficient safety margin after endoscopic submucosal dissection (Multivariate)

	Multivariate analysis	
	Odds ratio (95%CI)	<i>P</i> value
Location		
Upper	2.90 (1.11-7.58)	0.03
Mid	1.10 (0.48-2.55)	0.82
Lower	1 (ref)	
Ill-defined margin	2.32 (1.00-4.96)	0.03

unnecessary additional treatment, re-treatment, or

surgical treatment due to local recurrence is possible. Due to these advantages, ESD is being used as a major treatment method for EGC.

The current study investigated the factors related to recurrence in patients with EGC who had undergone *en bloc* resection using ESD. Even in cases in which *en bloc* resection was performed, local recurrence of neoplasia was observed in 36 patients (8.7%). When a comparison was performed between the recurrence group and the non-recurrence group, the identified risk factors for recurrence included unclear resection margins, long procedure times, and narrow safety margins, whereas

Table 5 Neoplasia recurrence and cancer recurrence by safety margin 1 mm *n* (%)

	Safety margin ≤ 1 mm <i>n</i> = 63	Safety margin > 1 mm <i>n</i> = 352	<i>P</i> value
Neoplasia recurrence	9 (14.3)	27 (7.7)	0.09
Cancer recurrence	4 (6.3)	2 (0.6)	0.006

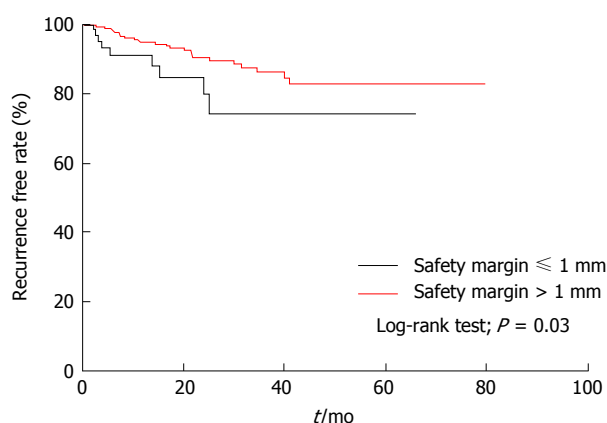


Figure 2 Cumulative neoplasia recurrence free rate according to period after endoscopic submucosal dissection. The probability of no recurrence up to 24 mo was 79.9% in those with the safety resection margin ≤ 1 mm and 89.5% in those exceeded 1 mm.

among the factors related to sufficient safety resection margins, it was found that the location of the tumor was an important factor. In particular, tumor location in the upper third of stomach was identified as having the greatest association with recurrence.

The visual tumor boundaries and safety resection margins of tumors had been identified as the risk factors for local recurrence. The introduction of ESD has increased the rates of *en bloc* resection and complete resection, but incomplete resection, in which resection margins are found to be positive in the post-ESD pathological testing, remains problematic. This results in cases in which the degree of horizontal invasion at the lesion is not assessed accurately and there is a failure to secure sufficient safety resection margins prior to performing the procedure^[15-17]. In the current study as well, the group with visually unclear tumor margins showed a higher rate of post-ESD recurrences (33.3% vs 17.4%, $P = 0.03$), and more incidences of recurrent tumors were found among those with safety resection margins ≤ 1 mm. Thus, good visual observation of the boundaries of lesions and the securing of sufficient safety resection margins before performing the procedures would be helpful in reducing local recurrence. However, since it is better to attempt minimal incision in order to minimize the procedure time and complications, as possible, accurate diagnosis is required before performing ESD. There have been reports suggesting that in cases in which the boundaries of the tumor are unclear, a preoperative biopsy on the ambient area of the lesion could be useful^[18,19], and the horizontal degree of invasion of the tumor could be assessed *via* chromoendoscopy^[20]

or narrow-band imaging magnifying endoscopy^[21].

The most important factor that has effects on local recurrence following the implementation of EMR or ESD is whether complete resection is performed. Ono *et al.*^[22] reported that the rate of local recurrence was 2% in cases of complete resection, while in contrast, recurrence was found in 18% of 85 patients either who had incomplete resection or in whom it was impossible to make assessments. Isomoto *et al.*^[23] also reported that while only 0.2% of patients who underwent complete resection had experienced local recurrence, 10.3% of patients who had incomplete resection had been found to have local recurrence, indicating that the complete resection group had a statistically significant lower rate of local recurrence in comparison to the incomplete resection group. Takenaka *et al.*^[6] presented a study on factors affecting local recurrence following ESD. They reported no cases of local recurrence among lesions that had been completely resected, but patients who underwent incomplete resection had local recurrences. Statistical analysis had confirmed that incomplete resection and local recurrence had a very high level of correlation. The authors analyzed the factors that cause incomplete resection and identified tumor size ≥ 30 mm, tumor location in the mid-third or upper third, and any ulcer or ulcerative scar on the lesion as the risk factors that can cause incomplete resection. Imagawa *et al.*^[24] also reported that tumor location (upper third, 74% vs mid-third, 77% vs lower third, 91%, $P < 0.05$) and tumor size (> 20 mm, 59% vs < 20 mm, 89%, $P < 0.0001$) were important elements of complete resection. In our study, it was confirmed that the more lesions were located in the upper third, the more frequent local recurrences were. However, according to the results of our study, tumor size was identified as having no significant correlation with recurrence, and it was considered that the procedures were implemented after securing sufficient safety resection margins considering the risk of recurrence as the tumor sizes increased. The underlying causes of more frequent local recurrences when lesions are located in the upper third of the stomach are, first, when the tumor is located nearer to the upper third, the endoscopic approach becomes difficult, resulting in difficult setting of accurate boundaries; second, this region has unclear boundaries of the mucosa in many cases; and third, this area has a larger distribution of blood vessels than any other site, which causes frequent bleeding during the procedure^[25]. The use of side-view endoscopes or multi-bending endoscopes can offer easy access to these sites, which is very helpful in performing the procedures^[26].

A molecular pathological epidemiology approach, which analyzes tumor molecular pathology of resected tumors, can predict recurrence after ESD. Semba *et al.*^[27] reported that EGC demonstrating intestinal claudin-positive phenotype has a high risk of synchronous and metachronous gastric neoplasia. Hasuo *et al.*^[28] investigated the correlation between microsatellite instability (MSI) status and the incidence of metachronous recurrence after initial ESD. They demonstrated that patients with the MSI-type tumors showed a high incidence of metachronous recurrence within a 3-year observation period after initial ESD. These molecular approaches are expected to be of value for decisions regarding therapy and surveillance after ESD.

The advantage of the current study is that it was conducted in patients who underwent *en bloc* resection only, and those patients with deep and lateral resection margin invasion were excluded, so that we could analyze the risk factors depending on the safety resection margins. However, the study also has limitations in that the follow-up periods were different, as it was a retrospective study, and there were differences in the number of biopsies during the follow-up endoscopy.

In conclusion, even in cases in which *en bloc* resection using ESD is performed for EGC, local recurrence occurs. In terms of risk factors related to local recurrence, tumor location and the visual boundaries of the tumor are important. In order to reduce post-ESD local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important.

COMMENTS

Background

En bloc resection is suggested as the standard method of endoscopic submucosal dissection (ESD) as it increases the accuracy of pathological assessment of complete resection and lowers the ratio of local recurrence. However, although *en bloc* resection has been practiced, there are few studies regarding the risk factors associated with local recurrence after *en bloc* resection.

Research frontiers

The authors aimed to investigate factors related to recurrence in patients who had undergone *en bloc* resection using ESD for early gastric cancer (EGC).

Innovations and breakthroughs

Unclear resection margins, long procedure times, and narrow safety margins were identified as risk factors for recurrence lesions located in the upper third of the stomach demonstrated more recurrences than those located in the lower third of the stomach.

Applications

Even in cases in which *en bloc* resection for ESD is performed, local recurrence occurs. Regarding risk factors related to local recurrence, tumor location and the visual boundaries of the tumor are important. In order to reduce post-ESD local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as

the securing of sufficient safety resection margins will be important as well.

Terminology

EGC is defined as malignant tumor confined to the mucosa or the submucosa regardless of lymph node metastases. ESD is an endoscopic technique for the treatment of early gastrointestinal neoplasms allowing direct dissection of the submucosal layer of the lesion with *en bloc* resection.

Peer-review

This is a large retrospective study on risk factor for local recurrence after ESD of early gastric cancer. The topic is important and interesting.

REFERENCES

- 1 Kim SG. Endoscopic Resection of Early Gastric Cancer. *Korean J Gastroenterol* 2009; **54**: 77 [DOI: 10.4166/kjg.2009.54.2.77]
- 2 Nam SY, Choi IJ, Park KW, Kim CG, Lee JY, Kook MC, Lee JS, Park SR, Lee JH, Ryu KW, Kim YW. Effect of repeated endoscopic screening on the incidence and treatment of gastric cancer in health screenees. *Eur J Gastroenterol Hepatol* 2009; **21**: 855-860 [PMID: 19369882 DOI: 10.1097/MEG.0b013e328318ed42]
- 3 Choi KD. Endoscopic resection of early gastric cancer. *Korean J Med* 2011; **81**: 40-46
- 4 Ono H. Endoscopic submucosal dissection for early gastric cancer. *Chin J Dig Dis* 2005; **6**: 119-121 [PMID: 16045601 DOI: 10.1111/j.1443-9573.2005.00206.x]
- 5 Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
- 6 Takenaka R, Kawahara Y, Okada H, Hori K, Inoue M, Kawano S, Tanioka D, Tsuzuki T, Yagi S, Kato J, Uemura M, Ohara N, Yoshino T, Imagawa A, Fujiki S, Takata R, Yamamoto K. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. *Gastrointest Endosc* 2008; **68**: 887-894 [PMID: 18565523 DOI: 10.1016/j.gie.2008.03.1089]
- 7 Watanabe K, Ogata S, Kawazoe S, Watanabe K, Koyama T, Kajiwarra T, Shimoda Y, Takase Y, Irie K, Mizuguchi M, Tsunada S, Iwakiri R, Fujimoto K. Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest Endosc* 2006; **63**: 776-782 [PMID: 16650537 DOI: 10.1016/j.gie.2005.08.049]
- 8 Nakamoto S, Sakai Y, Kasanuki J, Kondo F, Ooka Y, Kato K, Arai M, Suzuki T, Matsumura T, Bekku D, Ito K, Tanaka T, Yokosuka O. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. *Endoscopy* 2009; **41**: 746-750 [PMID: 19681023 DOI: 10.1055/s-0029-1215010]
- 9 Jang JS, Lee EJ, Lee SW, Lee JH, Roh MH, Han SY, Choi SR, Jeong JS. Endoscopic submucosal dissection for early gastric cancer and gastric adenoma. *Korean J Gastroenterol* 2007; **49**: 356-363
- 10 Park JC, Lee SK, Seo JH, Kim YJ, Chung H, Shin SK, Lee YC. Predictive factors for local recurrence after endoscopic resection for early gastric cancer: long-term clinical outcome in a single-center experience. *Surg Endosc* 2010; **24**: 2842-2849 [PMID: 20428894 DOI: 10.1007/s00464-010-1060-8]
- 11 Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1998; **1**: 10-24 [PMID: 11957040 DOI: 10.1007/s10120980001610.1007/s00464-010-1060-8]
- 12 Ono H. Early gastric cancer: diagnosis, pathology, treatment techniques and treatment outcomes. *Eur J Gastroenterol Hepatol* 2006; **18**: 863-866 [PMID: 16825902 DOI: 10.1097/00042737-200608000-00009]
- 13 Miyata M, Yokoyama Y, Okoyama N, Joh T, Seno K, Sasaki M, Ohara H, Nomura T, Kasugai K, Itoh M. What are the appropriate indications for endoscopic mucosal resection for early gastric

- cancer? Analysis of 256 endoscopically resected lesions. *Endoscopy* 2000; **32**: 773-778 [PMID: 11068836 DOI: 10.1055/s-2000-7712]
- 14 **Noda M**, Kodama T, Atsumi M, Nakajima M, Sawai N, Kashima K, Pignatelli M. Possibilities and limitations of endoscopic resection for early gastric cancer. *Endoscopy* 1997; **29**: 361-365 [PMID: 9270916 DOI: 10.1055/s-2007-1004216]
 - 15 **Tanabe H**, Iwashita A, Haraoka S. Pathological evaluation concerning curability of endoscopic submucosal dissection of early gastric cancer including lesions with obscure margins. *Stom Intest* 2006; **41**: 53-66
 - 16 **Mishima T**, Miyake N, Chonan A. Incompletely resected case under the extended indication of endoscopic submucosal dissection for early gastric cancer. *Stomach Intestine* 2008; **43**: 33-43
 - 17 **Nagahama T**, Suketo S, Yorioka M. Current status of endoscopic submucosal dissection in early stomach cancer. *Stomach Intestine* 2008; **43**: 33-43
 - 18 **Kakushima N**, Ono H, Tanaka M, Takizawa K, Yamaguchi Y, Matsubayashi H. Factors related to lateral margin positivity for cancer in gastric specimens of endoscopic submucosal dissection. *Dig Endosc* 2011; **23**: 227-232 [PMID: 21699566 DOI: 10.1111/j.1443-1661.2010.01092.x]
 - 19 **Kang EJ**, Cho JY, Lee TH, Jin SY, Cho WY, Bok JH, Kim HG, Kim JO, Lee JS, Lee IH. Frozen Section Biopsy to Evaluation of Obscure Lateral Resection Margins during Gastric Endoscopic Submucosal Dissection for Early Gastric Cancer. *J Gastric Cancer* 2011; **11**: 155-161 [PMID: 22076220 DOI: 10.5230/jgc.2011.11.3.155]
 - 20 **Ida K**, Hashimoto Y, Takeda S. Endoscopic diagnosis of gastric cancer with dye scattering. *Am J Gastroenterol* 1975; **63**: 316-320
 - 21 **Nagahama T**, Yao K, Maki S, Yasaka M, Takaki Y, Matsui T, Tanabe H, Iwashita A, Ota A. Usefulness of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy (with video). *Gastrointest Endosc* 2011; **74**: 1259-1267 [PMID: 22136775 DOI: 10.1016/j.gie.2011.09.005]
 - 22 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645]
 - 23 **Isomoto H**, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut* 2009; **58**: 331-336 [PMID: 19001058 DOI: 10.1136/gut.2008.165381]
 - 24 **Imagawa A**, Okada H, Kawahara Y, Takenaka R, Kato J, Kawamoto H, Fujiki S, Takata R, Yoshino T, Shiratori Y. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. *Endoscopy* 2006; **38**: 987-990 [PMID: 17058162 DOI: 10.1055/s-2006-94471610.1007/s10120-006-0408-1]
 - 25 **Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838]
 - 26 **Isshi K**, Tajiri H, Fujisaki J, Mochizuki K, Matsuda K, Nakamura Y, Saito N, Narimiya N. The effectiveness of a new multibending scope for endoscopic mucosal resection. *Endoscopy* 2004; **36**: 294-297 [PMID: 15057677 DOI: 10.1055/s-2004-814203]
 - 27 **Semba S**, Hasuo T, Satake S, Nakayama F, Yokozaki H. Prognostic significance of intestinal claudins in high-risk synchronous and metachronous multiple gastric epithelial neoplasias after initial endoscopic submucosal dissection. *Pathol Int* 2008; **58**: 371-377 [PMID: 18477216 DOI: 10.1111/j.1440-1827.2008.02238.x]
 - 28 **Hasuo T**, Semba S, Li D, Omori Y, Shirasaka D, Aoyama N, Yokozaki H. Assessment of microsatellite instability status for the prediction of metachronous recurrence after initial endoscopic submucosal dissection for early gastric cancer. *Br J Cancer* 2007; **96**: 89-94 [PMID: 17179982 DOI: 10.1038/sj.bjc.6603532]

P- Reviewer: Bordas JM, Ogino S, Sperti C **S- Editor:** Qi Y

L- Editor: A **E- Editor:** Liu SQ



Retrospective Study

Stent type used does not impact complication rate or placement time but can decrease treatment cost for benign and malignant esophageal lesions

Camille McGaw, Ahmad Alkaddour, Kenneth J Vega, Juan Carlos Munoz

Camille McGaw, Juan Carlos Munoz, Division of Gastroenterology, University of Florida College of Medicine-Jacksonville, Jacksonville, FL 32209, United States

Ahmad Alkaddour, Department of Medicine, University of Florida College of Medicine-Jacksonville, Jacksonville, FL 32209, United States

Kenneth J Vega, Division of Digestive Diseases and Nutrition, University of Oklahoma Health Science Center, Oklahoma City, OK 73104, United States

Author contributions: McGaw C and Munoz JC designed the research and wrote the initial manuscript; McGaw C and Alkaddour A collected the data; Vega KJ, and Munoz JC reviewed the data for completeness and revised the manuscript for intellectual content; Vega KJ performed the statistical analysis; McGaw C, Alkaddour A, Vega KJ and Munoz JC approved the final version for submission.

Institutional review board statement: This study was approved by the University of Florida Health Science Center-Jacksonville Institutional Review Board (IRB).

Informed consent statement: This study was retrospective, using previously collected endoscopic and hospital data, which did not require a specific informed consent other than each patient agreeing to treatment with written consent at the time of procedure.

Conflict-of-interest statement: No conflict of interest exists for all authors.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

[licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)

Correspondence to: Kenneth J Vega, MD, Division of Digestive Diseases and Nutrition, University of Oklahoma Health Sciences Center, 920 Stanton L. Young Boulevard, WP 1345, Oklahoma City, OK 73104, United States. kenneth-vega@ouhsc.edu
Telephone: +1-405-2715428
Fax: +1-405-2715803

Received: July 28, 2015

Peer-review started: August 1, 2015

First decision: September 16, 2015

Revised: October 27, 2015

Accepted: January 21, 2016

Article in press: January 22, 2016

Published online: April 10, 2016

Abstract

AIM: To evaluate if differences exist between self-expanding esophageal metal stents (SEMS) and self-expanding esophageal plastic stents (SEPS) when used for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost.

METHODS: A retrospective analysis was performed to evaluate outcome in patients having SEPS/SEMS placed for malignant or benign esophageal conditions from January 2005 to April 2012. Inclusion criteria was completed SEMS/SEPS placement. Outcomes assessed included technical success of and time required for stent placement, procedure-related complications, need for repeat intervention, hospital stay, mortality and costs.

RESULTS: Forty-three patients underwent stent placement for either benign/malignant esophageal

disease during the study period. Thirty patients had SEMS (25 male, mean age 59.6 years old) and 13 patients had SEPS (10 male, mean age 61.7 years old). Placement outcome as well as complication rate (SEPS 23.1%, SEMS 25.2%) and in-hospital mortality (SEPS 7.7%, SEMS 6.7%) after placement did not differ between stent types. Migration was the most frequent complication reported occurring equally between types (SEPS 66.7%, SEMS 57.1%). SEPS was less costly than SEMS, decreasing institutional cost by \$255/stent.

CONCLUSION: SEPS and SEMS have similar outcomes when used for benign or malignant esophageal conditions. However, SEPS use results in decreased costs without impacting care.

Key words: Esophageal; Stent; Benign; Malignant; Complication; Placement; Cost

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Self-expanding esophageal metal stents (SEMS) are preferable to self-expanding esophageal plastic stents (SEPS) for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties. Comparative studies between stent types evaluating differences between SEMS and SEPS for these conditions with regard to safety, efficacy, clinical outcomes, placement ease and cost are lacking. Retrospective analysis indicated placement outcome, complication rate, most frequent complication and in-hospital mortality after placement was equivalent between stent types. SEPS was less costly than SEMS. SEPS and SEMS have similar outcomes when used for malignant/benign esophageal conditions but SEPS results in decreased costs without impacting care.

McGaw C, Alkaddour A, Vega KJ, Munoz JC. Stent type used does not impact complication rate or placement time but can decrease treatment cost for benign and malignant esophageal lesions. *World J Gastrointest Endosc* 2016; 8(7): 338-343 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i7/338.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i7.338>

INTRODUCTION

Placement of an esophageal stent is a minimally invasive procedure regularly used in both malignant and benign disease. Since the initial description in 1976, treatment using esophageal stents has advanced into a commonly accepted therapeutic technique for malignant esophageal strictures, fistulas and other complications^[1-3]. The aim of esophageal stenting is to restore luminal patency and thereby nutritional intake, improving patient quality of life^[2,4,5]. In addition, esophageal stent use has expanded to various inoperable malignancies localized in the esophagus, gastroesophageal

junction and cardia as well as benign conditions including benign refractory strictures, anastomotic leaks, perforations, and trachea-esophageal fistulas^[2-7].

Presently, the two most common types of self-expandable esophageal stents are the self-expandable esophageal plastic stent (SEPS), made from durable polymers and multiple self-expandable esophageal metal stent (SEMS), made from metal alloy compounds (Table 1)^[3,7]. SEMS are considered preferable to SEPS for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties at or following placement^[8,9]. However, comparative studies of between stent types used for either benign or malignant esophageal conditions are limited with inconsistent results reported regarding technical outcome and migration^[10-12]. The aim of the present investigation was to evaluate if differences exist between SEMS and SEPS placed for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost.

MATERIALS AND METHODS

A retrospective analysis was performed at the University of Florida Health Science Center-Jacksonville to evaluate the outcomes of patients undergoing endoscopic SEPS placement compared to endoscopic SEMS placement for malignant or benign esophageal conditions. Inclusion criteria were the following: Endoscopic esophageal stent placement between January 1, 2005 to April 30, 2012, presence of adenocarcinoma or squamous cell carcinoma of the esophagus, recurrent fistula caused by malignant tumor, benign esophageal strictures, and esophageal perforation or leak. Exclusion criteria were tumor above 2 cm from the upper esophageal sphincter. Clinical data obtained and assessed included technical success of stent placement, procedure-related complications, need for subsequent re-intervention, hospital stay, and mortality. Demographic and clinical data were collected from the local electronic medical record. Stent type selected for use was based on endoscopist and referring physician preference. Stent length was determined according to the size and localization of the tumor. All endoscopic treatments occurred under conscious sedation, monitored anesthesia, or general anesthesia. Initial evaluation occurred using standard esophagogastroduodenoscopy (EGD). If dilation was required, this was performed by means of fluoroscopic guidance prior to stent placement. Proximal and distal ends of the lesion to be stented was determined during EGD and hemoclips were used as markers to delineate both ends. A 0.35 mm tracer metro direct wire or Savary guide wire was used to assist placement. All stents used in the present investigation were from Boston Scientific, Marlborough, MA. The SEMS used was WallFlex fully covered with an institutional cost of \$2650 and patient insurance cost of \$4500. The SEPS used was Polyflex with an institutional cost of \$2395 and patient insurance cost of \$4090. All SEMS were placed under dual vision (fluoroscopy and endoscopy) while

Table 1 Currently available stents in the United States

Stent	Manufacturer	Material	Diameter body/flare (mm)	Length (cm)	Covering
Alimaxx-E	Alveolus	Nitinol	18/22	7/10/12	FC with antimigration struts
Esophageal Z-stent	Cook	Stainless steel	18/25	8/10/12/14	PC
Evolution	Cook	Nitinol	20/25	8/10/12.5/15	PC
Flamingo Wallstent	Boston Scientific	Stainless steel	20/30	12/14	PC
Gianturco-Z	Cook	Stainless steel	18/25	8/10/12/14	FC
Niti-S	Taewong Medical	Nitinol	16/20	8/10/12/14	FC
			18/23		
			20/25		
Niti-S; double layered	Taewong Medical	Nitinol	18/26	9/12/15	FC with additional uncovered outer nitinol wires
Niti-S; single layered	Taewong Medical	Nitinol	18/26	9/12/15	FC
Polyflex	Boston Scientific	Polyester	16/20	9/12/15	FC
			18/23		
			21/28		
SX-ELLA	Ella-CS	Nitinol	20/25	8.5/11/13.5/15	FC with antimigration ring
Ultraflex	Boston Scientific	Nitinol	18/23	10/12/15	PC
			23/28		
Wallflex	Boston Scientific	Nitinol	18/23	10/12/15	PC/FC
			23/28		

Adapted with permission from Curr Gastroenterol Rep 2013; 15: 319. PC: Partially covered; FC: Fully covered.

Table 2 Overall demographics in patients having self-expanding esophageal metal stents/self-expanding esophageal plastic stents placed for malignant or benign esophageal conditions from January 2005 to April 2012

	Overall (<i>n</i> = 43)	nHw (<i>n</i> = 25)	AA (<i>n</i> = 15)	Other (<i>n</i> = 3)
Mean age (yr)	60.2	57.7	60.4	80 ¹
% male	85.1	80	80	100

¹Compared to nHw ($P < 0.01$) and AA ($P < 0.03$). nHw: Non-Hispanic White; AA: African American.

SEPS were placed under fluoroscopy vision only due to the delivery system. Appropriate placement of the SEPS was confirmed by direct visualization using EGD to verify positioning. A contrast esophagogram was performed postoperatively at the discretion of the endoscopist. This study was approved by the University of Florida Health Science Center-Jacksonville Institutional Review Board.

Statistical analysis

Continuous data were described as mean \pm SD and compared using two sided student *t* tests. Categorical data were presented as numbers or percentages and analyzed using appropriate χ^2 testing. Results were analyzed in relation to stent type placed (SEMS or SEPS). A *P* value of less than 0.05 was considered statistically significant. Data analysis was performed using the GraphPad Prism statistical analysis program (Kenneth J Vega, version 6, La Jolla, CA).

RESULTS

Patient characteristics

Forty-three patients underwent stent placement for either benign (8 patients) or malignant (35 patients) esophageal disease during the study period. Patients

with benign esophageal disease had the following diagnosis: 3 with esophageal fistulas, 2 with extrinsic compression and 1 each with esophageal stricture, perforation or iatrogenic tear. Of the 35 patients with malignant esophageal disease, 14 patients had squamous cell carcinoma, 16 patients had adenocarcinoma and 5 patients had mixed malignant histology. Mean patient age of the overall group was 60.2 years (SD 13.5 years) and 81.4% were male (Table 2). Ethnicity was distributed as follows, 25 non-Hispanic Whites (nHw), 15 African Americans (AA) and 3 from other groups (2 Asian Americans and 1 Hispanic American). Compared to both nHw and AA, the other group was older [80 (other) vs 57.7 (nHw), $P < 0.01$ or 60.4 (AA) years, $P < 0.03$]. No significant difference was seen in the number of males in each ethnic group.

Stent groups

SEMS were placed in 30 patients and SEPS used in 13 patients. Patient characteristics of both stent groups are seen in Table 3. Mean age, percentage of male patients and ethnic distribution was equivalent in the SEMS and SEPS groups (Table 3). Both stent groups also were similar with regard to esophageal lesion location, percentage of malignant esophageal lesions and comorbid diseases (Table 3).

Stent placement, outcome and cost

Successful stent placement occurred in all SEMS and SEPS patients. No patient in either stent group required more than 1 stent initially. Table 4 illustrates placement and outcome comparisons between SEMS and SEPS. Dilation was more frequent in the SEPS group compared to SEMS ($P = 0.023$). No significant difference was seen between stent groups in initial placement time, complication rate, time to first complication, in hospital mortality, repeat intervention required frequency, length

Table 3 Patient characteristics based on stent type placed

	SEMS (<i>n</i> = 30)	SEPS (<i>n</i> = 13)	<i>P</i> value
Mean age (yr ± SD)	59.6 ± 14.87	61.7 ± 9.95	0.645
% male	83.3%	76.9%	0.681
Race/ethnicity, <i>n</i> (%)	AA: 9 (30%) nHw: 18 (60%) Other: 3 (10%)	AA: 6 (46%) nHw: 7 (54%) Other: 0	0.704
Malignant esophageal lesion, <i>n</i> (%)	25 (83.3%)	10 (76.9%)	0.681
Esophageal lesion location, <i>n</i> (%)	Upper third: 0 Middle third: 9 (30%) Lower third: 21 (70%)	Upper third: 1 (7.7%) Middle third: 6 (46.2%) Lower third: 6 (46.2%)	0.15
Comorbid diseases, <i>n</i> (%)	HTN: 16 (53.3%) CAD: 7 (23.3%) COPD: 5 (16.7%) DM: 11 (36.7%)	HTN: 6 (46.2%) CAD: 2 (15.4%) COPD: 1 (7.7%) DM: 3 (23.1%)	0.747 0.699 0.649 0.491

SEMS: Self-expanding esophageal metal stents; SEPS: Self-expanding esophageal plastic stents; nHw: Non-Hispanic White; AA: African American; HTN: Hypertension; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus.

Table 4 Placement and outcome comparisons between self-expanding esophageal metal stents and self-expanding esophageal plastic stents

	SEMS (<i>n</i> = 30)	SEPS (<i>n</i> = 13)	<i>P</i> value
Initial placement procedure time (min, mean ± SD)	33.17 ± 16.88	35.85 ± 27.39	0.696
Dilation required prior to stent placement	0	23%	0.023
Complications, <i>n</i> (%)	7 (23%)	3 (23%)	1
Time to first complication (<i>n</i>)	< 30 d: 6 > 30 d: 1	< 30 d: 2 > 30 d: 1	1
In-hospital mortality (%)	7%	8%	1
Re-intervention required (%)	20%	23%	1
30 d survival after procedure (%)	95%	80%	0.251
Length of stay (d, mean ± SD)	11.47 ± 12.78	12.15 ± 16.21	0.883

SEMS: Self-expanding esophageal metal stents; SEPS: Self-expanding esophageal plastic stents.

of stay and 30 d survival (Table 4). Stent migration was the most frequent complication, occurring in 4 SEMS and 2 SEPS patients. Interestingly, SEMS resulted in increased costs than SEPS with an average cost savings of \$255-410 for each SEPS used instead of SEMS for hospital and patient insurance cost, respectively.

DISCUSSION

SEMS are considered preferable to SEPS for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties^[8,9]. However, comparative studies between stent types are limited^[10-12]. The present study was designed to assess whether if differences exist between SEMS and SEPS use for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost. The results indicate SEPS and SEMS are equivalent when used for benign or malignant esophageal conditions with regard to initial placement time, complication frequency, time to initial complication, in-hospital mortality, repeat intervention need, 30 d post procedure survival and length of hospital stay. In addition, SEPS use results in decreased costs without impacting care for either benign or malignant esophageal conditions.

The current investigation is the first to compare use of SEMS and SEPS on a combined population of benign and malignant conditions of the esophagus. All stents were placed successfully which is consistent with previous literature evaluating stent placement in exclusive subsets of either benign or malignant esophageal disease (98%-100%)^[10-12]. Comparison of procedure time required for initial SEMS and SEPS placement was only performed by 1 group previously^[10]. Conio *et al*^[10] found initial SEPS placement was significantly longer than SEMS by a median of 12 min. However, no difference was seen between mean initial placement procedure time based on stent type in the present study. Moreover, no significant difference was present regarding lesion type stented in the SEMS and SEPS groups removing a potential confounder for initial placement time and suggesting equivalent placement ease in all cases in spite of different delivery systems used.

Complication rates following SEMS and SEPS were equal in both stent groups. Interestingly, the rate observed (23% for both SEMS and SEPS) was less than the reported in the literature (46%-48%)^[10-12]. The main complication seen was stent migration in both stent groups which is consistent with the majority of studies

evaluating stent type for either benign or malignant esophageal lesions^[11,12]. However, no difference was seen between SEMs and SEPS in frequency of migration. Of note, earlier data has been inconclusive with regard to migration rates with one study suggesting fully covered stents (either metal or plastic) are more likely to migrate while another indicated SEPS migrated more frequently^[10,12]. Only one patient had recurrent dysphagia following stent placement (received SEMs) which was treated conservatively. Furthermore, no difference was observed in re-intervention requirement, in-hospital mortality, length of initial hospital stay and 30 d survival between SEMs and SEPS groups.

Health care costs remain a significant concern in the United States in spite of the Affordable Care Act of 2010^[13]. In addition, placement of esophageal stents decrease costs for both benign and malignant esophageal conditions^[14]. The present study indicated that if using SEPS in contrast to SEMs for either benign or malignant conditions reduced cost between \$255-410 per SEPS used. Moreover, as outcome was not affected by stent type used in our investigation, significant cost savings could be achieved with SEPS use only for esophageal conditions requiring endoscopic intervention.

Of note, a third, less commonly used self-expandable esophageal stent, the biodegradable (BD) - stent, has been developed as an alternative to SEPS. Currently available BD stent designs are the ELLA-BD stent (ELLA-CS, Hradec Kralove, Czech Republic), which is composed of polydioxanone, a surgical suture material and the poly-L-lactic acid (PLLA)-BD stent (Marui Textile Machinery, Osaka, Japan), which consists of knitted PLLA monofilament. These stents can be degraded by hydrolysis, which is accelerated at low ambient pH. Generally, BD stents begin to degrade after 4 to 5 wk following placement and dissolve completely after a period of 2 to 3 mo. The major strength of BD stent over SEMs or SEPS is that it does not require removal, even after migration, as it is dissolved by gastric acid, thus avoiding further procedures and potential morbidity^[15].

We are aware of the limitations of the present investigation. The primary limitation is the retrospective design. In addition, our study had a small sample size for SEPS patients. Nevertheless, the majority of previously published studies have included small samples of SEPS patients as well. Furthermore, classification of stents used according to degree covered (fully or partially) may have had an impact in the results but given the small number of subjects, this was not performed. Finally, selection bias could have impacted the results observed as stent type selected for insertion was dependent on the endoscopist performing the procedure.

In conclusion, SEPS should be considered as a treatment option for any esophageal indication, benign or malignant, with no increase in complications and equivalent efficacy to SEMs. In addition, SEPS use appears cost effective for management of esophageal lesions requiring restoration of luminal patency compared to SEMs. Performance of prospective clinical trials

comparing SEMs and SEPS should be implemented to validate these findings. Furthermore, investigations comparing esophageal stents should occur and include biodegradable stents as well as longitudinal evaluations of biodegradable stents with an increased *in vivo* half-life, to assess longer term stent patency, mitigate stent-related complications, and whether the need for repeat interventions is required.

COMMENTS

Background

Self-expanding esophageal metal stents (SEMS) are preferable to self-expanding esophageal plastic stents (SEPS) for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties. Comparative studies between stent types evaluating differences between SEMs and SEPS for these conditions with regard to safety, efficacy, clinical outcomes, placement ease and cost are lacking.

Research frontiers

To evaluate if differences exist between SEMs and SEPS placed for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost.

Innovations and breakthroughs

Stent placement outcome, complication rate, most frequent complication and in-hospital mortality after placement was equivalent between stent types. SEPS was less costly than SEMs. SEPS and SEMs have similar outcomes when used for malignant/benign esophageal conditions but SEPS results in decreased costs without impacting care.

Applications

SEPS should be considered as a treatment option for any esophageal indication, benign or malignant, with no increase in complications and equivalent efficacy to SEMs. In addition, SEPS use appears cost effective for management of esophageal lesions requiring restoration of luminal patency compared to SEMs.

Terminology

SEPS are made from durable polymers and SEMs are made from metal alloy compounds.

Peer-review

Both SEMs and SEPS are considered useful for treatment of malignant or benign esophageal conditions. However, few comparative studies between stent types have been reported. The study compared the safety, efficacy, clinical outcomes, placement ease and cost between SEMs and SEPS for benign or malignant esophageal disorders and found SEPS is cheaper. This may be helpful for clinical doctors in choosing stent types.

REFERENCES

- 1 Hill JL, Norberg HP, Smith MD, Young JA, Reyes HM. Clinical technique and success of the esophageal stent to prevent corrosive strictures. *J Pediatr Surg* 1976; **11**: 443-450 [PMID: 957069]
- 2 Sharma P, Kozarek R. Role of esophageal stents in benign and malignant diseases. *Am J Gastroenterol* 2010; **105**: 258-273; quiz 274 [PMID: 20029413 DOI: 10.1038/ajg.2009.684]
- 3 Didden P, Spaander MC, Bruno MJ, Kuipers EJ. Esophageal stents in malignant and benign disorders. *Curr Gastroenterol Rep* 2013; **15**: 319 [PMID: 23463153 DOI: 10.1007/s11894-013-0319-3]
- 4 Diamantis G, Scarpa M, Bocus P, Realdon S, Castoro C, Ancona E, Battaglia G. Quality of life in patients with esophageal stenting for the palliation of malignant dysphagia. *World J Gastroenterol* 2011; **17**: 144-150 [PMID: 21245986 DOI: 10.3748/wjg.v17.i2.144]
- 5 Balazs A, Kokas P, Lukovich P, Kupcsulik PK. Experience with

- stent implantation in malignant esophageal strictures: analysis of 1185 consecutive cases. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 286-291 [PMID: 23751994 DOI: 10.1097/SLE.0b013e31828ba120]
- 6 **Kochman ML**, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition. *Gastrointest Endosc* 2005; **62**: 474-475 [PMID: 16111985 DOI: 10.1016/j.gie.2005.04.050]
- 7 **Hindy P**, Hong J, Lam-Tsai Y, Gress F. A comprehensive review of esophageal stents. *Gastroenterol Hepatol* (N Y) 2012; **8**: 526-534 [PMID: 23293566]
- 8 **Szegedi L**, Gál I, Kósa I, Kiss GG. Palliative treatment of esophageal carcinoma with self-expanding plastic stents: a report on 69 cases. *Eur J Gastroenterol Hepatol* 2006; **18**: 1197-1201 [PMID: 17033441 DOI: 10.1097/01.meg.0000236886.67085.2e]
- 9 **Conigliaro R**, Battaglia G, Repici A, De Pretis G, Ghezzi L, Bittinger M, Messmann H, Demarquay JF, Togni M, Bianchi S, Filiberti R, Conio M. Polyflex stents for malignant oesophageal and oesophagogastric stricture: a prospective, multicentric study. *Eur J Gastroenterol Hepatol* 2007; **19**: 195-203 [PMID: 17301645 DOI: 10.1097/MEG.0b013e328013a418]
- 10 **Conio M**, Repici A, Battaglia G, De Pretis G, Ghezzi L, Bittinger M, Messmann H, Demarquay JF, Bianchi S, Togni M, Conigliaro R, Filiberti R. A randomized prospective comparison of self-expandable plastic stents and partially covered self-expandable metal stents in the palliation of malignant esophageal dysphagia. *Am J Gastroenterol* 2007; **102**: 2667-2677 [PMID: 18042102 DOI: 10.1111/j.1572-0241.2007.01565.x]
- 11 **Verschuur EM**, Repici A, Kuipers EJ, Steyerberg EW, Siersema PD. New design esophageal stents for the palliation of dysphagia from esophageal or gastric cardia cancer: a randomized trial. *Am J Gastroenterol* 2008; **103**: 304-312 [PMID: 17900325]
- 12 **van Boeckel PG**, Dua KS, Weusten BL, Schmits RJ, Surapaneni N, Timmer R, Vleggaar FP, Siersema PD. Fully covered self-expandable metal stents (SEMS), partially covered SEMS and self-expandable plastic stents for the treatment of benign esophageal ruptures and anastomotic leaks. *BMC Gastroenterol* 2012; **12**: 19 [PMID: 22375711 DOI: 10.1186/1471-230X-12-19]
- 13 **Geyman JP**. A five-year assessment of the affordable care act: market forces still trump the common good in U.S. Health care. *Int J Health Serv* 2015; **45**: 209-225 [PMID: 25674797 DOI: 10.1177/0020731414568505]
- 14 **Kang HW**, Kim SG. Upper Gastrointestinal Stent Insertion in Malignant and Benign Disorders. *Clin Endosc* 2015; **48**: 187-193 [PMID: 26064817 DOI: 10.5946/ce.2015.48.3.187]
- 15 **Ham YH**, Kim GH. Plastic and biodegradable stents for complex and refractory benign esophageal strictures. *Clin Endosc* 2014; **47**: 295-300 [PMID: 25133114]

P- Reviewer: Liu DL, Nakajima N **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Liu SQ



Retrospective Study

What is the impact of capsule endoscopy in the long term period?

Asli Ormeci, Filiz Akyuz, Bulent Baran, Suut Gokturk, Tugrul Ormeci, Binnur Pinarbasi, Ozlem Mutluay Soyer, Sami Evirgen, Umit Akyuz, Cetin Karaca, Kadir Demir, Sabahattin Kaymakoglu, Fatih Besisik

Asli Ormeci, Filiz Akyuz, Bulent Baran, Suut Gokturk, Binnur Pinarbasi, Ozlem Mutluay Soyer, Sami Evirgen, Cetin Karaca, Kadir Demir, Sabahattin Kaymakoglu, Fatih Besisik, Division of Gastroenterohepatology, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, 34590 Capa, Istanbul, Turkey

Tugrul Ormeci, Department of Radiology, Medipol University, 34214 Bageilar, Istanbul, Turkey

Umit Akyuz, Department of Gastroenterology, Yeditepe University, 34752 Kozyatagi, Istanbul, Turkey

Author contributions: Akyuz F evaluated the recorded capsule endoscopy images; Ormeci A and Akyuz F collected the clinical data and wrote the manuscript, with contributions from Gokturk S, Pinarbasi B, Soyer OM, Evirgen S, Akyuz U and was responsible for the design of the study and collected the clinical data; Passage opening was evaluated with computerized tomography from Ormeci T; Akyuz F and Baran B performed the statistical analyses; Karaca C, Demir K, Kaymakoglu S and Besisik F participated in the design and coordination of the study; all authors read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Istanbul University, Istanbul Medical Faculty.

Informed consent statement: All patients provided written consent to undergo capsule endoscopy. All data are anonymized and there were no prospective interventions.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at filizakyuz@hotmail.com.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license,

which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Filiz Akyuz, Professor, Division of Gastroenterohepatology, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Turgut Ozal Millet St., Fatih, 34590 Capa, Istanbul, Turkey. filizakyuz@hotmail.com
Telephone: +90-212-4142000
Fax: +90-212-6319743

Received: June 19, 2015

Peer-review started: June 20, 2015

First decision: July 27, 2015

Revised: October 12, 2015

Accepted: January 27, 2016

Article in press: January 29, 2016

Published online: April 10, 2016

Abstract

AIM: To assess the clinical impact of capsule endoscopy (CE) in the long-term follow-up period in patients with obscure gastrointestinal bleeding (OGIB).

METHODS: One hundred and forty-one patients who applied CE for OGIB between 2009 and 2012 were retrospectively analyzed, and this cohort was then questioned prospectively. Demographic data of the patients were determined *via* the presence of comorbid diseases, use of non-steroidal anti-inflammatory drugs anticoagulant-antiaggregant agents, previous diagnostic tests for bleeding episodes, CE findings, laboratory tests and outcomes.

RESULTS: CE was performed on 141 patients because

of OGIB. The capsule was retained in the upper gastrointestinal (GI) system in two of the patients, thus video monitoring was not achieved. There were 139 patients [62% male, median age: 72 years (range: 13-93 years) and a median follow-up duration: 32 mo (range: 6-82 mo)]. The overall diagnostic yield of CE was 84.9%. Rebleeding was determined in 40.3% (56/139) of the patients. The rebleeding rates of patients with positive and negative capsule results at the end of the follow-up were 46.6% (55/118) and 4.8% (1/21), respectively. In the multivariate analysis, usage of NSAIDs, anticoagulant-antiaggregant therapies (OR = 5.8; 95%CI: 1.86-18.27) and vascular ectasia (OR = 6.02; 95%CI: 2.568-14.146) in CE were detected as independent predictors of rebleeding. In the univariate analysis, advanced age, comorbidity, and overt bleeding were detected as predictors of rebleeding.

CONCLUSION: CE is a reliable method in the diagnosis of obscure GI bleeding. Negative CE correlated with a significantly lower rebleeding risk in the long-term follow-up period.

Key words: Capsule endoscopy; Small bowel; Obscure gastrointestinal bleeding; Rebleeding

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This study determines the results of using capsule endoscopy in obscure gastrointestinal bleeding in long-term. Our main aim was to describe the long-term clinical impact of capsule endoscopy during follow-up period. Positive capsule endoscopy results correlated with higher rebleeding rates. Independent predictors of rebleeding were detected to be usage of non-steroidal anti-inflammatory drugs, anticoagulant/antiaggregant therapy and vascular ectasia.

Ormeçi A, Akyuz F, Baran B, Gokturk S, Ormeçi T, Pinarbasi B, Soyer OM, Evirgen S, Akyuz U, Karaca C, Demir K, Kaymakoglu S, Besisik F. What is the impact of capsule endoscopy in the long term period? *World J Gastrointest Endosc* 2016; 8(7): 344-348 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i7/344.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i7.344>

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is a frequent problem in the daily gastroenterology practice that represents nearly 5% of all gastrointestinal (GI) hemorrhages^[1-3]. The most extensive location of OGIB is small bowel, where it is usually far beyond the range of a standard endoscopic examination. Therefore, capsule endoscopy (CE) is the preferred technique to assess patients with OGIB^[4-6]. The high specificity and sensitivity of CE in OGIB cases and increased diagnostic value of this method was shown in several previously published

studies. Even though diagnostic value of CE is the focus point of most studies, in the literature there is not enough data about the long-term results of using CE and its effectiveness in predicting and assessment of rebleeding risks. In this study, our main aim was to determine the long-term clinical impact of capsule endoscopy during follow-up period.

MATERIALS AND METHODS

Patients

The data obtained from the patients presented to gastroenterology department and referred to endoscopy unit with OGIB from January 2009 to December 2012 was analyzed in a retrospective design. This cohort was then questioned prospectively.

Before the CE procedure, all of the patients were applied colonoscopy and upper GI endoscopy (GIE) in our endoscopy unit. The collected data from the patients included their demographics, previous intake of anticoagulant/antiaggregant therapy, non-steroidal anti-inflammatory drugs (NSAIDs), present comorbidities, their previous diagnostic test results [upper GIE, colonoscopy, radiological studies of small bowel, computerized tomography (CT) imaging], CE findings and follow-up data.

Before the CE procedure, the passage opening was evaluated using CT. CE was not undertaken in patients who had strictures or obstructions.

The study was done after the patients were informed about this study and the patients' written informed consents were taken according to Helsinki Declaration. The study was obtained from local ethics committee.

CE procedure

CE procedures were performed on an outpatient basis without hospitalization. Pillcam SB2 (Given Imaging, Yoqneam, Israel) was used for the procedure. Patients' bowel preparation was done using 4 L polyethylene glycol solution one day before the procedure. The patients swallowed the capsules (Pillcam SB2) in the outpatient clinic. Fluid intake was permitted 2 h and eating was allowed 4 h after the initial administration of capsules. Patients were instructed to check their stool for the ejection of capsule and to notify the endoscopy unit if it was not ejected. Failure of the capsule ejection in more than 2 wk was defined as capsule retention in the GI tract. One gastroenterologist (F-A) with extensive experience in small bowel endoscopy evaluated the recorded CE images.

Follow-up

Charts were used to gather full follow-up information including OGIB recurrence and CE complications. Each patient was called and reevaluated for the follow-up results. The period between the initial CE and last recorded follow-up appointment was defined as follow-up period. Overt bleeding or the decrease in Hb levels >

Table 1 Capsule endoscopy findings in patients with obscure gastrointestinal bleeding

Findings	n (%)
Positive findings in CE	118 (84.9)
Normal	21 (15.1)
Angiodysplasia	27 (19.42)
Polypoid lesion	25 (17.98)
Ulcer	25 (17.98)
Erosions	22 (15.82)
Malign lesions	7 (5.12)
Active bleeding	4 (2.87)
Portal hypertensive enteropathy	2 (1.43)
Mucosal bleeding	2 (1.43)
Arteriovenous malformation	2 (1.43)
Diverticulum	1 (0.71)
Parasite infection	1 (0.71)

CE: Capsule endoscopy.

2 g/dL were considered as "rebleeding".

Statistical analysis

Statistical analysis was performed using Number Cruncher Statistical System 2007 with Power Analysis and Sample Size 2008 statistical software. The data was analyzed by definitive methods (mean, standard deviation, median, minimum, maximum, frequency, ratio,) together with Pearson's χ^2 test, Fisher-Freeman-Halton test, Yates's Continuity Correction test. In the determination of multivariate effects of the variables on rebleeding, Stepwise logistic regression analysis was used. Significance levels were determined as $P < 0.01$ and $P < 0.05$.

RESULTS

CE was performed on 141 patients with OGIB. The capsule was retained in the upper GI tract in two patients thus video monitoring was not achieved. The first patient was diagnosed as having achalasia after CE, and the second had gastric diabetic gastroparesis by further investigation. A total of 139 patients (62% male) who applied CE had available follow-up data. Median age of patients was 72 years (13-93) and median follow-up duration was 32 mo (6-82 mo). In 112 of the 139 (80.6%) patients, capsule transit time to caecum was within the recording time. Spontaneous elimination of the capsule within 2 wk was seen in 133 (95.4%) patients. Capsule retention was found in 6 patients (4.6%). The overt obscure bleeding rate was 61.9% ($n = 86$), whereas the rate for occult obscure bleeding was 38.1% ($n = 53$). Comorbidities were detected in 35.5% ($n = 50$) of the patients. NSAIDs, anticoagulant-antiaggregant drugs were used at a rate of 18.9% ($n = 26$). CE was positive in 118 (84.9%) patients (Table 1).

Long-term outcome of CE

Rebleeding was seen in 40.3% of the patients (26.4% occult and 48.8% overt bleeding, $P = 0.015$). The rebleeding rate was 46.6% (55/118) in patients with positive CE

Table 2 Evaluation of rebleeding according to the demographic data n (%)

		Rebleeding		P
		(+)	(-)	
Age, n (%)	< 70 yr	32 (32)	68 (68)	¹ 0.001 ^b
	> 70 yr	24 (61.5)	15 (38.5)	
Comorbidity		33 (66)	17 (34)	² 0.001 ^b
	OGIB			
Overt		42 (48.8)	44 (51.2)	² 0.015 ^a
	Occult	14 (26.4)	39 (73.6)	
Vascular lesion		31 (72.1)	12 (27.9)	² 0.001 ^b
Positive capsule result		55 (46.6)	63 (53.4)	² 0.001 ^b
NSAIDs-anticoagulant		19 (73.1)	7 (26.9)	² 0.001 ^b
antiaggregant therapy				

¹Pearson Ki-kare test; ²Yates' Continuity Correction test. ^a $P < 0.05$; ^b $P < 0.01$.

OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs.

and 4.8% (1/21) with negative CE results at the end of follow-up period. Evaluation of rebleeding in relation with the demographic data is shown in Table 2. Both univariate and multivariate analyses were performed to find out the factors related with a higher risk of rebleeding. When we evaluated the effects of comorbidity, age, overt presentation, NSAIDs-anticoagulant-antiaggregant therapy and vascular lesion on rebleeding by stepwise logistic regression analysis, the OR for the effect of NSAIDs-anticoagulant-antiaggregant therapy on rebleeding was 5.8 (95%CI: 1.86-18.27), and 6.027 (95%CI: 2.56-14.14) for vascular lesions. Although, OR was 2.274 (95%CI: 0.86-5.98) for comorbidities, it was not statistically significant. The association analysis is detailed in Table 3. One patient who had diverticulosis coli and negative CE died because of bleeding at 46 mo. The specificity of the CE was found to be 95.2% and positive predictive value was 98.2% in the prediction of rebleeding. Treatment was applied to 29 patients (51.7%): Surgery ($n = 4$), argon plasma coagulation ($n = 11$), transcatheter aortic valve implantation (TAVI) (the reason of the bleeding was aortic stenosis so to treat that TAVI procedure was applied) ($n = 2$), hormonal therapy ($n = 2$), reason based treatment (NSAIDs, anticoagulant, antiplatelet, antiaggregant drugs withdrawal) ($n = 10$). Seven patients died at the end of the follow-up and six of them died because of a rebleeding episode.

DISCUSSION

For the diagnosis of OGIB, capsule endoscopy is a useful imaging technique. Therefore, it is accepted as a gold standard method and should be the first step in the management of patients with OGIB^[7]. The number of studies about the results of CE in long-term is limited^[8-10]. In this study, we assessed the impact of CE in the long-term period (median: 32 mo) in patients with OGIB. The diagnostic yield of CE was 84.9%. Rebleeding was determined in 40.3% (56/139) in patients with OGIB. Specificity of CE was 95.2% and positive predictive value for rebleeding was 98.2%. Previous studies in the

Table 3 Risk factors for rebleeding (univariate-multivariate analysis)

	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
Comorbidity	5.176	2.442-10.972	0.001 ^b	2.274	0.864-5.986	0.096
Age	3.400	1.574-7.342	0.001 ^b	1.735	0.595-5.057	0.313
Overt OGIB	2.659	1.265-5.589	0.015 ^a	1.222	0.490-3.048	0.667
NSAIDs-anticoagulant-antiagregant therapy	5.575	2.153-14.438	0.001 ^b	5.843	1.868-18.275	0.002 ^b
Vascular lesion	6.458	2.852-14.625	0.001 ^b	6.027	2.568-14.146	0.001 ^b
Positive CE results	17.460	2.269-134.371	0.001 ^b	-	-	-

^a $P < 0.05$; ^b $P < 0.01$. OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs; CE: Capsule endoscopy.

Table 4 Rebleeding rates in different studies

Ref.	Total number of case	Follow-up duration (mo)	Rebleeding rates after negative CE (%)
Lai <i>et al</i> ^[11]	49	12	6
Macdonald <i>et al</i> ^[12]	49	17	11
Park <i>et al</i> ^[13]	51	32	36
Delvaux <i>et al</i> ^[14]	44	12	0
Iwamoto <i>et al</i> ^[16]	78	6	4
Lorenceanu-Savale <i>et al</i> ^[17]	35	12	0
Koh <i>et al</i> ^[18]	51	23	23

CE: Capsule endoscopy.

literature reported lower bleeding ratios in patients with negative CE results in comparison with positive^[11-13]. Delvaux *et al*^[14]'s study on 44 patients in one-year follow-up period reported that the negative predictive values was 100% in patients with negative CE and the positive predictive values of CE were 94.4% in patients with positive CE results. Arakawa *et al*^[15] also reported that none of their patients who had a normal CE had rebleeding. As compatible with the literature, only one patient has a rebleed who had a normal CE in our group. The follow-up time is important for patients who have negative CE. In our study, the mean follow-up duration for patients was 46 ± 21 mo (range: 6-82 mo). The rebleeding rate is variable in the literature (0%-36%, Table 4)^[11-14,16-18]. However, the main restriction of these studies is the small group of patients and their relatively short follow-up periods. Rahmi *et al*^[19] showed that overt OGIB at presentation was a risk factor for rebleeding. We also found that the rebleeding ratio was higher in overt obscure bleeding when compared with occult obscure bleeding (48.8% vs 26.4%, $P = 0.015$). Vascular lesions were more susceptible to rebleeding when it was compared with the others (72.1% vs 27.9%, $P = 0.001$). These results also confirm the results of previous studies^[20,21]. In present study, NSAIDs-anticoagulant-antiagregant therapy (OR = 5.8; 95%CI: 1.86-18.27) and vascular ectasia (OR= 6.02; 95%CI: 2.568-14.146) were detected as an independent risk factors for rebleeding in the multivariate analysis. In univariate analysis; advanced age, comorbidity, overt bleeding, were also detected as a predictors of rebleeding. Therefore, anticoagulant/antiagregant/NSAIDs users, and vascular lesions in CE should be follow-up carefully because of the high rebleeding rate. Our long-term follow-up results

were compatible with the short-term follow-up results in the literature^[20-23].

In conclusion, CE is a reliable method in the diagnosis of obscure GI bleeding. Negative CE correlated with a significantly lower rebleeding risk in the long-term follow-up period.

COMMENTS

Background

Obscure gastrointestinal bleeding (OGIB) is a frequent problem in the daily gastroenterology practice that represents nearly 5% of all gastrointestinal (GI) hemorrhages. The most extensive location of OGIB is small bowel, where it is usually far beyond the range of a standard endoscopic examination. Therefore, capsule endoscopy (CE) is the preferred technique to assess patients with OGIB. The high specificity and sensitivity of CE in OGIB cases and increased diagnostic value of this method was shown in several previously published studies. Even though diagnostic value of CE is the focus point of most studies, in the literature there is not enough data about the long-term results of using CE and its effectiveness in predicting and assessment of rebleeding risks.

Research frontiers

Diagnosis of OGIB is mostly dependent on CE. However, there is not enough data about the long-term outcomes of patients with OGIB who applied CE.

Innovations and breakthroughs

The authors evaluated 139 patients with OGIB diagnosed by CE in a long-term follow-up study. Several risk factors for rebleeding were detected. Negative CE correlated with a significantly lower rebleeding rate.

Applications

CE is a safe, well-tolerated and powerful diagnostic tool which may also provide prognostic implications.

Terminology

OGIB usually originates from small bowel and is not detected by both

esophagogastroduodenoscopy and colonoscopy. CE is a device with a tiny camera. Following the administration of the capsule, the camera within the capsule can obtain pictures of GI tract and gut as it passes through the GI system of the patient. The images obtained are transferred into an external disk using wireless technology and those images are later reviewed by the gastroenterologist.

Peer-review

It is an important novel study on CE for diagnosis of obscure GI bleeding and rebleeding rates on long term basis.

REFERENCES

- Pennazio M**, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: 25826168 DOI: 10.1055/s-0034-1391855]
- Carey EJ**, Leighton JA, Heigh RI, Shiff AD, Sharma VK, Post JK, Fleischer DE. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. *Am J Gastroenterol* 2007; **102**: 89-95 [PMID: 17100969 DOI: 10.1111/j.1572-0241.2006.00941.x]
- Rockey DC**. Occult gastrointestinal bleeding. *N Engl J Med* 1999; **341**: 38-46 [PMID: 10387941 DOI: 10.1056/NEJM199907013410107]
- Scapa E**, Jacob H, Lewkowicz S, Migdal M, Gat D, Glukhovski A, Gutmann N, Fireman Z. Initial experience of wireless-capsule endoscopy for evaluating occult gastrointestinal bleeding and suspected small bowel pathology. *Am J Gastroenterol* 2002; **97**: 2776-2779 [PMID: 12425547 DOI: 10.1111/j.1572-0241.2002.07021.x]
- Iddan G**, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. *Nature* 2000; **405**: 417 [PMID: 10839527 DOI: 10.1038/35013140]
- Swain P**, Fritscher-Ravens A. Role of video endoscopy in managing small bowel disease. *Gut* 2004; **53**: 1866-1875 [PMID: 15542530 DOI: 10.1136/gut.2003.035576]
- Raju GS**, Gerson L, Das A, Lewis B; American Gastroenterological Association. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. *Gastroenterology* 2007; **133**: 1697-1717 [PMID: 17983812 DOI: 10.1053/j.gastro.2007.06.007]
- Magalhães-Costa P**, Bispo M, Santos S, Couto G, Matos L, Chagas C. Re-bleeding events in patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *World J Gastrointest Endosc* 2015; **7**: 403-410 [PMID: 25901220 DOI: 10.4253/wjge.v7.i4.403]
- Tan W**, Ge ZZ, Gao YJ, Li XB, Dai J, Fu SW, Zhang Y, Xue HB, Zhao YJ. Long-term outcome in patients with obscure gastrointestinal bleeding after capsule endoscopy. *J Dig Dis* 2015; **16**: 125-134 [PMID: 25495855 DOI: 10.1111/1751-2980.12222]
- Pennazio M**, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, De Franchis R. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. *Gastroenterology* 2004; **126**: 643-653 [PMID: 14988816 DOI: 10.1053/j.gastro.2003.11.057]
- Lai LH**, Wong GL, Chow DK, Lau JY, Sung JJ, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *Am J Gastroenterol* 2006; **101**: 1224-1228 [PMID: 16771942]
- Macdonald J**, Porter V, McNamara D. Negative capsule endoscopy in patients with obscure GI bleeding predicts low rebleeding rates. *Gastrointest Endosc* 2008; **68**: 1122-1127 [PMID: 19028220 DOI: 10.1016/j.gie.2008.06.054]
- Park JJ**, Cheon JH, Kim HM, Park HS, Moon CM, Lee JH, Hong SP, Kim TI, Kim WH. Negative capsule endoscopy without subsequent enteroscopy does not predict lower long-term rebleeding rates in patients with obscure GI bleeding. *Gastrointest Endosc* 2010; **71**: 990-997 [PMID: 20304392 DOI: 10.1016/j.gie.2009.12.009]
- Delvaux M**, Fassler I, Gay G. Clinical usefulness of the endoscopic video capsule as the initial intestinal investigation in patients with obscure digestive bleeding: validation of a diagnostic strategy based on the patient outcome after 12 months. *Endoscopy* 2004; **36**: 1067-1073 [PMID: 15578296]
- Arakawa D**, Ohmiya N, Nakamura M, Honda W, Shirai O, Itoh A, Hirooka Y, Niwa Y, Maeda O, Ando T, Goto H. Outcome after enteroscopy for patients with obscure GI bleeding: diagnostic comparison between double-balloon endoscopy and videocapsule endoscopy. *Gastrointest Endosc* 2009; **69**: 866-874 [PMID: 19136098 DOI: 10.1016/j.gie.2008.06.008]
- Iwamoto J**, Mizokami Y, Shimokobe K, Yara S, Murakami M, Kido K, Ito M, Hirayama T, Saito Y, Honda A, Ikegami T, Ohara T, Matsuzaki Y. The clinical outcome of capsule endoscopy in patients with obscure gastrointestinal bleeding. *Hepatogastroenterology* 2011; **58**: 301-305 [PMID: 21661386]
- Lorenceanu-Savale C**, Ben-Soussan E, Ramirez S, Antonietti M, Lerebours E, Ducrotte P. Outcome of patients with obscure gastrointestinal bleeding after negative capsule endoscopy: results of a one-year follow-up study. *Gastroenterol Clin Biol* 2010; **34**: 606-611 [PMID: 20822872 DOI: 10.1016/j.gcb.2010.06.009]
- Koh SJ**, Im JP, Kim JW, Kim BG, Lee KL, Kim SG, Kim JS, Jung HC. Long-term outcome in patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *World J Gastroenterol* 2013; **19**: 1632-1638 [PMID: 23539070 DOI: 10.3748/wjg.v19.i10.1632]
- Rahmi G**, Samaha E, Vahedi K, Delvaux M, Gay G, Lamouliatte H, Filoche B, Saurin JC, Ponchon T, Rhun ML, Coumaros D, Bichard P, Manière T, Lenain E, Chatellier G, Cellier C. Long-term follow-up of patients undergoing capsule and double-balloon enteroscopy for identification and treatment of small-bowel vascular lesions: a prospective, multicenter study. *Endoscopy* 2014; **46**: 591-597 [PMID: 24830401 DOI: 10.1055/s-0034-1365514]
- Min YW**, Kim JS, Jeon SW, Jeon YT, Im JP, Cheung DY, Choi MG, Kim JO, Lee KJ, Ye BD, Shim KN, Moon JS, Kim JH, Hong SP, Chang DK. Long-term outcome of capsule endoscopy in obscure gastrointestinal bleeding: a nationwide analysis. *Endoscopy* 2014; **46**: 59-65 [PMID: 24254387 DOI: 10.1055/s-0033-1358803]
- Shinozaki S**, Yamamoto H, Yano T, Sunada K, Hayashi Y, Shinhata H, Sato H, Despott EJ, Sugano K. Favorable long-term outcomes of repeat endotherapy for small-intestine vascular lesions by double-balloon endoscopy. *Gastrointest Endosc* 2014; **80**: 112-117 [PMID: 24444670 DOI: 10.1016/j.gie.2013.11.029]
- Sakai E**, Endo H, Taniguchi L, Hata Y, Ezuka A, Nagase H, Yamada E, Ohkubo H, Higurashi T, Sekino Y, Koide T, Iida H, Hosono K, Nonaka T, Takahashi H, Inamori M, Maeda S, Nakajima A. Factors predicting the presence of small bowel lesions in patients with obscure gastrointestinal bleeding. *Dig Endosc* 2013; **25**: 412-420 [PMID: 23368528 DOI: 10.1111/den.12002]
- Sidhu R**, Sanders DS, Sakellariou VP, McAlindon ME. Capsule endoscopy and obscure gastrointestinal bleeding: are transfusion dependence and comorbidity further risk factors to predict a diagnosis? *Am J Gastroenterol* 2007; **102**: 1329-1330 [PMID: 17531021 DOI: 10.1111/j.1552-0241.2007.01171.x]

P- Reviewer: ElGeidie AAR, Yu B S- Editor: Gong XM
L- Editor: A E- Editor: Liu SQ



Retrospective Study

Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics

Yuji Shindo, Satoshiro Matsumoto, Hiroyuki Miyatani, Yukio Yoshida, Hirosato Mashima

Yuji Shindo, Satoshiro Matsumoto, Hiroyuki Miyatani, Yukio Yoshida, Hirosato Mashima, Department of Gastroenterology, Jichi Medical University, Saitama Medical Center, Saitama 330-8503, Japan

Author contributions: Shindo Y collected and analyzed the data, and drafted the manuscript; Matsumoto S provided analytical oversight and designed and supervised the study; Miyatani H, Yoshida Y and Mashima H revised the manuscript for important intellectual content; all authors have read and approved the final version to be published.

Institutional review board statement: The study design was reviewed and approved by the Ethics Committee of Jichi Medical University, Saitama Medical Center (Approval No. RIN14-07).

Informed consent statement: This study was a retrospective patient's medical records review using a de-identified patient database.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Yuji Shindo, MD, Department of Gastroenterology, Jichi Medical University, Saitama Medical Center, 1-847 Amanuma, Omiya, Saitama 330-8503, Japan. yujimax7777@jichi.ac.jp
Telephone: +81-48-6472111
Fax: +81-48-6485188

Received: October 29, 2015
Peer-review started: October 30, 2015
First decision: December 11, 2015
Revised: December 27, 2015
Accepted: January 29, 2016
Article in press: January 31, 2016
Published online: April 10, 2016

Abstract

AIM: To evaluate the risk factors for postoperative bleeding after gastric endoscopic submucosal dissection (ESD) based on the latest guidelines.

METHODS: A total of 262 gastric neoplasms were treated by ESD at our center during a 2-year period from October 2012. We analyzed the data of these cases retrospectively to identify the risk factors for post-ESD bleeding.

RESULTS: Of the 48 (18.3%) cases on antithrombotic treatment, 10 were still receiving antiplatelet drugs perioperatively, 13 were on heparin replacement after oral anticoagulant withdrawal, and the antithrombotic therapy was discontinued perioperatively in 25 cases. Postoperative bleeding occurred in 23 cases (8.8%). The postoperative bleeding rate in the heparin replacement group was 61.5%, significantly higher than that in the non-antithrombotic therapy group (6.1%). Univariate analysis identified history of antithrombotic drug use, heparin replacement, hemodialysis, cardiovascular disease, diabetes mellitus, elevated prothrombin time-international normalized ratio, and low hemoglobin level on admission as risk factors for post ESD bleeding. Multivariate analysis identified only heparin replacement (OR = 13.7, 95%CI: 1.2-151.3, $P = 0.0329$) as a significant risk factor for post-ESD bleeding.

CONCLUSION: Continued administration of antiplatelet agents, based on the guidelines, was not a risk factor for postoperative bleeding after gastric ESD; however, heparin replacement, which is recommended after withdrawal of oral anticoagulants, was identified as a significant risk factor.

Key words: Postoperative bleeding; Antithrombotic treatment; Gastric neoplasms; Endoscopic submucosal dissection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There are few data on the risk factors for postoperative bleeding after gastric endoscopic submucosal dissection (ESD) in patients continued on antithrombotic treatment during the perioperative period. This study was aimed to evaluate the risk factors for postoperative bleeding after gastric ESD in patients continued or not continued on antithrombotic treatment. Univariate analysis showed that an antithrombotic agent user, especially heparin replacement was significantly associated with risk factors for postoperative bleeding. Multivariate analysis identified heparin replacement as the independent risk factor for post ESD bleeding. Therefore, patients with heparin replacement should be carefully observed after gastric ESD.

Shindo Y, Matsumoto S, Miyatani H, Yoshida Y, Mashima H. Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics. *World J Gastrointest Endosc* 2016; 8(7): 349-356 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i7/349.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i7.349>

INTRODUCTION

Early gastric cancer is defined as a tumor confined to the mucosa or submucosa, irrespective of the presence/absence of lymph node metastasis^[1]. Endoscopic submucosal dissection (ESD) is a widely used procedure now for early gastric cancers and gastric adenomas^[2,3]. The major complications of this procedure are perforation and postoperative bleeding. Postoperative bleeding after gastric ESD is reported to occur in 4.8%-9.4% of patients not receiving antithrombotic agents/patients in whom these drugs are discontinued during the perioperative period^[4-9]. While several factors (large resected tumor size^[6,8], advanced age of the patient, long procedure time^[10,11], patient under dialysis, and ulcerative lesions^[12,13]) have been suggested as risk factors for postoperative bleeding after gastric ESD, no consensus has been reached yet with regard to the precise risk factors for postoperative bleeding after gastric ESD.

Recently, the incidence of gastric cancer has been increasing, owing to the increasing lifespan of the general population^[14]. The number of patients suffering

from gastric cancer and taking antithrombotic agents is also growing as a result of the increasing prevalence of ischemic heart disease, cerebrovascular disease, and other arteriosclerotic diseases. The previous guidelines published by the Japan Gastroenterological Endoscopy Society (JGES) focused primarily on the prevention of hemorrhage after gastrointestinal endoscopy associated with continuation of antithrombotic therapy in the perioperative period, without considering the risk of thrombosis associated with withdrawal of the therapy^[15]. The new edition of the JGES guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment was published in July 2012. The new guidelines include discussions of the risk of gastroenterological hemorrhage associated with continuation of antithrombotic therapy, as well as of the risk of thromboembolism associated with discontinuation of antithrombotic therapy^[16]. There are few data on the risk factors for postoperative bleeding after gastric ESD in patients continued on antithrombotic treatment during the perioperative period.

We have been performing ESD for gastric neoplasms based on the new guidelines since October 2012. This study was aimed at evaluating the risk factors for postoperative bleeding after gastric ESD in patients continued or not continued on antithrombotic treatment.

MATERIALS AND METHODS

Patients

The subjects were 283 cases who underwent ESD for gastric neoplasms at Saitama Medical Center from October 2012 to September 2014. Of these cases, 21 cases were excluded from this retrospective study for the following reasons: Multiple lesions were removed on the same day (19 cases), and the procedure could not be completed (2 cases).

Patient characteristics

We retrospectively reviewed the patient's medical records and collected the following data: Age, sex, hemoglobin level, prothrombin time-international normalized ratio (PT-INR), comorbidities (hypertension, diabetes mellitus, cardiovascular disease, hemodialysis, or liver cirrhosis), the Charlson comorbidity index^[17,18], and details about any antithrombotic therapy. Patients taking antithrombotic agents were classified into three groups based on the guidelines: A group in which the antithrombotic therapy was discontinued, a group in which antiplatelet drug therapy was continued (including replacement of thienopyridine with aspirin or cilostazol)^[16], and a group in which oral anticoagulant treatment was replaced by heparin. We used continuous infusion of unfractionated heparin for heparin replacement. The start dose of unfractionated heparin was 10000 to 15000 units. Check activated partial thromboplastin time during continuous infusion; adjust to target of 1.5 to 2 times the upper limit of control. We stopped continuous heparin infusion four to six hours

before procedure.

ESD procedure

ESD was performed using the conventional single-channel endoscope (GIF-Q260J, or -H260Z; Olympus, Tokyo, Japan) and a high-frequency electrical generator (VIO 300D; Erbe, Tübingen, Germany) by 15 endoscopists. An expert endoscopist was defined as one who had the experience of performing more than 50 gastric ESDs. After marking dots circumferentially on the surrounding normal mucosa 5–10 mm away from the lesion demarcation line, a mixture of 10% glycerin and 0.4% sodium hyaluronate solution (Mucoup; Johnson and Johnson, Tokyo, Japan) containing indigo carmine and 0.01% epinephrine was injected submucosally. A circumferential incision was performed using the Dual knife (KD-650L; Olympus, Tokyo, Japan) or Flush knife (DK2618JN20; Fujinon, Tokyo, Japan). After the circumferential incision was completed, the submucosa was dissected using the Dual knife, Flush knife, or IT2 knife (KD-611L; Olympus, Tokyo, Japan). Hemostatic forceps (FD-410LR; Olympus, Tokyo, Japan) were used to control the bleeding during and after the procedure. A second-look endoscopy was performed routinely the following weekday, and preventive coagulation of visible vessels was performed^[19]. A proton pump inhibitor, that is, omeprazole 20 mg, was administered intravenously twice a day starting on the day of the ESD until the day before the start of a soft diet. Then, oral administration of esomeprazole 20 mg was started and continued for 8 wk after the ESD.

Lesion characteristics and curability

All lesions were pathologically examined on the basis of the Japanese Classification of Gastric Carcinoma^[1]. The macroscopic type was classified as the protruded type, flat type, or depressed type. The size of the tumor and the resected area were measured on the specimen. The location of the tumor was classified as the upper third, middle third, or lower third of the stomach. The depth of the tumor invasion was classified as pT1a (up to the mucosa) or pT1b (up to the submucosa). Invasion of the submucosal layer (SM) was divided into SM1 (less than 0.5 mm from the muscularis mucosae) and SM2 (more than 0.5 mm submucosal invasion). The tumor differentiation grade was based on the most dominant differentiation grade, and the tumors were classified as adenoma, differentiated cancer (including well-differentiated, moderately differentiated, tubular, and papillary adenocarcinoma), or undifferentiated cancer (poorly differentiated adenocarcinoma and signet-ring cell carcinoma).

En bloc resection was defined as resection in a single piece. Complete resection was defined as *en bloc* resection of a tumor with a negative horizontal margin and vertical margin. Curative resection was defined as follows: *En bloc* resection, tumor size ≤ 2 cm, differentiated-type tumor, pT1a, ulceration (UI)-negative, no lymphovascular infiltration [ly(-), v(-)],

negative horizontal margin (HM0), and negative vertical margin (VM0). The expanded indications of curative resection were as follows: *En bloc* resection, ly(-), v(-), HM0, and VM0, as well as: (1) tumor size ≥ 2 cm, differentiated-type tumor, pT1a, UI(-); (2) tumor size ≤ 3 cm, differentiated-type tumor, pT1a, UI(+); (3) tumor size ≤ 2 cm, undifferentiated-type tumor, pT1a, UI(-); and (4) tumor size ≤ 3 cm, differentiated-type tumor, pT1b (SM1)^[20,21]. All other lesions were classified as non-curative resection.

Adverse events

Postoperative bleeding was defined as bleeding events, including hematemesis and/or melena, after the procedure requiring endoscopic hemostasis, or a decrease of the hemoglobin level by more than 2 mg/dL as compared to the preoperative hemoglobin level.

Statistical analysis

Data are expressed as mean \pm SD or as percentages. Statistical analysis was carried out using student's *t*-test or Fisher's exact test. Factors identified as significant by the univariate analysis ($P < 0.15$) were entered into a multivariate logistic regression analysis model. All data analyses were carried out using the StatView software (version 5.0; SAS Institute Inc., Cary, North Carolina, United States). Differences with *P* values of less than 0.05 were considered as denoting significance. The statistical methods of this study were reviewed by Dr. Satoshihiro Matsumoto from the Department of Gastroenterology, Jichi Medical University, Saitama Medical Center, Saitama, Japan.

RESULTS

The overall clinicopathological profiles of the 262 gastric neoplasms in 250 patients are shown in Table 1. Twelve patients had received treatment for 2 lesions occurring metachronously during the investigation period, and were counted twice. The mean age of the patients was 71 ± 8 years (range 32–87) (M:F = 190:72). Of the 262 cases, 48 (18.3%) had a history of receiving antithrombotic therapy for cardiovascular diseases. The details of the antithrombotic therapy were as follows: Aspirin 28 cases, clopidogrel 6 cases, ticlopidine 1 case, cilostazol 4 cases, and warfarin 14 cases. Perioperative management of the antithrombotic therapy was as follows: The antithrombotic drugs were discontinued in 25 cases, the antiplatelet agents were continued in 10 cases, and oral anticoagulant treatment was replaced by heparin in 13 cases (most of the patients who were under warfarin treatment received heparin replacement, except one patient who had past history of paroxysmal atrial fibrillation).

The mean tumor size was 15.9 ± 10.9 mm (range, 2–85 mm). The gastric tumors were mainly located in the lower third and in the lesser curvature of the stomach. The *en bloc* resection rate was 98.8% (259 cases) and the curative resection rate was 66.8%

Table 1 Overall clinicopathological profiles of 262 gastric neoplasms in 250 patients

Patients background factors	
Age (yr, mean \pm SD) (range)	71 \pm 8 (32-87)
Sex (male/female)	190/72
Antithrombotic agent user	48 (18.3%)
Detail	
Aspirin	28
Clopidogrel	6
Ticlopidine	1
Cilostazol	4
Warfarin	14
Heparin replacement (withdrawal warfarin)	13
Hemodialysis	6 (2.3%)
Hypertension	130 (49.6%)
Diabetes mellitus	54 (20.6%)
Cardiovascular disease	48 (18.3%)
Resected lesion factors	
Curability (curative/expanding indications curative/non-curative)	175/57/30
Macroscopic type (depressed/flat/protruded)	151/101/10
Location (upper third/middle third/lower third)	38/73/151
Circumference (anterior wall, greater curvature, lesser curvature, posterior wall)	38/52/124/48
Tumor size (mm, mean \pm SD) (range)	15.9 \pm 10.9 (2-85)
Differentiation (adenoma/differentiated cancer/undifferentiated cancer)	34/216/12
Depth (M:SM1:SM2)	236/12/14
Ulcer findings positive	16 (6.1%)
Lymphovascular infiltration positive	18 (6.9%)
Horizontal or vertical margin positive	8 (3.1%)
Perioperative factors	
<i>En bloc</i> resection	259 (98.8%)
Operator (beginner/expert)	97/165
Operation time (min, mean \pm SD) (range)	81.5 \pm 50.9 (16-307)
Resected size (mm, mean \pm SD) (range)	36.1 \pm 11.6 (12-88)
Perforation	2 (0.8%)
Postoperative bleeding	23 (8.8%)
Blood transfusion (%)	7 (2.7%)

SM: Submucosal layer.

(175 cases). The curative resection rate according to the expanded indications was 21.8% (57 cases). The non-curative resection rate was 11.5% (30 cases). Postoperative bleeding occurred in 23 cases (8.8%). Perforation during ESD occurred in 2 cases. No events of thromboembolism occurred with discontinuation of the antithrombotic therapy. Among the 23 patients who had postoperative bleeding, 6 (26.1%) needed blood transfusion. One patient needed blood transfusion due to underlying anemic disease.

Univariate analysis carried out to determine the risk factors for postoperative bleeding identified antithrombotic agent user ($P = 0.0011$), heparin replacement ($P < 0.0001$), hemodialysis ($P = 0.0321$), diabetes mellitus ($P = 0.0435$), cardiovascular disease ($P = 0.0069$), PT-INR ($P < 0.0001$), and the hemoglobin level on admission ($P < 0.0153$) as risk factors for postoperative bleeding (Table 2).

The postoperative bleeding rates in the group in which the antithrombotic therapy was discontinued and the group in which the antiplatelet agents were continued were 0% (0/25) and 20% (2/10), respectively. These rates were not significantly different from the rate in the non-antithrombotic therapy group (6.1%, 13/201). On the other hand, the postoperative bleeding

rate in the heparin replacement group was 61.5% (8/13), which was significantly higher than the rate in the non-antithrombotic group (6.1%) ($P < 0.0001$) (Figure 1).

Multivariate analysis identified heparin replacement (OR = 13.7; 95%CI: 1.2-151.3, $P = 0.0329$) as the only significant risk factor for post ESD bleeding. It appeared that the tumor location in the lower third of the stomach may be related to postoperative bleeding; however, the difference in the bleeding rate was not statistically significant (OR = 2.9, 95%CI: 0.92-8.94, $P = 0.0697$) (Table 3).

DISCUSSION

We investigated risk factors for postoperative bleeding in patients undergoing gastric ESD based on the new guidelines published by the JGES^[16]. The postoperative bleeding rate in the group not under anti-thrombotic therapy was 6.1% (13/214), which was consistent with previous reports (4.81%-9.4%)^[4-9]. Antithrombotic agents were used in 18.3% of the cases (48/262), and the postoperative bleeding rate increased in the following order, depending on the perioperative management of antithrombotic therapy: Group in which the antithrombotic therapy was discontinued (0%, 0/25), group in

Table 2 Univariate analysis of postoperative bleeding

	Present (<i>n</i> = 23)	Absent (<i>n</i> = 239)	<i>P</i> value
Patients background factors			
Age (yr, mean ± SD) (range)	73 ± 7 (58-82)	71 ± 8 (32-87)	0.4304
Sex (male/female)	7/16	174/65	0.7397
Antithrombotic agent user	10 (43.5%)	38 (15.9%)	0.0011 ¹
Category of antithrombotic treatment (non-antithrombotic therapy/discontinuation of antithrombotic agents/continuation of antiplatelet agents/heparin replacement)	13/0/2/8	201/25/8/5	< 0.0001 ¹
Hemodialysis	2 (8.7%)	4 (1.7%)	0.0321 ¹
Hypertension	10 (43.5%)	120 (50.2%)	0.5375
Diabetes mellitus	1 (4.3%)	53 (22.1%)	0.0435 ¹
Cardiovascular disease	9 (39.1%)	39 (16.3%)	0.0069 ¹
PT-INR (mean ± SD) (range)	1.2 ± 0.5 (0.9-2.1)	0.9 ± 0.1 (0.9-2.0)	< 0.0001 ¹
Charlson comorbidity index (mean ± SD) (range)	3.5 ± 1.2 (1-6)	3.2 ± 1.3 (0-8)	0.2674
Hemoglobin levels on admission (g/dL, mean ± SD) (range)	12.5 ± 1.3 (9.6-14.4)	13.3 ± 1.5 (7.8-17.1)	0.0153 ¹
Resected lesion factors			
Curability (curative/expanding indications curative/non-curative)	19/3/1	156/54/29	0.2305
Macroscopic type (depressed/flat/protruded)	11/11/1	140/90/9	0.6058
Location (upper third/middle third/lower third)	2/3/18	36/70/133	0.0907
Circumference (anterior wall, greater curvature, lesser curvature, posterior wall)	3/4/11/5	35/48/113/43	0.9645
Tumor size (≥ 21 mm)	3 (13.0%)	51 (21.3%)	0.3476
Differentiation (adenoma/differentiated cancer/undifferentiated cancer)	3/2/18	31/198/10	0.6108
Depth (M:SM1:SM2)	22/0/1	214/12/13	0.525
Ulcer findings positive	0 (0%)	16 (6.7%)	0.2003
Lymphovascular infiltration positive	1 (4.3%)	17 (7.1%)	0.6166
Horizontal or vertical margin positive	1 (4.3%)	7 (2.9%)	0.7204
Tumor size (mm, mean ± SD)	17.3 ± 16.1 (6-85)	15.7 ± 10.3 (2-70)	0.5147
Perioperative factors			
Operator (beginner/expert)	9/14	88/151	0.8265
Resected size (mm, mean ± SD) (range)	38.9 ± 12.8 (25-88)	35.8 ± 11.5 (12-85)	0.5147
Perforation (%)	1 (4.3%)	1 (0.4%)	0.1286
Operation time (min, mean ± SD) (range)	87.4 ± 63.5 (31-260)	80.9 ± 49.6 (16-307)	0.5608

¹Significantly different. SM: Submucosal layer; PT-INR: Prothrombin time-international normalized ratio.**Table 3** Multivariate analysis of postoperative bleeding

Risk factors	Odds ratio	95%CI	<i>P</i> value
Cardiovascular disease	1.1	0.09-13.2	0.931
Diabetes mellitus	0.2	0.02-1.8	0.156
Hemodialysis	3.3	0.17-65.1	0.434
Heparin replacement	13.7	1.2-151.3	0.033 ¹
Location lower third	2.9	0.9-8.9	0.07

¹Significantly different.

which antiplatelet agents were continued (20%, 2/10), and the group which received heparin replacement (61.5%, 8/13).

While one previous report suggests that antiplatelet drugs do not increase the risk of postoperative bleeding after ESD^[22], there are several reports contending that antiplatelet drugs increase the risk of postoperative bleeding^[23-25]. On the other hand, withdrawal of anti-thrombotic therapy has been reported to increase the risk of development of thromboembolic events^[22].

Although there is no mention about ESD, the 2009 guidelines published by the American Society for Gastrointestinal Endoscopy (ASGE) recommend continuation of aspirin in endoscopy candidates at a high risk of thrombosis. And in patients taking thienopyridines, ASGE recommends substitution of the thienopyridine with aspirin for 7-10 d^[26]. The 2011 guidelines of the

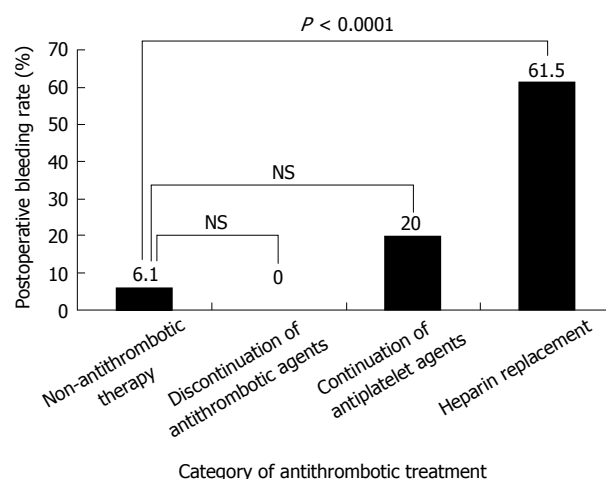


Figure 1 Comparison of the postoperative bleeding rate after gastric endoscopic submucosal dissection according to category of antithrombotic treatment. NS: Not significant.

European Society of gastrointestinal Endoscopy also recommend continuation of aspirin in patients at a high risk of thrombosis. However, the risk of bleeding doubles when the lesions are removed by ESD rather than by endoscopic mucosal resection. Discontinuation of all antiplatelet agents, including aspirin, is recommended, provided that the patient is not at a high risk for thrombotic events^[27]. The new JGES guidelines suggest

that withdrawal of aspirin monotherapy is not required in patients who would be at a high risk of thromboembolic events following withdrawal of the drug. Aspirin can be withdrawn for 3 to 5 d in patients who are low-risk candidates for thromboembolism. Thienopyridines should be discontinued for 5 to 7 d, and substitution with aspirin or cilostazol should be considered^[16]. In our study, the postoperative bleeding rate in the patient group that was continued on antiplatelet drug therapy during the perioperative period was 20%, which is not significantly higher than the reported rate in patients not on antithrombotic drug therapy.

On the other hand, the JGES guidelines recommend heparin replacement after oral anticoagulant agent withdrawal for patients who need to be continued on anticoagulant therapy. Such patients should be treated as high-risk patients, because once thromboembolic complications have occurred, they are often serious^[16]. In this study, 13 of the 14 patients who were on oral anticoagulant therapy received heparin replacement. Although the sample size in this study was small, the postoperative bleeding rate in the heparin replacement group was significantly higher (61.3%, 8/13) as compared with that in the patient group not on antithrombotic drug therapy (6.1%, 13/201). Thus, heparin replacement was identified as an independent, significant risk factor for postoperative bleeding after gastric ESD by both univariate analysis and multivariate analysis. Four of the 6 patients who required blood transfusion after gastric ESD were from the heparin replacement group (data not shown). This suggests that heparin replacement is associated with a significant increase in the risk of massive bleeding as compared to the other groups once postoperative bleeding occurred. There are few reports of investigation of the safety of heparin replacement after withdrawal of anticoagulant therapy in patients undergoing gastric ESD; however, all report high postoperative bleeding rates (23.8%-37.5%)^[24,28]. In our study, the postoperative bleeding rate was much higher (61.3%, 8/13) than that reported in previous studies. According to Yoshio *et al.*^[28] reported that in the heparin replacement group, postoperative bleeding occurred in 2 of 8 cases with tumors in the upper third of the stomach, 5 of 9 cases with tumors in the middle third, and 2 of 7 cases with tumors in the lower third of the stomach. The corresponding values in our study were 2/3, 0/0 and 6/10. Thus, the tumor location might have some influence on the postoperative bleeding rate; however, investigation including a larger number of cases would be required.

Recently, several new oral anticoagulants (NOACs) have been introduced. The NOACs show prompt effects and have shorter half-lives than warfarin^[29,30]. Therefore, in patients on anticoagulant therapy scheduled for gastric ESD, it may be better to substitute warfarin with NOACs rather than with heparin. Tsuji *et al.* reported that use of polyglycolic acid sheets and fibrin glue decreased the risk of bleeding after gastric ESD^[31]. This technique, as well as preventive coagulation of visible vessels^[19], should be

considered to prevent postoperative bleeding in high-risk patients, such as those receiving heparin replacement.

Our investigation had some limitations, as follows: The study was a retrospective study from a single center, and the sample size was small. Detailed prospective investigations are necessary in the future.

In regard to the risks associated with gastric ESD in patients on antithrombotic therapy, continuation of antiplatelet drugs, based on the guidelines, during the perioperative period was not associated with an elevated risk of postoperative bleeding after gastric ESD; the heparin replacement after oral anticoagulant agent withdrawal for patients should be considered carefully for postoperative bleeding after gastric ESD.

COMMENTS

Background

The latest guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment, published in July 2012 by the Japan Gastroenterological Endoscopy Society, include discussions of postoperative bleeding associated with continuation of antithrombotic therapy, as well as of the risk of thromboembolism associated with withdrawal of antithrombotic treatment.

Research frontiers

The new guidelines include discussions of the risk of gastroenterological hemorrhage associated with continuation of antithrombotic therapy, as well as of the risk of thromboembolism associated with discontinuation of antithrombotic therapy. There are few data on the risk factors for postoperative bleeding after gastric endoscopic submucosal dissection (ESD) in patients continued on antithrombotic treatment during the perioperative period.

Innovations and breakthroughs

The postoperative bleeding rate in the heparin replacement group was 61.5%, significantly higher than that in the non-antithrombotic therapy group (6.1%). Multivariate analysis identified only heparin replacement as a significant risk factor for post-ESD bleeding.

Applications

The heparin replacement after oral anticoagulant agent withdrawal for patients should be considered carefully for postoperative bleeding after gastric ESD.

Terminology

Polyglycolic acid is an absorbent suture reinforcement material, which expected for the prevention of post-ESD bleeding in patients with a high risk of bleeding undergoing gastric ESD.

Peer-review

This study was well written and presented. ESD is a novel technique. Endoscopists have to accept the need for advanced endoscopic techniques for performing this technique. Anti-coagulants and anti-platelet agents are widely used to prevent thromboembolic disease.

REFERENCES

- 1 **Japanese Gastric Cancer Association.** Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
- 2 **Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S.** A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]
- 3 **Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T,**

- Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
- 4 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or anti-platelet agents. *Dig Liver Dis* 2009; **41**: 725-728 [PMID: 19230799 DOI: 10.1016/j.dld.2009.01.007]
 - 5 **Ono S**, Kato M, Ono Y, Nakagawa M, Nakagawa S, Shimizu Y, Asaka M. Effects of preoperative administration of omeprazole on bleeding after endoscopic submucosal dissection: a prospective randomized controlled trial. *Endoscopy* 2009; **41**: 299-303 [PMID: 19340731 DOI: 10.1055/s-0029-1214530]
 - 6 **Mannen K**, Tsunada S, Hara M, Yamaguchi K, Sakata Y, Fujise T, Noda T, Shimoda R, Sakata H, Ogata S, Iwakiri R, Fujimoto K. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. *J Gastroenterol* 2010; **45**: 30-36 [PMID: 19760133 DOI: 10.1007/s00535-009-0137-4]
 - 7 **Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838]
 - 8 **Okada K**, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]
 - 9 **Goto O**, Fujishiro M, Oda I, Kakushima N, Yamamoto Y, Tsuji Y, Ohata K, Fujiwara T, Fujiwara J, Ishii N, Yokoi C, Miyamoto S, Itoh T, Morishita S, Gotoda T, Koike K. A multicenter survey of the management after gastric endoscopic submucosal dissection related to postoperative bleeding. *Dig Dis Sci* 2012; **57**: 435-439 [PMID: 21901257 DOI: 10.1007/s10620-011-1886-5]
 - 10 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]
 - 11 **Higashiyama M**, Oka S, Tanaka S, Sanomura Y, Imagawa H, Shishido T, Yoshida S, Chayama K. Risk factors for bleeding after endoscopic submucosal dissection of gastric epithelial neoplasm. *Dig Endosc* 2011; **23**: 290-295 [PMID: 21951088 DOI: 10.1111/j.1443-1661.2011.01151.x]
 - 12 **Mukai S**, Cho S, Kotachi T, Shimizu A, Matuura G, Nonaka M, Hamada T, Hirata K, Nakanishi T. Analysis of delayed bleeding after endoscopic submucosal dissection for gastric epithelial neoplasms. *Gastroenterol Res Pract* 2012; **2012**: 875323 [PMID: 22536221 DOI: 10.1155/2012/875323]
 - 13 **Miyahara K**, Iwakiri R, Shimoda R, Sakata Y, Fujise T, Shiraishi R, Yamaguchi K, Watanabe A, Yamaguchi D, Higuchi T, Tominaga N, Ogata S, Tsuruoka N, Noda T, Hidaka H, Mannen K, Endo H, Yamanouchi K, Yamazato T, Sakata H, Fujimoto K. Perforation and postoperative bleeding of endoscopic submucosal dissection in gastric tumors: analysis of 1190 lesions in low- and high-volume centers in Saga, Japan. *Digestion* 2012; **86**: 273-280 [PMID: 22986899 DOI: 10.1159/000341422]
 - 14 **Saito H**, Osaki T, Murakami D, Sakamoto T, Kanaji S, Tatebe S, Tsujitani S, Ikeguchi M. Effect of age on prognosis in patients with gastric cancer. *ANZ J Surg* 2006; **76**: 458-461 [PMID: 16768768 DOI: 10.1111/j.1445-2197.2006.03756.x]
 - 15 **Committee JGESPE**. Guidelines for Gastroenterological Endoscopy version 3. Japan Gastroenterological Endoscopy Society. Tokyo: Igaku Shoin, 2006
 - 16 **Fujimoto K**, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, Mine T, Yoshino J, Kinoshita Y, Ichinose M, Matsui T. Guidelines for gastroenterological endoscopy in patients undergoing anti-thrombotic treatment. *Dig Endosc* 2014; **26**: 1-14 [PMID: 24215155 DOI: 10.1111/den.12183]
 - 17 **Charlson ME**, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-383 [PMID: 3558716]
 - 18 **Charlson M**, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; **47**: 1245-1251 [PMID: 7722560]
 - 19 **Takizawa K**, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy* 2008; **40**: 179-183 [PMID: 18322872 DOI: 10.1055/s-2007-995530]
 - 20 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739]
 - 21 **Hirasawa T**, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 2009; **12**: 148-152 [PMID: 19890694 DOI: 10.1007/s10120-009-0515-x]
 - 22 **Sanomura Y**, Oka S, Tanaka S, Numata N, Higashiyama M, Kanao H, Yoshida S, Ueno Y, Chayama K. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2014; **17**: 489-496 [PMID: 24142107 DOI: 10.1007/s10120-013-0305-3]
 - 23 **Cho SJ**, Choi IJ, Kim CG, Lee JY, Nam BH, Kwak MH, Kim HJ, Ryu KW, Lee JH, Kim YW. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; **44**: 114-121 [PMID: 22271021 DOI: 10.1055/s-0031-1291459]
 - 24 **Matsumura T**, Arai M, Maruoka D, Okimoto K, Minemura S, Ishigami H, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. *BMC Gastroenterol* 2014; **14**: 172 [PMID: 25280756 DOI: 10.1186/1471-230X-14-172]
 - 25 **Takeuchi T**, Ota K, Harada S, Edogawa S, Kojima Y, Tokioka S, Umegaki E, Higuchi K. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol* 2013; **13**: 136 [PMID: 24010587 DOI: 10.1186/1471-230X-13-136]
 - 26 **Anderson MA**, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Lichtenstein DR, Maple JT, Shen B, Strohmeyer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; **70**: 1060-1070 [PMID: 19889407 DOI: 10.1016/j.gie.2009.09.040]
 - 27 **Boustière C**, Veitch A, Vanbiervliet G, Bulois P, Deprez P, Laquiere A, Laugier R, Lesur G, Mosler P, Nalet B, Napoleon B, Rembacken B, Ajzenberg N, Collet JP, Baron T, Dumonceau JM. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2011; **43**: 445-461 [PMID: 21547880 DOI: 10.1055/s-0030-1256317]
 - 28 **Yoshio T**, Nishida T, Kawai N, Yuguchi K, Yamada T, Yabuta T, Komori M, Yamaguchi S, Kitamura S, Iijima H, Tsutsui S, Michida T, Mita E, Tsujii M, Takehara T. Gastric ESD under Heparin Replacement at High-Risk Patients of Thromboembolism Is Technically Feasible but Has a High Risk of Delayed Bleeding: Osaka University ESD Study Group. *Gastroenterol Res Pract* 2013; **2013**: 365830 [PMID: 23843783 DOI: 10.1155/2013/365830]
 - 29 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in

- patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]
- 30 **Hori M**, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study -. *Circ J* 2012; **76**: 2104-2111 [PMID: 22664783]
- 31 **Tsuji Y**, Fujishiro M, Kodashima S, Ono S, Niimi K, Mochizuki S, Asada-Hirayama I, Matsuda R, Minatsuki C, Nakayama C, Takahashi Y, Sakaguchi Y, Yamamichi N, Koike K. Polyglycolic acid sheets and fibrin glue decrease the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms (with video). *Gastrointest Endosc* 2015; **81**: 906-912 [PMID: 25440679 DOI: 10.1016/j.gie.2014.08.028]

P- Reviewer: Konigsrainer A, Lee HW, Ozkan OV
S- Editor: Qi Y **L- Editor:** A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 April 25; 8(8): 357-377





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hirotoshi Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hirotoshi Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

ORIGINAL ARTICLE

Prospective Study

- 357 Application of the Prague C and M criteria for endoscopic description of columnar-lined esophagus in South Korea

Choe JW, Kim YC, Joo MK, Kim HJ, Lee BJ, Kim JH, Yeon JE, Park JJ, Kim JS, Byun KS, Bak YT

EVIDENCE-BASED MEDICINE

- 362 Impact of endoscopic ultrasound quality assessment on improving endoscopic ultrasound reports and procedures

Schwab R, Pahk E, Lachter J

CASE REPORT

- 368 Delayed perforation after endoscopic submucosal dissection for early gastric cancer: Clinical features and treatment

Yano T, Tanabe S, Ishido K, Azuma M, Wada T, Suzuki M, Kawanishi N, Yamane S, Sasaki T, Katada C, Mikami T, Katada N, Koizumi W

- 374 Diagnosis of a submucosal mass at the staple line after sigmoid colon cancer resection by endoscopic cutting-mucosa biopsy

Morimoto M, Koinuma K, Lefor AK, Horie H, Ito H, Sata N, Hayashi Y, Sunada K, Yamamoto H

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 8 April 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Vincent Lam, MD, Associate Professor, Surgeon, Discipline of Surgery, Sydney Medical School, the University of Sydney, Sydney, NSW 2006, Australia

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Su-Qing Liu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE
April 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Prospective Study

Application of the Prague C and M criteria for endoscopic description of columnar-lined esophagus in South Korea

Jung Wan Choe, Young Choon Kim, Moon Kyung Joo, Hyo Jung Kim, Beom Jae Lee, Ji Hoon Kim, Jong Eun Yeon, Jong-Jae Park, Jae Seon Kim, Kwan Soo Byun, Young-Tae Bak

Jung Wan Choe, Young Choon Kim, Moon Kyung Joo, Hyo Jung Kim, Beom Jae Lee, Ji Hoon Kim, Jong Eun Yeon, Jong-Jae Park, Jae Seon Kim, Kwan Soo Byun, Young-Tae Bak, Department of Gastroenterology, Korea University Guro Hospital, Seoul 08308, South Korea

Author contributions: Choe JW and Kim YC worked in data interpretation, and writing this manuscript; Bak YT worked in data acquisition, data analysis, data interpretation and in writing of this manuscript; all authors read and approved the final form of the manuscript.

Institutional review board statement: The study was reviewed and approved by the institutional review boards of Korea University Guro Hospital in South Korea.

Clinical trial registration statement: Although this research is a prospective study, there is no need to register clinical trial. This study only analyzed the results of endoscopic features, not evaluated or compare the clinical outcome. So, we are so sorry not to provide the trial's registry.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: The authors of this manuscript having no conflicts of interest to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Young-Tae Bak, MD, Department of Gastroenterology, Korea University Guro Hospital, 148 Guro-

dong-ro, Guro-gu, Seoul 08308, South Korea. drbakyt@korea.ac.kr
Telephone: +82-2-26261778
Fax: +82-504-3666381

Received: July 7, 2015

Peer-review started: July 8, 2015

First decision: September 8, 2015

Revised: September 30, 2015

Accepted: December 1, 2015

Article in press: December 2, 2015

Published online: April 25, 2016

Abstract

AIM: To ascertain whether the Prague circumferential (C) length and maximal (M) length criteria for grading the extent of Barrett's esophagus can be applied prior to its widespread application in South Korea.

METHODS: Two hundred and thirteen consecutive cases with endoscopic columnar-lined esophagus (CLE) were included and classified according to the Prague C and M criteria.

RESULTS: Of 213 cases with CLE, the distribution of maximum CLE lengths was: 0.5-0.9 cm in 99 cases (46.5%); 1.0-1.4 cm in 63 cases (29.6%); 1.5-1.9 cm in 15 cases (7.0%); 2.0-2.4 cm in 14 cases (6.6%); 2.5-2.9 cm in 1 case (0.5%); and 7.0 cm in 1 case (0.5%). Twenty cases (9.4%) had columnar islands alone. Two hundred and eight cases (97.7%) lacked the circumferential CLE component (COMx). Columnar islands were found in 70 cases (32.9%), of which 20 cases (9.4%) had columnar islands alone.

CONCLUSION: In regions where most CLE patients display short or ultrashort tongue-like appearance, more detailed descriptions of CLE's in < 1.0 cm lengths and

columnar islands, as well as avoidance of repeating the prefix "C0" need to be considered in parallel with the widespread application of the Prague system in South Korea.

Key words: Barrett's esophagus; Endoscopy; Columnar-lined esophagus; Prague criteria

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This was a prospective study to assess the feasibility of the Prague circumferential length and maximal length criteria for the endoscopic description of columnar-lined esophagus in South Korea. In regions like South Korea where the prevalence and endoscopic features of this condition are quite different from the West, we suggest possible modifications that may fit the characteristics of the South Korean source population more properly.

Choe JW, Kim YC, Joo MK, Kim HJ, Lee BJ, Kim JH, Yeon JE, Park JJ, Kim JS, Byun KS, Bak YT. Application of the Prague C and M criteria for endoscopic description of columnar-lined esophagus in South Korea. *World J Gastrointest Endosc* 2016; 8(8): 357-361 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i8/357.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i8.357>

INTRODUCTION

Barrett's esophagus (BE) is defined as a histological change of the distal tubular esophagus, from squamous to columnar epithelium, which displays an intestinal metaplasia containing goblet cells^[1,2]. Because BE is characterized by an upward shift of the squamocolumnar junction (SCJ) proximal to the gastroesophageal junction (GEJ), the resulting columnar-lined mucosa of the distal esophagus can be identified by its salmon-pink color during endoscopic examination^[3,4]. Moreover, multiple endoscopic biopsies at the extended columnar-lined epithelium are needed to confirm BE diagnosis.

BE is associated with gastroesophageal reflux disease (GERD) and is considered a premalignant lesion for esophageal adenocarcinoma^[5,6], the incidence of which is steadily rising in the United States and Europe^[7,8]. Increasing GERD incidence in South Korea is considered to result from more consumption of westernized foods^[9,10]. As patients with chronic GERD are at a higher risk of developing BE^[11,12], the expected increase in BE and esophageal cancer incidence rates in the future is a matter of potential concern in South Korea.

Various studies have examined BE length as a risk factor for esophageal adenocarcinoma^[13-15]. Results from a study showed that a doubling in BE length resulted in a 1.7-fold increase in the risk of developing esophageal adenocarcinoma^[15], and others revealed that a significantly increased risk of dysplasia or adeno-

carcinoma was related to greater lengths of BE^[13,14]. Therefore, accurate measuring of columnar-lined esophagus (CLE) lengths and describing in well-defined clinical terms are important in appropriate risk assessment and surveillance. Although previous diagnostic criteria for BE were based on the 3-cm length threshold of columnar-lined esophagus (CLE), by which BE was divided into 2 types, long (≥ 3 cm) and short (< 3 cm), this simple classification of variable endoscopic findings of CLE was a rather crude approach in describing BE. Furthermore, as considerable inter- and intra-observer variability in detecting and describing the CLE are common, the establishment of an accurate BE diagnosis and surveillance may be tricky^[16-18].

Therefore, the Prague classification system that measures the circumferential (C) and maximal (M) extents for endoscopic standardization of BE lengths was developed and finally introduced by the International Working Group for the Classification of Oesophagitis (IWGCO) in 2004^[19]. However, the overall reliability and validity of the Prague C and M criteria for BE diagnosis continues to be challenged^[20-22]. Moreover, its performance in South Korea where the incidence of BE is low and the short-segment BE is the predominant type remains unclear.

In the present study, we aimed to assess the feasibility of the Prague C and M criteria for the endoscopic description of CLE in South Korea where the prevalence and endoscopic features of this condition are quite different from the West and to suggest possible modifications that may fit the characteristics of the South Korean source population more properly.

MATERIALS AND METHODS

This prospective study was conducted from the endoscopy data of consecutive CLE patients who underwent esophagogastroduodenoscopy (EGD) at Endoscopy Center of the Korea University Guro Hospital, Seoul, South Korea. Exclusion criteria included the presence of esophageal varices, acute upper gastrointestinal bleeding, malignancy near GEJ, and history of gastric surgery. Before each EGD, written informed consent was obtained. All endoscopic procedures were performed by an experienced endoscopist.

GEJ and SCJ were carefully assessed during the insertion of the endoscope. The distal margin of the palisade blood vessels of the lower esophagus was used as a marker of GEJ^[23]. If the palisade vessels could not be seen adequately, the proximal margins of the gastric folds were used to identify GEJ. SCJ was used as a marker for upper border of CLE. The length of CLE, that is the distance from GEJ to SCJ, was measured by the insertion depths with the centimeter markings on the endoscope. CLE's shorter than 0.5 cm in length were ignored to avoid possible observation errors that may lead to overdiagnosis. Careful observation was done to look for any presence of islands of columnar mucosa.

The C and M extents of CLE were recorded accord-

Table 1 Application of Prague circumferential and maximal criteria in cases with ultrashort, short, and long columnar-lined esophagus (*n* = 213)

Lengths of CLE (cm)	<i>n</i> (%)	COMx cases (%)
0 (islands only)	20 (9.4)	20 (100)
0.5-0.9	99 (46.5)	99 (100)
1.0-1.5	63 (29.6)	61 (96.8)
1.5-1.9	15 (7.0)	14 (93.3)
2.0-2.4	14 (6.6)	12 (85.7)
2.5-2.9	1 (0.5)	1 (100)
≥ 3.0	1 (0.5)	1 (100)
Total	213 (100)	208 (97.7) ¹

¹Exceptions: 2 cases with C1M1 and 3 cases with either C1M1.5, C1M2, or C1.5M2. CLE: Columnar-lined esophagus.

Table 2 Application of Prague circumferential and maximal criteria in cases with short and long columnar-lined esophagus (*n* = 139)

Lengths of CLE (cm)	<i>n</i> (%)	COMx cases (%)
0 (islands only)	45 (32.4)	45 (100)
1.0-1.4	63 (45.3)	61 (96.8)
1.5-1.9	15 (10.8)	14 (93.3)
2.0-2.4	14 (10.1)	12 (85.7)
2.5-2.9	1 (0.7)	1 (100)
≥ 3.0	1 (0.7)	1 (100)
Total	139 (100)	134 (96.4) ¹

¹Exceptions: 2 patients with C1M1 and 3 patients with either C1M1.5, C1M2, or C1.5M2. CLE: Columnar-lined esophagus.

ing to the Prague C and M criteria proposed by the IWGCO^[19]. M lengths were divided into long (≥ 3 cm), short (1-2.9 cm), and ultrashort (< 1 cm) segments.

RESULTS

Patient demographic characteristics

A total of 213 CLE patients consisting of 154 men and 59 women, with 53.8 ± 12.3 years in age (mean ± SD) were enrolled.

Distribution of CLE lengths and application of the Prague C and M criteria

Analysis of cases with CLE's including ultrashort CLE's:

Distribution of CLE's according to their M values, including those with ultrashort CLE's, is shown in Table 1. Among the total 213 cases, 99 (46.5%), 63 (29.6%), 15 (7.0%), 14 (6.6%), 1 (0.5%), and 1 (0.5%) had CLE's of 0.5-0.9 cm, 1.0-1.4 cm, 1.5-1.9 cm, 2.0-2.4 cm, 2.5-2.9 cm, and ≥ 3.0 cm in lengths, respectively. The remaining 20 cases (9.4%) had columnar islands alone. Therefore, 99 cases (46.5%) had ultrashort CLE's (CLE < 1.0 cm), 113 (53.1%) had short CLE's (1-2 cm) and only one (0.5%) had a long CLE (≥ 3 cm), showing a CLE of 7.0 cm in length.

When the cases were classified by the Prague criteria, 208 (97.7%) had no C component (COMx). Two cases had C1M1 and the remaining three cases had

either, C1M1.5, C1M1, or C1.5M2. Columnar islands were observed in 70 (32.9%) cases, of which 20 (9.4%) had columnar islands alone.

Analysis of cases with CLE's excluding ultrashort CLE's:

Distribution of CLE's according to their M values among those excluding ultrashort CLE's is shown in Table 2. Among 139 cases, 63 (45.3%), 15 (10.8%), 14 (10.1%), 1 (0.7%), and 1 (0.7%) had CLE's of 1.0-1.4 cm, 1.5-1.9 cm, 2.0-2.4 cm, 2.5-2.9 cm and ≥ 3.0 cm in lengths, respectively. Therefore, 138 (99.3%) out of all 139 cases had short CLE's, and only one showed an exceptionally long CLE.

When 139 cases were classified by the Prague criteria, 134 (96.4%) had CLE's without C component (COMx). Two cases had C1M1 and the remaining three patients had either C1M1.5, C1M1, or C1.5M2. Columnar islands were found in 70 (50.4%) cases, of which 45 (32.4%) showing columnar islands alone.

DISCUSSION

BE is a very well known risk factor for the development of dysplasia and esophageal adenocarcinoma^[24-26]. The risk of dysplasia and adenocarcinoma in metaplastic epithelium reportedly increases in parallel to the lengths of BE^[13-15]. A recent multicenter study conducted by Gaddam *et al.*^[13] revealed that for every 1-cm extension in BE length, the risk of high-grade dysplasia and esophageal adenocarcinoma increased by 21%. The study demonstrated that the increase in BE lengths significantly widens the area of metaplasia, which is associated with the progression to high-grade dysplasia/esophageal adenocarcinoma^[13]. Although a novel technique using a computer software program to create a two-dimensional image map of the esophagus has been introduced to accurately and reproducibly measure the extent of CLE^[27], such a complicated approach is not suitable for a daily clinical practice. Therefore, assessment of BE extent by simple measurement of the height of metaplastic CLE remains as the most commonly used procedure to distinguish short- from long-segment BE^[13-15]. However, the study of the clinical course and therapeutic response of BE has been limited because this classic method only provides gross estimates of the area. This system does not measure the surface areas of metaplastic mucosa, which may be more important than the endoscopic lengths^[19]. The presence of an irregular border of columnar tissue or interspersed metaplastic mucosal islands can hamper the precise measurement of the extent of CLE^[20].

The Prague C and M criteria, suggested by IWGCO, not only allows a more detailed description of the length of the endoscopically recognized CLE, using "C" and "M" values above the GEJ, but can also assist the objective calculation of the actual surface area, which may be more important in the risk assessment of the neoplastic transformation^[19-21]. These advances in CLE description have facilitated the depiction and reporting of various

circumferential and tongue-like longitudinal CLE lengths by using a method that can be understood easily and comprehensively. Importantly, high inter-observer reliability in the grading of endoscopically suspected CLE was demonstrated among gastroenterology experts and trainees^[22].

In recent years, accelerated life style changes have increased the prevalence of GERD in Asian populations, including South Koreans^[9,10,28,29], and BE incidence is also expected to increase^[12]. BE prevalence in South Korea was 0.2%-3.6% in the year 2000^[11,12,30], lower than in Western countries. Lengths and shapes of CLE's as well as their prevalence in South Korea are quite different from those of the Western countries. Long-segment BE is more common in Western countries, wherein 14%-31% of BE patients show this type^[31,32]. However, most cases of BE are short-segment type in South Korea, where long-segment type BE's are extremely rare^[11]. In our study, with the exception of the only one case, 212 (99.5%) out of 213 CLE cases were short-segment type (< 3 cm); and from these, 99 cases (46.5%) had ultrashort CLE (< 1 cm). Lee *et al.*^[33] reported that the reliability coefficients of the C and M values in the endoscopic recognition of short-segment type CLE were 0.90 (95%CI: 0.80%-1.00%) and 0.92 (95%CI: 0.87%-0.98%), respectively. However, the reliability of such coefficients for the recognition of the ultrashort (< 1 cm) CLE extent type was very low, with C and M coefficients of 0.18 (95%CI: 0.03%-0.32%) and 0.21 (95%CI: 0.00%-0.51%), respectively^[33].

Therefore, the routine applicability of the Prague C and M criteria as a standardized validated method for the detailed endoscopic description of ultrashort BE and short-segment BE, the most dominant BE types in South Korea, requires further analysis. As our study showed, all ultrashort CLE and almost all short-segment CLE cases lacked the C component and were classified as C0Mx. Therefore, it appears appropriate for us to propose to omit of the prefix "C0" from all C0Mx cases in order to avoid needless repetitions when describing most cases in regions like South Korea. Because the presence of columnar islands is a frequent finding as we have observed in this study and they also may change to dysplasia^[34], we propose to add this to the Prague system, which currently does not include this category. Resultant examples following our proposals are: C2M5, if 2.0 cm of C component with 5.0 cm of M component; M2, if 2.0 cm of M component without C component; C2M5i or M2i, if columnar island(s) is/are found in addition to C2M5 or M2 CLE; and M0i, if only columnar island(s) is/are found.

In summary, the Prague C and M system is simple and useful in daily description of endoscopic feature of CLE's. However, in regions like South Korea where most cases with CLE display only short or ultrashort types without C component, we propose to omit the needless repetition of "C0" prefix from C0Mx and to add i component to describe the presence of columnar islands which also may have a potential to be dysplastic.

COMMENTS

Background

The Prague circumferential (C) length and maximal (M) length criteria have been adopted widely for grading the extent of Barrett's esophagus (BE). However, its validity in regions with low prevalence of BE, remains unclear. This study was designed to ascertain whether these criteria can be applied prior to its widespread application in South Korea.

Research frontiers

The Prague C and M system is simple and useful in daily description of endoscopic feature of BE's. But, the overall reliability and validity of the Prague C and M criteria for BE diagnosis continues to be challenged. In this study, there are some suggestions of possible modifications that may fit the characteristics of the South Korean source population more properly.

Innovations and breakthroughs

In regions like South Korea where most cases with columnar-lined esophagus display only short or ultrashort types without C component, the authors propose to omit the needless repetition of "C0" prefix from C0Mx and to add "i" component to describe the presence of columnar islands which also may have a potential to be dysplastic.

Applications

This study serves as additional evidence supporting the investigation in parallel with the widespread application of the Prague system in South Korea.

Terminology

Barrett's esophagus: A histological change of the distal tubular esophagus, from squamous to columnar epithelium, which displays an intestinal metaplasia containing goblet cells; The Prague classification criteria: A system to measure the C and M extents for endoscopic standardization of BE lengths.

Peer-review

The study is has clear defined inclusion and exclusion criteria and is well conducted despite the lack of a control group. This study is innovative and would be interesting to see if the findings are reproducible in other countries where BE is not as common as in the West.

REFERENCES

- 1 **Spechler SJ**, Goyal RK. Barrett's esophagus. *N Engl J Med* 1986; **315**: 362-371 [PMID: 2874485 DOI: 10.1056/NEJM198608073150605]
- 2 **Wang KK**, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008; **103**: 788-797 [PMID: 18341497 DOI: 10.1111/j.1572-0241.2008.01835.x]
- 3 **Barrett NR**. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg* 1950; **38**: 175-182 [PMID: 14791960]
- 4 **Sharma P**, McQuaid K, Dent J, Fennerty MB, Sampliner R, Spechler S, Cameron A, Corley D, Falk G, Goldblum J, Hunter J, Jankowski J, Lundell L, Reid B, Shaheen NJ, Sonnenberg A, Wang K, Weinstein W. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. *Gastroenterology* 2004; **127**: 310-330 [PMID: 15236196]
- 5 **Mann NS**, Tsai MF, Nair PK. Barrett's esophagus in patients with symptomatic reflux esophagitis. *Am J Gastroenterol* 1989; **84**: 1494-1496 [PMID: 2596449]
- 6 **Winters C**, Spurling TJ, Chobanian SJ, Curtis DJ, Esposito RL, Hacker JF, Johnson DA, Cruess DF, Cotelingam JD, Gurney MS. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology* 1987; **92**: 118-124 [PMID: 3781178]
- 7 **Botterweck AA**, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J*

- Epidemiol* 2000; **29**: 645-654 [PMID: 10922340]
- 8 **Powell J**, McConkey CC, Gillison EW, Spychal RT. Continuing rising trend in oesophageal adenocarcinoma. *Int J Cancer* 2002; **102**: 422-427 [PMID: 12402314 DOI: 10.1002/ijc.10721]
 - 9 **Lee SJ**, Song CW, Jeon YT, Chun HJ, Lee HS, Um SH, Lee SW, Choi JH, Kim CD, Ryu HS, Hyun JH. Prevalence of endoscopic reflux esophagitis among Koreans. *J Gastroenterol Hepatol* 2001; **16**: 373-376 [PMID: 11354273]
 - 10 **Yoo SS**, Lee WH, Ha J, Choi SP, Kim HJ, Kim TH, Lee OJ. [The prevalence of esophageal disorders in the subjects examined for health screening]. *Korean J Gastroenterol* 2007; **50**: 306-312 [PMID: 18159162]
 - 11 **Kim JY**, Kim YS, Jung MK, Park JJ, Kang DH, Kim JS, Song CW, Lee SW, Bak YT. Prevalence of Barrett's esophagus in Korea. *J Gastroenterol Hepatol* 2005; **20**: 633-636 [PMID: 15836715 DOI: 10.1111/j.1440-1746.2005.03749.x]
 - 12 **Park JJ**, Kim JW, Kim HJ, Chung MG, Park SM, Baik GH, Nah BK, Nam SY, Seo KS, Ko BS, Jang JY, Kim BG, Kim JW, Choi YS, Joo MK, Kim JI, Cho MY, Kim N, Park SH, Jung HC, Chung IS. The prevalence of and risk factors for Barrett's esophagus in a Korean population: A nationwide multicenter prospective study. *J Clin Gastroenterol* 2009; **43**: 907-914 [PMID: 19417682 DOI: 10.1097/MCG.0b013e318196bd11]
 - 13 **Gaddam S**, Young PE, Alsop BR, Gupta N, Gavini H, Higbee AD, Wani SB, Singh M, Rastogi A, Bansal A, Cash BD, Lieberman DA, Sampliner RE, Falk GW, Sharma P. Relationship Between Barrett's Esophagus (BE) Length and the Risk of High Grade Dysplasia (HGD) and Esophageal Adenocarcinoma (EAC) in Patients With Non Dysplastic Barrett's Esophagus Results From a Large Multicenter Cohort. *Gastroenterology* 2011; **140**: S81-S81 [DOI: 10.1016/S0016-5085(11)60329-6]
 - 14 **Iftikhar SY**, James PD, Steele RJ, Hardcastle JD, Atkinson M. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. *Gut* 1992; **33**: 1155-1158 [PMID: 1427364]
 - 15 **Menke-Pluymers MB**, Hop WC, Dees J, van Blankenstein M, Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett) esophagus. The Rotterdam Esophageal Tumor Study Group. *Cancer* 1993; **72**: 1155-1158 [PMID: 8339208]
 - 16 **Sharma P**, Morales TG, Sampliner RE. Short segment Barrett's esophagus--the need for standardization of the definition and of endoscopic criteria. *Am J Gastroenterol* 1998; **93**: 1033-1036 [PMID: 9672325 DOI: 10.1111/j.1572-0241.1998.00324.x]
 - 17 **Dekel R**, Wakelin DE, Wendel C, Green C, Sampliner RE, Garewal HS, Martinez P, Fass R. Progression or regression of Barrett's esophagus--is it all in the eye of the beholder? *Am J Gastroenterol* 2003; **98**: 2612-2615 [PMID: 14687805 DOI: 10.1111/j.1572-0241.2003.07680.x]
 - 18 **Kim SL**, Waring JP, Spechler SJ, Sampliner RE, Doos WG, Krol WF, Williford WO. Diagnostic inconsistencies in Barrett's esophagus. Department of Veterans Affairs Gastroesophageal Reflux Study Group. *Gastroenterology* 1994; **107**: 945-949 [PMID: 7926484]
 - 19 **Sharma P**, Dent J, Armstrong D, Bergman JJ, Gossner L, Hoshihara Y, Jankowski JA, Junghard O, Lundell L, Tytgat GN, Vieth M. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology* 2006; **131**: 1392-1399 [PMID: 17101315 DOI: 10.1053/j.gastro.2006.08.032]
 - 20 **Anand O**, Wani S, Sharma P. When and how to grade Barrett's columnar metaplasia: the Prague system. *Best Pract Res Clin Gastroenterol* 2008; **22**: 661-669 [PMID: 18656823]
 - 21 **Chang CY**, Lee YC, Lee CT, Tu CH, Hwang JC, Chiang H, Tai CM, Chiang TH, Wu MS, Lin JT. The application of Prague C and M criteria in the diagnosis of Barrett's esophagus in an ethnic Chinese population. *Am J Gastroenterol* 2009; **104**: 13-20 [PMID: 19098843 DOI: 10.1038/ajg.2008.43]
 - 22 **Vahabzadeh B**, Seetharam AB, Cook MB, Wani S, Rastogi A, Bansal A, Early DS, Sharma P. Validation of the Prague C & M criteria for the endoscopic grading of Barrett's esophagus by gastroenterology trainees: a multicenter study. *Gastrointest Endosc* 2012; **75**: 236-241 [PMID: 22248595 DOI: 10.1016/j.gie.2011.09.017]
 - 23 **Choi DW**, Oh SN, Baek SJ, Ahn SH, Chang YJ, Jeong WS, Kim HJ, Yeon JE, Park JJ, Kim JS, Byun KS, Bak YT, Lee CH. Endoscopically observed lower esophageal capillary patterns. *Korean J Intern Med* 2002; **17**: 245-248 [PMID: 12647639]
 - 24 **Cameron AJ**, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. *N Engl J Med* 1985; **313**: 857-859 [PMID: 4033716 DOI: 10.1056/NEJM198510033131404]
 - 25 **Hameeteman W**, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology* 1989; **96**: 1249-1256 [PMID: 2703113]
 - 26 **Van der Veen AH**, Dees J, Blankenstein JD, Van Blankenstein M. Adenocarcinoma in Barrett's oesophagus: an overrated risk. *Gut* 1989; **30**: 14-18 [PMID: 2920919]
 - 27 **Kim R**, Baggott BB, Rose S, Shar AO, Mallory DL, Lasky SS, Kressloff M, Faccenda LY, Reynolds JC. Quantitative endoscopy: precise computerized measurement of metaplastic epithelial surface area in Barrett's esophagus. *Gastroenterology* 1995; **108**: 360-366 [PMID: 7835577]
 - 28 **Rosaia MS**, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and non-erosive reflux disease in a multiracial Asian population: a prospective, endoscopy based study. *Eur J Gastroenterol Hepatol* 2004; **16**: 495-501 [PMID: 15097043]
 - 29 **Wong WM**, Lam SK, Hui WM, Lai KC, Chan CK, Hu WH, Xia HH, Hui CK, Yuen MF, Chan AO, Wong BC. Long-term prospective follow-up of endoscopic oesophagitis in southern Chinese--prevalence and spectrum of the disease. *Aliment Pharmacol Ther* 2002; **16**: 2037-2042 [PMID: 12452935 DOI: 10.1046/j.1365-2036.2002.01373.x]
 - 30 **Kim JH**, Rhee PL, Lee JH, Lee H, Choi YS, Son HJ, Kim JJ, Rhee JC. Prevalence and risk factors of Barrett's esophagus in Korea. *J Gastroenterol Hepatol* 2007; **22**: 908-912 [PMID: 17565647 DOI: 10.1111/j.1440-1746.2006.04448.x]
 - 31 **Ronkainen J**, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Talley NJ, Agr us L. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005; **129**: 1825-1831 [PMID: 16344051 DOI: 10.1053/j.gastro.2005.08.053]
 - 32 **Csendes A**, Smok G, Burdiles P, Korn O, Gradiz M, Rojas J, Recio M. Prevalence of intestinal metaplasia according to the length of the specialized columnar epithelium lining the distal esophagus in patients with gastroesophageal reflux. *Dis Esophagus* 2003; **16**: 24-28 [PMID: 12581250]
 - 33 **Lee YC**, Cook MB, Bhatia S, Chow WH, El-Omar EM, Goto H, Lin JT, Li YQ, Rhee PL, Sharma P, Sung JJ, Wong JY, Wu JC, Ho KY. Interobserver reliability in the endoscopic diagnosis and grading of Barrett's esophagus: an Asian multinational study. *Endoscopy* 2010; **42**: 699-704 [PMID: 20806154 DOI: 10.1055/s-0030-1255629]
 - 34 **Dunbar KB**, Okolo P, Montgomery E, Canto MI. Confocal laser endomicroscopy in Barrett's esophagus and endoscopically inapparent Barrett's neoplasia: a prospective, randomized, double-blind, controlled, crossover trial. *Gastrointest Endosc* 2009; **70**: 645-654 [PMID: 19559419 DOI: 10.1016/j.gie.2009.02.009]

P- Reviewer: Meshikhes AWN, Slomiany BL S- Editor: Ji FF

L- Editor: A E- Editor: Liu SQ



Impact of endoscopic ultrasound quality assessment on improving endoscopic ultrasound reports and procedures

Ryan Schwab, Eugene Pahk, Jesse Lachter

Ryan Schwab, Jesse Lachter, Department of Gastroenterology, Rambam Healthcare Campus, Haifa 35000, Israel

Eugene Pahk, Department of Gastroenterology, Technion Medical School, Haifa 35000, Israel

Author contributions: Schwab R analyzed data and performed research; Pahk E wrote the manuscript and edited; Lachter J designed the research and edited.

Conflict-of-interest statement: The authors report no conflict of interest or sources of funding in this work.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Eugene Pahk, BS, Department of Gastroenterology, Technion Medical School, 21 Sharl Luts No.6, Haifa 35000, Israel. eugenepahk@gmail.com
Telephone: +972-58-5055335
Fax: +972-4-8295326

Received: November 29, 2015
Peer-review started: November 30, 2015
First decision: December 22, 2015
Revised: December 30, 2015
Accepted: February 23, 2016
Article in press: February 24, 2016
Published online: April 25, 2016

Abstract

AIM: To evaluate the impact of endoscopic ultrasonography (EUS) quality assessment on EUS procedures

by comparing the most recent 2013-2014 local EUS procedural reports against relevant corresponding data from a 2009 survey of EUS using standardized quality indicators (QIs).

METHODS: Per EUS exam, 27 QIs were assessed individually and by grouping pre-, intra-, and post-procedural parameters. The recorded QI frequencies from 200 reports (2013-2014) were compared to corresponding data of 100 reports from the quality control study of EUS in 2009. Data for QIs added after 2009 to professional guidelines (added after 2010) were also tabulated.

RESULTS: Significant differences (P -value < 0.05) were found for 13 of 20 of the relevant QIs examined. 4 of 5 pre-procedural QIs, 6 of 10 intra-procedural QIs, and 3 of 5 post-procedural QIs all demonstrated significant upgrading with a P -value < 0.05.

CONCLUSION: Significant improvements were demonstrated in QI adherence and thus EUS reporting and delivery quality when the 2013-2014 reports were compared to 2009 results. QI implementation facilitates effective high-quality EUS exams by ensuring comprehensive documentation while limiting error.

Key words: Endoscopic ultrasound; Improvement; Fine needle aspiration; Quality indicators

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Consistent implementation of these endoscopic ultrasonography (EUS) quality indicators by endosonographers facilitates effective high-quality EUS procedures by ensuring comprehensive procedural documentation while also limiting error.

Schwab R, Pahk E, Lachter J. Impact of endoscopic ultrasound quality assessment on improving endoscopic ultrasound reports

and procedures. *World J Gastrointest Endosc* 2016; 8(8): 362-367
Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i8/362.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i8.362>

INTRODUCTION

Endoscopic ultrasonography (EUS) is an endoscopic procedure that has benefited from quality control (QC) analysis and quality indicator (QI) analysis, a benchmark of widely-used guidelines being those of the American Society of Gastrointestinal Endoscopy (ASGE)^[1]. Bluen *et al*^[2] 2012 demonstrated how responsible QC, including systemic monitoring and evaluation, is critical to rendering EUS fine needle aspiration (EUS-FNA) protocol more effective. The consistency with which practitioners adhere to or comply with these QIs, whether they are pre-, intra- or post-procedure, goes a long way in optimizing the significance of the endoscopic exam. Coe *et al*^[3] 2009 studied physician adherence to EUS QIs over an eight-year span and observed statistically significant findings: Improvement was achieved in the EUS areas previously evaluated to have been weak by quality assessment. Lachter *et al*^[4] in 2013, explored adherence to EUS QIs at ten different Israeli medical centers with international comparison to the University of Chicago when measured using a standardized table of relevant QIs and observed that an overall improvement in documented quality of EUS exams was found in centers ensuring comprehensive documentation and stronger guideline adherence.

The ASGE and the American College of Gastroenterology (ACG) formed a task force of expert endoscopists and pioneered a way in which efforts of QC could be efficiently carried out to document the quality of endoscopic services and to promote optimal procedural performance^[1]. These QIs were developed by the task force to serve as guidelines for the 4 major endoscopic procedures: Esophagogastroduodenoscopy, colonoscopy, endoscopic retrograde cholangiopancreatography, and EUS. A recent update of QIs common to all GI endoscopic procedures was put forth prioritizing indicators that have wide-ranging clinical application, are associated with variation in practice and outcomes, and were validated in clinical studies^[5]. This update to the original version in 2006, framed by the ASGE/ACG task force, promotes performance targets for the QIs to help direct continuous quality improvement and an evidence-based system of benchmarks for each QI^[5].

The present study aims to evaluate the impact of the EUS quality assessment on the improvement of these procedures by comparing 2013-14 local EUS procedural reports against relevant corresponding data from a 2009 survey of QIs (Lachter *et al*^[4]). That is, whether the EUS operators are improving their adherence/compliance to the QIs, and if the incorporation of and adherence to the QIs enhance the overall quality of EUS

exams and patient outcomes.

MATERIALS AND METHODS

Two hundred EUS exam reports from 2013-2014 in Rambam were reviewed for each of the active echo-endoscopists. Each EUS report was assessed by a pre-established standardized table of EUS QIs (Table 1). Per EUS exam, QIs are evaluated individually as well as by the following categories: Pre-procedural, intra-procedural, and post-procedural. The hospital medical statistician was consulted and statistics are in accord with her recommendations using SPSS version 21. The comparison group for this study was from a 2009 survey of QIs for 100 EUS examinations. This was used as a comparative baseline to determine whether measures to increase implementation of these QIs were successful in yielding improvements in EUS procedure documentation and quality.

The methods of collection of data are that each of ten echoendoscopists was asked to submit ten EUS anonymized reports in 2008. The results were shared, at a meeting of the national gastroenterology society, without naming any of the echoendoscopists regarding the scores for their respective EUS reports, but rather only giving the pooled results, and comparison of the per-echoendoscopist results, regardless of their years of experience in performing EUS or their volume of procedures performed yearly. The images from EUS were not used, only the verbal reports. The reports were from multiple institutions. Each echoendoscopist could use either radial or linear or both kinds of endoscope. For the 2014 review, three echoendoscopists were reviewed, with varying experience from 3-18 years of experience, from only one institution. Trainees are not authorized to sign off on final EUS reports.

We also emphasize that we cannot be sure that every one of the many echoendoscopists nationally are always maintaining the highest quality standards, but we believe that continual monitoring and reporting the results publically of quality assessments lead to the long-term knowledge that reviews will be made and will be made public. This method of ensuring quality has been shown by various authors, including most recently by Abdul-Baki *et al*^[6], to be of significant value in raising quality of procedural documentation of endoscopies.

Reporting frequencies of each QI in EUS reports were calculated. Comparison between our study results with those of the previous study, regarding 20/27 listed standardized QI parameters (Table 1) plus demographics, were tested by Fisher Exact Test. Frequencies for indications for EUS procedures were calculated and then compared in 6 out of the 10 total indications as that was the number of indications that matched the 2009 study. A $P < 0.05$ was considered as significant. Twenty out of the 27 listed QIs were compared with 2009 data for statistical analysis because only 20/27 QIs

Table 1 Endoscopic ultrasound quality indicators (American Society of Gastrointestinal Endoscopy 2006)

Pre-EUS indicators
Indications for procedure
Detailed description of the patient by the referring physician
Patient completed procedural preparation of minimum 6 h NPO
Antibiotics per protocol were given in the need to perform FNA of pancreatic cysts
Listing of sedatives administered prior to and during EUS
Patient signed agreement of informed consent for EUS and/or if consented for research
Intra-procedural indicators
A detailed description of the methods used to visualize routinely evaluated EUS organs. If there is any suspicion of organ pathology, the respective organ parenchyma should be described:
Suspected pancreatic lesions should include a parenchymal description including the body, head, tail, and duct
Common bile ducts and gallbladder contents should be detailed and a description of the biliary tree for sludge, stones, or other findings
If found, prominent lymph nodes should be described in detail as well as the kidneys and left liver lobe for the presence or absence of lesions
The celiac axis should be described for general arterial structure along with the aorta and superior mesenteric artery as well as the presence or absence of identifiable lymph nodes
Description of abnormal/pathological results:
Description of any tumor by the tumor, node, and metastasis system
Accurate detailing of the lesions and its surroundings in accordance with layers visualized by EUS degree of tumor penetration into organ mucosa and surrounding structures
Detailing the presence of lymph nodes when suspicious for malignancy and when performing FNA
Presence or absence of any mechanical problems or difficulties including past abdominal surgeries or ascites
Patient awakened/uncooperative during the procedure
Details of the number of FNAs performed with respective number of passes into each suspected lesion including:
Number of passes
Needle size
Number of needles
Impressions of aspirate (bloody, mucinous, color, etc.)
Cytology and/or histological examination
In-room tentative diagnosis
Post-procedural indicators
Summary of medical diagnoses
Examination findings, even if not relevant to the reason for EUS referral, should be listed
Physician recommendations shall be listed with respect to examination findings including instructions for the patient
Instructions for how patients will receive the results and for referring physician
After EUS, the incidence of adverse events should be listed, including pancreatitis, bleeding, and/or infections and the need for hospitalization

EUS: Endoscopic ultrasonography; NPO: Nil Per Os; FNA: Fine needle aspiration.

corresponded exactly with the previous study's data.

RESULTS

Significant differences (P -value < 0.05) were found in 13/20 QIs (Table 2). For pre-procedural QIs: Minimum 6 h Nil Per Os (NPO); Antibiotics per protocol prior to FNA of pancreatic cysts; Listing of anesthesia administered prior to and during EUS; Patient signed agreement of informed consent. For intra-procedural QIs (P -value < 0.05): Suspected pancreatic lesions should include parenchymal regional descriptions citing pancreatic head, body, tail, and duct; common bile duct (CBD) and gallbladder imaging should be detailed including a description for sludge, stones or other findings; lymph node (LN) description as well as pole of left kidney and left liver lobe for lesions; Celiac axis described for arterial structures along w/aorta, superior mesenteric artery and LNs; Presence or absence of mechanical problems or difficulties including past abdominal surgeries or ascites; Patient awakened or uncooperative during procedure. For post-procedural QIs (P -value < 0.05): Exam findings, even if not relevant to reason/indications for EUS referral, instructions for how patient will receive cytology/chemistry results, and incidence or

absence of adverse events should also be documented.

The mean patient age was 57 years old with a standard deviation of 16 and a range of 18-92 years of age. Fifty-nine point five percent of patients were females. Although there were specific differences in QI adherence among the three EUS operators, there was no statistical significance in such differences found. The primary indications for referral for EUS included suspected CBD (19%), pathologic findings on imaging (9%), mostly of the pancreas, and need for FNA and/or biopsy, as shown in Table 3.

DISCUSSION

Pre-procedural 6-h NPO preparation was found in 100% of EUS reports, a statistically significant improvement over the 8% of the 2009 results (P < 0.001). The considerable disparity in this result may or may not be due to simple documentation error as opposed to so many patients not aptly preparing for the procedure. Antibiotics per protocol was documented as being given to every (100%) relevant patient prior to FNA of pancreatic cyst, which is a significant improvement over the 40% coverage of the previous study. Although the efficacy of antibiotics prophylaxis is as yet unproven, it

Table 2 Endoscopic ultrasonography quality indicator frequencies and comparative statistical analysis

EUS QIs	Rambam 2013-2014 EUS reports % documented (n = 200)	WJGE Lachter <i>et al</i> 2013 (data from 2009), EUS reports % documented (n = 100)	Improvement significance (P value)
Pre-procedural			
Indications for procedure	99%	97%	NS
Detailed patient description from referring physician	100%	8%	P < 0.001
Minimum 6 h NPO	100%	40%	P < 0.001
Antibiotics per protocol prior to FNA of pancreatic cysts	99.5%	94%	P = 0.0014
Listing of anesthesia administered prior to and during EUS	100%	61%	P < 0.001
Patient signed agreement of informed consent	100%	61%	P < 0.001
Intra-procedural			
Suspected pancreatic lesions should include parenchymal description of body, head, tail, and duct	95%	64%	P < 0.001
CBD and GB contents should be detailed and a description for sludge, stones or other findings	98%	0%	P < 0.001
LN detailed description as well as kidney and left liver lobe for lesions	50%	35%	P = 0.04
Celiac axis described for arterial structure along w/ aorta, SMA and LNs	13%	5%	NS
Description by TNM system	100%	95%	NS
Detailing of lesions and surroundings in accordance with layers visualized by EUS	75%	65%	NS
Degree of tumor penetration into organ mucosa and surrounding structures	80%	46%	NS
Detailing presence of LN when suspicious for malignancy and when performing FNA	100%	6%	P < 0.001
Presence or absence of mechanical problems or difficulties including past abdominal surgeries or ascites	100%	2%	P < 0.001
Patient awakened or uncooperative during procedure	78%	-	-
No. of passes (FNA)	67%	-	-
Needle size	99%	-	-
No. of needles	40%	-	-
Impressions of aspirate (bloody, mucinous, color)	100%	-	-
Cytology/histology	100%	-	-
In-room tentative Dx	100%	-	-
Post-procedural			
Summary of Dx	95%	37%	P < 0.001
Exam findings, even if not relevant to reason for EUS referral	100%	80%	NS
Physician recommendations with respect to exam findings	99%	52%	P < 0.001
Instructions for how patient will receive results	100%	0%	P < 0.001
Incidence of adverse events should be listed			

NS: Not Significant; Dx: Diagnosis; LN: Lymph node; TNM: Tumor node metastasis; EUS: Endoscopic ultrasonography; NPO: Nil Per Os; FNA: Fine needle aspiration; CBD: Common bile duct; GB: Gallbladder; SMA: Superior mesenteric artery.

Table 3 Indications for endoscopic ultrasonography referral

	Rambam 2013-2014 EUS reports	2009 EUS reports
Suspected CBD stone	19%	31%
Pancreatic tumor suspicion	8%	17%
Pathologic findings on imaging	19%	16%
Suspicion of esophageal or stomach tumor	6%	12%
Pancreatic cyst	8%	8%
Pancreatitis	6%	3%
FNA/biopsy	11%	-
Submucosal lesion clarification	4%	-
Screening/followup	5%	-
Other	12%	-

EUS: Endoscopic ultrasonography; FNA: Fine needle aspirations; CBD: Common bile duct.

is considered by professional societies to be warranted and should be documented. Anesthesia administered was listed prior to and during EUS for 99.5% of patients reported, statistically more significant than the 94% of the 2009 data. The specifics of sedation and/or anesthesia for EUS procedures is an important area

for research, involving the use of large endoscopes and sometimes prolonged procedures. One hundred percent of patients signed informed consent agreement for procedures compared with the 61% documented by Lachter *et al*^[4] (Table 2). While it is likely that every patient also gave consent in the latter study, it is critical

that it all be documented so as to maintain the integrity, quality, and completeness of the reports.

As evidenced by the above results (Table 2), most of the intra-procedural QIs saw significant improvement in operator compliance, making for better-executed and well-reported EUS exams. Adherence to a parenchymal description of suspected pancreatic lesions and detailing of biliary contents and pathology (stones, sludge, etc.) was 100% and 95% respectively. These were significant improvements over the 40% and 64%, respectively, of the previous study. Prominent LN and/or kidney and left liver lobe lesions were detailed when relevant and present in 98% of patients, which was a QI not adhered to previously. Also, the celiac axis was described half the time, an apparently significant improvement over the 35% in 2009 ($P = 0.04$). Description of tumors by the Tumor Node Metastasis system is an area for great improvement as only 13% of patients with tumors were reported accordingly. The detailing of submucosal lesions and surroundings in accordance with layers visualized by EUS was always adhered to (100%), but this was not a significant improvement over the previous study's outcome (95%). This difference highlights the difficulty of demonstrating statistically significant improvement when dealing with high outcomes (the upper limit of adherence can't exceed 100%). The 200 EUS reports detailed level of tumor penetration in 75% of patients and detailed LN presence when suspicious for malignancy and when performing FNA for 80% of patients (Table 2). More intra-procedural issues such as mechanical problems like past abdominal surgeries or ascites and patient awakening or uncooperativeness during procedure were documented for 100% of patients, showing a very significant improvement over the 6% and 2% results, respectively, in the 2009 data (Table 2). Checklisting of these items facilitated documentation without having "mandatory" fields.

While the 2009 results consolidated the FNA performance details (number of passes, needle size, etc.) into one QI entity, our study meticulously examined each of the QIs for detailing FNAs individually in the EUS procedural reports. As such these QIs (numbered 17-22 in the table) were not comparable as is for statistical analysis. Frequencies were computed: 78% of reports documented number of passes, 67% for needle size, 99% for number of needles, 40% described impressions of aspirate, and 100% adhered to the cytology/histological examination and in-room tentative diagnosis indicators (Table 2).

Post-procedural QIs were documented for almost all of the patients: 100% of reports included summary of diagnoses, 95% of examination reports contained findings unrelated to the original reason for referral—a significant improvement from the 37% adherence previously. Physician recommendations and instructions for patients including how they receive results were included in 100% and 99% respectively, showing an improvement in the latter QI from 52% ($P < 0.001$). As per Table 2, the incidence of adverse events was

listed 100% of the EUS procedural reports. A caveat, however, must be noted: Incidence of post-EUS adverse events, as pancreatitis, bleeding, and/or infection, were checked and recorded only for immediate (within 48 h) follow-up of patients. Long-term adverse effects (14 d following) of procedures were not documented and this was an area in post-hoc analysis considered to be in need of QC monitoring.

Limitations

This study had limitations. It was a comparative retrospective study, and as such did not garner the intrinsic advantages that it would have if done prospectively, such as better oversight and control over variables, confounders, and study conditions. Second, while most of the QIs evaluated overlapped for proper statistical comparison, not every QI did. Thirdly, there was no patient satisfaction data collected and assessed in this study, an area which should be developed. Notably, in the past, a local survey was of importance in determining the satisfaction of referring physicians from the EUS examinations; this too should be revisited periodically, as such a survey may improve an EUS service, recognizing that the secondary clients of an EUS service include the referring physicians^[7].

In conclusion, consistent implementation of these EUS QIs by endosonographers facilitates effective high-quality EUS procedures by ensuring comprehensive procedural documentation while also limiting error. Moreover, results of the present study demonstrated that there have been significant improvements in EUS delivery quality and QI adherence when comparing this study to a previous audit of EUS results. The Hawthorne effect describes how workers do better when knowing that their work is being watched and evaluated. By this token, vigilance regarding QIs in EUS, when recorded and published, seems to enhance the adherence to optimizing EUS reports and examinations, as such is the case for this center.

With increasing demand for EUS and the robust number of physicians performing these procedures, recommendations for QIs will continue to evolve and excellence in quality of care will continually be collaboratively pursued.

COMMENTS

Background

Endoscopic ultrasonography (EUS) is an endoscopic procedure that has benefited from quality control analysis and quality indicator (QI) analysis, a benchmark of widely-used guidelines being those of the American Society of Gastrointestinal Endoscopy.

Innovations and breakthroughs

The present study aims to evaluate the impact of the EUS quality assessment on the improvement of these procedures by comparing 2013-14 local EUS procedural reports against relevant corresponding data from a 2009 survey of QIs. That is, whether the EUS operators are improving their adherence/compliance to the QIs, and if the incorporation of and adherence to the QIs enhance the overall quality of EUS exams and patient outcomes.

Applications

Vigilance regarding QIs in EUS, when recorded and published, seems to enhance the adherence to optimizing EUS reports and examinations, as such is the case for this center.

Peer-review

This manuscript evaluated the impact of EUS quality assessment on EUS procedures by comparing the most recent 2013-2014 local EUS procedural reports against relevant corresponding data from a 2009 survey of EUS. The authors used standardized QIs for EUS quality assessment.

REFERENCES

- 1 **Jacobson BC**, Chak A, Hoffman B, Baron TH, Cohen J, Deal SE, Mergener K, Petersen BT, Petrini JL, Safdi MA, Faigel DO, Pike IM. Quality indicators for endoscopic ultrasonography. *Am J Gastroenterol* 2006; **101**: 898-901 [PMID: 16635234 DOI: 10.1111/j.1572-0241.2006.00674.x]
- 2 **Bluen BE**, Lachter J, Khamaysi I, Kamal Y, Malkin L, Keren R, Epelbaum R, Kluger Y. Accuracy and Quality Assessment of EUS-FNA: A Single-Center Large Cohort of Biopsies. *Diagn Ther Endosc* 2012; **2012**: 139563 [PMID: 23197929 DOI: 10.1155/2012/139563]
- 3 **Coe SG**, Raimondo M, Woodward TA, Gross SA, Gill KR, Jamil LH, Al-Haddad M, Heckman MG, Crook JE, Diehl NN, Wallace MB. Quality in EUS: an assessment of baseline compliance and performance improvement by using the American Society for Gastrointestinal Endoscopy-American College of Gastroenterology quality indicators. *Gastrointest Endosc* 2009; **69**: 195-201 [PMID: 19185684 DOI: 10.1016/j.gie.2008.04.032]
- 4 **Lachter J**, Bluen B, Waxman I, Bellan W. Establishing a quality indicator format for endoscopic ultrasound. *World J Gastrointest Endosc* 2013; **5**: 574-580 [PMID: 24255750 DOI: 10.4253/wjge.v5.i11.574]
- 5 **Rizk MK**, Sawhney MS, Cohen J, Pike IM, Adler DG, Dornitz JA, Lieb JG, Lieberman DA, Park WG, Shaheen NJ, Wani S. Quality indicators common to all GI endoscopic procedures. *Gastrointest Endosc* 2015; **81**: 3-16 [PMID: 25480102 DOI: 10.1016/j.gie.2014.07.055]
- 6 **Abdul-Baki H**, Schoen RE, Dean K, Rose S, Leffler DA, Kuganeswaran E, Morris M, Carrell D, Mehrotra A. Public reporting of colonoscopy quality is associated with an increase in endoscopist adenoma detection rate. *Gastrointest Endosc* 2015; **82**: 676-682 [PMID: 26385276 DOI: 10.1016/j.gie.2014.12.058]
- 7 **Lachter J**, Feldman R, Krief I, Reshef R. Satisfaction of the referring physician: a quality control study focusing on EUS. *J Clin Gastroenterol* 2007; **41**: 889-893 [PMID: 18090156 DOI: 10.1097/01.mcg.0000225688.83206.2c]

P- Reviewer: Carrara S, Kitano M, Sun SY **S- Editor:** Qi Y

L- Editor: A **E- Editor:** Liu SQ



Delayed perforation after endoscopic submucosal dissection for early gastric cancer: Clinical features and treatment

Takafumi Yano, Satoshi Tanabe, Kenji Ishido, Mizutomo Azuma, Takuya Wada, Mizuto Suzuki, Natsuko Kawanishi, Sakiko Yamane, Tohru Sasaki, Chikatoshi Katada, Tetsuo Mikami, Natsuya Katada, Wasaburo Koizumi

Takafumi Yano, Kenji Ishido, Mizutomo Azuma, Takuya Wada, Mizuto Suzuki, Natsuko Kawanishi, Sakiko Yamane, Tohru Sasaki, Chikatoshi Katada, Wasaburo Koizumi, Department of Gastroenterology, Kitasato University School of Medicine, Kanagawa 252-0375, Japan

Satoshi Tanabe, Research and Development Center for New Frontiers, Kitasato University School of Medicine, Kanagawa 252-0374, Japan

Tetsuo Mikami, Department of Pathology, Toho University School of Medicine, Tokyo 143-8540, Japan

Natsuya Katada, Department of Surgery, Kitasato University School of Medicine, Kanagawa 252-0374, Japan

Author contributions: Yano T and Tanabe S designed the report and analyzed the data and wrote the paper; Ishido K, Azuma M, Wada T, Suzuki M, Kawanishi N, Yamane S, Sasaki T, Katada C, Mikami T, Katada N and Koizumi W collected the patient's clinical data.

Institutional review board statement: This retrospective study was approved by the Institutional Review Board of Kitasato University.

Informed consent statement: Informed consent has been obtained publishing website or posting information in our hospital.

Conflict-of-interest statement: All other authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Takafumi Yano, Department of Gastroenterology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagami-hara, Kanagawa 252-0374, Japan. yano1371@kitasato-u.ac.jp
Telephone: +81-42-7788111
Fax: +81-42-7788390

Received: October 26, 2015
Peer-review started: October 27, 2015
First decision: December 22, 2015
Revised: December 29, 2015
Accepted: February 23, 2016
Article in press: February 24, 2016
Published online: April 25, 2016

Abstract

Perforation is an important procedural complication of endoscopic submucosal dissection (ESD) for early gastric cancer. Although the incidence of delayed perforation after ESD is low, extreme caution is necessary because many cases require surgical intervention. Among 1984 lesions of early gastric cancer treated in our hospital by ESD in 1588 patients from September 2002 through March 2015, delayed perforation developed in 4 patients (4 lesions, 0.25%). A diagnosis of delayed perforation requires prompt action, including surgical intervention when required.

Key words: Endoscopic submucosal dissection; Early gastric cancer; Delayed perforation

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Delayed perforation is a serious complication of endoscopic submucosal dissection for early gastric cancer. A diagnosis of delayed perforation requires

prompt action, including surgical intervention when required.

Yano T, Tanabe S, Ishido K, Azuma M, Wada T, Suzuki M, Kawanishi N, Yamane S, Sasaki T, Katada C, Mikami T, Katada N, Koizumi W. Delayed perforation after endoscopic submucosal dissection for early gastric cancer: Clinical features and treatment. *World J Gastrointest Endosc* 2016; 8(8): 368-373 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i8/368.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i8.368>

INTRODUCTION

The development of endoscopic submucosal dissection (ESD) has facilitated the *en bloc* endoscopic resection of larger lesions, as well as lesions with an ulcer scar. Such lesions are now included in the expanded indications for ESD^[1].

Perforation is an important procedural complication of ESD, reported to occur at an incidence of 3.6% to 8.7%. Most cases of intraoperative perforation can be closed by clipping^[2-4]. In contrast to intraoperative perforation diagnosed during endoscopic treatment, delayed perforation detected after ESD is often associated with peritonitis at time of diagnosis and frequently requires emergency treatment, including surgical intervention^[5]. Few studies have reported on delayed perforation, and its management remains controversial. We describe our experience with 4 patients (4 lesions) who underwent emergency surgery for delayed perforation that developed after ESD in our hospital.

CASE REPORT

Patients and methods

A total of 1984 consecutive lesions of early gastric cancer treated by endoscopic resection between September 2002 and March 2015 were studied. Informed consent was obtained from all patients in accordance with our institutional protocol.

We defined delayed perforation as the abrupt onset of abdominal pain and signs and symptoms of peritoneal irritation accompanied by the presence of free air on chest and abdominal radiography or abdominal computed tomography (CT) in a patient who showed no evidence of perforation during ESD or free air immediately after ESD, as proposed by Hanaoka *et al.*^[5].

ESD procedures

The circumference of the lesion was marked with a needle knife. After injecting glycerol solution into the submucosa, an initial cut was made with a needle knife outside the marking. An IT Knife (Olympus Medical Systems, Tokyo, Japan) was inserted into this cut and operated to cut around the lesion^[6]. The marked lesion was separated from the surrounding normal mucosa.

Then, the submucosal layer was dissected using the IT Knife, and the lesion was finally removed. An IT Knife was used to perform ESD until the end of March 2007, and an IT Knife2 (Olympus Medical Systems) was used from April 2007 onward^[7].

Results

We have described our experience with 4 patients (0.25%) who underwent surgery for delayed perforation that developed after ESD. The clinicopathological features and clinical outcomes of the patients with delayed perforation are summarized in cases 1 to 4 of Table 1. Among the 4 patients, 1 lesion was resected in 3 patients, and 2 lesions were resected in the other patient. The lesions were located the lower third of the stomach in 3 patients and the upper third of the remnant stomach in 1 patient. The diameters of resected specimens were large, exceeding 50 mm in 3 of the 4 patients; the longest diameter was 102 mm. In 1 of these patients, the ulcer floor had fused together after two adjacent lesions had been resected, and the resected specimen was 80 mm in diameter. The procedure time was longer than 90 min in all 4 patients, and the longest time was 240 min.

All cases of delayed perforation occurring in our hospital developed within 24 h in all except 1 patient. Because all patients had peritonitis at the time of detection of delayed perforation, emergency surgery was required. However, none of the 4 patients died of delayed perforation.

Case 1

The patient was an 89-year-old man with a superficial and depressed type (0-IIc) differentiated adenocarcinoma, 84 mm × 50 mm, arising in the posterior wall of the lesser curvature at the gastric angle. The tumor invaded the first layer of the submucosa (SM1). ESD was performed using an IT Knife, and the procedure time was 4.0 h. The resected specimen measured 102 mm × 73 mm (Table 1).

In the early morning 2 d after ESD, the patient had dyspnea and abdominal distension. Abdominal CT showed the presence of free air, and emergency surgery was performed on the same day. A perforation was found at the site resected by ESD. Omental implantation was performed at the site. Delayed perforation was apparently caused by the transfer of heat generated by extensive resection and prolonged local dissection to the muscular layer.

Case 2

The patient was a 74-year-old man with 2 adjacent 0-IIc lesions (20 mm × 17 mm and 17 mm × 10 mm) arising in the anterior and posterior walls of the greater curvature at the gastric angle (Table 1 case No. 2). ESD was performed with the use of an IT Knife2 (Figure 1A). The time required for ESD was 2.4 h. The ulcers had fused together to form a single ulcer on the resected

Table 1 Clinicopathological features and clinical outcomes in 16 patients with delayed perforation after endoscopic submucosal dissection

Case No.	Age	Sex	Location	Tumor size (mm)	Resected specimen size (mm)	Depth of tumor	Scar in tumor	Histological type	Time required for ESD (h)	Device	Time until peritonitis (h)	Size of perforation (mm)	Treatment of perforation	Hospital stay (d)
1	89	Male	L, Lc	84 × 50	102 × 73	SM1	Absent	Diff.	4	IT	> 24	3	Surgery	23
2	74	Male	L, Gc	17 × 10, 20 × 17	80 × 45 (2 lesions)	M	Absent	Diff.	2.4	IT2	10	-	Surgery	15
3	63	Male	R, P	15 × 12	28 × 28	M	Absent	Diff.	1.5	IT2	15	-	Surgery	30
4	83	Female	L, Lc	37 × 15	53 × 30	SM2	Present	Diff.	2.5	IT2	11	2	Surgery	23
5 ^[4]	50	Female	U, Lc	20	50	M	Present	Diff.	3.5	IT2	24	20	Surgery	16
6 ^[4]	60	Male	M, A	18	32	SM	Absent	Diff.	2	IT	19	-	Surgery	14
7 ^[4]	70	Male	U, A	15	45	M	Absent	Diff.	3	IT	21	-	Conservative	15
8 ^[4]	61	Male	U, P	50	85	SM	Absent	Diff.	9	IT	15	-	Surgery	33
9 ^[4]	64	Female	U, Lc	12	50	M	Absent	Diff.	2.2	IT	23	-	Surgery	20
10 ^[4]	64	Male	U, P	15	45	M	Present	Diff.	1.5	IT2	10	-	Surgery	12
11 ^[13]	70	Female	R, Lc	5	30	M	Absent	Diff.	2	IT	> 24	-	Conservative	21
12 ^[14]	60	Female	U, P	4	19	M	Absent	Signet	1.1	IT2	> 24	2	Endo clips	12
13 ^[8]	70	Female	L, Gc	26	38	M	Absent	Diff.	0.5	IT	-	3	Endo clips	13
14 ^[15]	60	Male	M, Gc	6 × 4	18 × 17	M	Absent	Diff.	0.4	-	10	1	Surgery	10
15 ^[16]	64	Male	L, A	18 × 15	40 × 38	SM2	Present	Diff.	-	-	> 24 (49 d)	8	Surgery	-
16 ^[9]	59	Female	L, A	10	-	M	Present	Diff.	0.4	-	> 24	20	Conservative	33

U: Upper body; M: Middle body; L: Lower body; R: Remnant stomach; Lc: Lesser curvature; P: Posterior; A: Anterior; Gc: Greater curvature; Diff.: Differentiated adenocarcinoma; Signet: Signet ring cell carcinoma; IT: Triangle-tip knife; ESD: Endoscopic submucosal dissection.

surface. The resected specimen measured 80 mm × 45 mm (Figure 1B) (Table 1).

The patient had fever and abdominal pain at night on the day of ESD. Chest radiography and abdominal CT on the day after ESD showed the presence of free air, and emergency surgery was performed on the same day (Figure 2). Although there was no distinct evidence of perforation, the muscular layer had become thin. The site was therefore partially resected. Pathological examination showed no distinct signs of perforation. However, the muscular layer had become necrotic (Figure 3). Delayed perforation was most likely ascribed to the transmission of heat resulting from the extensive hemostatic procedure to the muscular layer.

Case 3

The patient was a 63-year-old man who had previously undergone distal gastrectomy with Billroth I reconstruction for gastric cancer. A superficial and elevated type (0-II a) lesion, measuring 15 mm × 12 mm, had arisen in the posterior wall of the greater curvature in the remnant stomach. ESD was performed using an IT Knife2. The time required for ESD was 1.5 h. The resected specimen measured 30 mm × 24 mm (Table 1).

The patient vomited during the night of the day of ESD. In the early morning of the next day, fever and abdominal pain developed. Abdominal CT showed free air, and emergency surgery was performed on the same day. A perforation was noted at the treatment site. Omental implantation and antecolic Roux-en-Y reconstruction were performed. Delayed perforation was apparently caused by direct exposure of the muscular layer of the remnant stomach to acid and bile after surgery.

Case 4

The patient was an 83-year-old woman with a tumor, 37 mm × 15 mm, in the lesser curvature of the antrum. ESD was performed with an IT Knife2 for local recurrent lesions with an ulcer scar that had developed after ESD. The ESD procedure time was 2.5 h, and the resected specimen measured 53 mm × 30 mm.

Abdominal pain developed during the night of the day of ESD. On the following day, abdominal CT revealed the presence of free air, and emergency surgery was

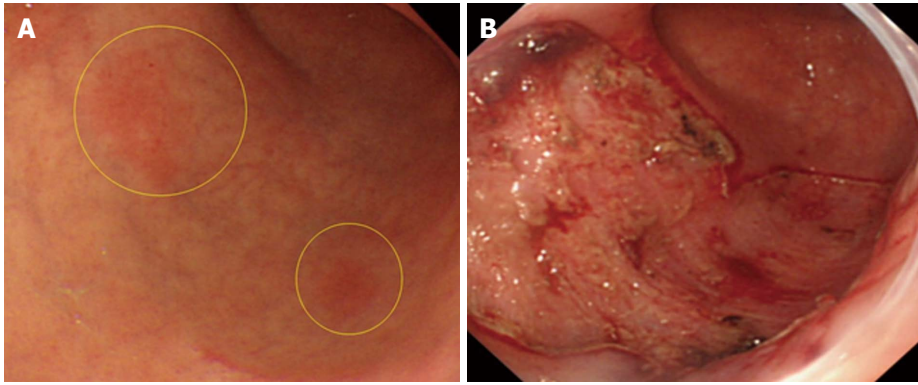


Figure 1 Endoscopic submucosal dissection. A: Findings on upper gastrointestinal endoscopy (conventional examination). Patient 2 had delayed perforation after undergoing endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). 0-II c lesions were found in the anterior and posterior walls of the greater curvature at the gastric angle (circles); B: Findings after ESD. Patient 2 had delayed perforation after ESD for EGC. The 2 lesions were adjacent. The ulcer floor had fused together.

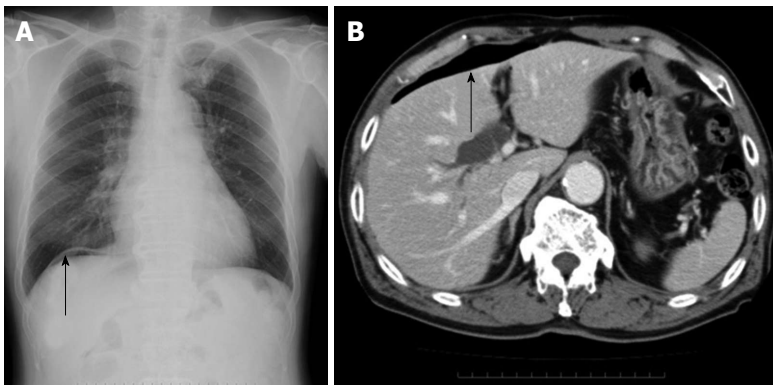


Figure 2 Radiography and abdominal computed tomography. A: A chest radiograph, showing free air below the right diaphragm (arrow); B: An abdominal computed tomography scan, showing free air (arrow).

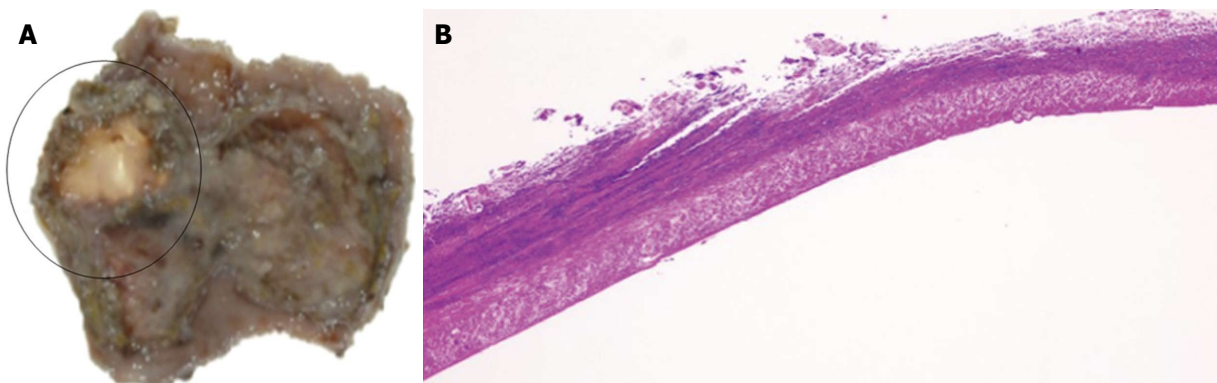


Figure 3 Muscular layer had become necrotic. A: The surgically resected specimen. Although no distinct site of perforation was found in the surgically resected specimen, the ulcer floor had become thin after endoscopic submucosal dissection (circled); B: The histopathological specimen stained with hematoxylin and eosin. At the ulcer floor, the muscular layer was exposed, and all layers had become necrotic.

performed on the same day. A perforation was found at the site of treatment. Because the resected lesions were strongly suspected to invade the submucosa, distal gastrectomy with Billroth I reconstruction was performed. Delayed perforation was apparently attributed to the transmission of heat generated by the prolonged local dissection procedure, necessitated by the presence of an ulcer scar, to the muscular layer of the stomach

(Table 1).

DISCUSSION

Perforation can be classified into 2 types according to the time of onset: Intraoperative perforation, which occurs during ESD, and delayed perforation, which is detected after treatment with no evidence of free air during ESD

or on abdominal radiographs obtained immediately after surgery.

There are several possible causes of the delayed perforation that occurred in our hospital: (1) the transmission of heat generated by the prolonged local dissection procedure to the muscular layer of the stomach; (2) direct exposure of the muscular layer to acid and bile in the postoperative remnant stomach; and (3) ischemic changes of the mucosa caused by excessive hemostatic procedures. Patient 1 and patient 2 were treated when we had relatively little experience, shortly after the introduction of ESD. Delayed perforation in these patients was suggested to have been caused by the transmission of excessive heat caused by prolonged dissection to the muscular layer.

It is difficult to predict the risk of delayed perforation occurring after ESD because the incidence is low and unknown risk factors are most likely involved. Hanaoka *et al.*^[5] proposed that delayed perforation is most likely to occur at sites of lesions involving the lesser curvature of the stomach, which is anatomically susceptible to decreased blood flow. Two of the 4 patients in our study had lesions located in the lesser curvature of the stomach.

As for the treatment of perforations, most intraoperative perforations can be closed by clipping the perforation site and then be followed up conservatively^[3]. In contrast, delayed perforations are already associated with peritonitis at the time of detection, and surgical intervention is generally required.

Table 1 summarizes the clinical and histopathological characteristics and the clinical courses of 16 patients (8 men and 8 women) with delayed perforation, including the 4 patients in the present study as well as those reported previously. The median age was 64 years (range, 50-89). Lesions were located in the upper third of the stomach in 6 patients, the middle third in 2 patients, the lower third in 6 patients, and the remnant stomach in 2 patients. Lesions were located along the lesser curvature in 4 patients. The median specimen diameter was 45 mm (range, 18-102). The depth of invasion was intramucosal in 11 patients and submucosal in 5. The median ESD procedure time was 2.0 h (range, 0.4-9.0). Delayed perforation most frequently occurred in patients with a long resected specimen diameter, a deep depth of invasion, and a prolonged ESD procedure time.

Delayed perforation was treated by surgery in 11 patients and conservative therapy including closure with an endoclip and follow-up in 5. The median hospital stay was 16 d (range, 10-33) in the patients who underwent surgery and 21 d (range, 15-33) in the patients who were followed up. The hospital stay thus tended to be longer in the conservatively treated patients. In previous studies, some patients with delayed perforation had minimal abdominal symptoms at the time of diagnosis. In other patients, a small perforation several millimeters in diameter was detected by chance on follow-up

endoscopy performed the day after ESD. The perforation was closed by clipping. Patients with localized peritonitis who responded to conservative therapy have also been reported^[4]. However, an intraperitoneal abscess developed in some patients who were followed up conservatively, and drainage was required. Long-term hospitalization was also necessary in some patients^[8].

Increased intragastric pressure has been reported to reduce mucosal blood flow and cause ischemic changes^[9,10]. Therefore, one of the solutions to prevent delayed perforation would be insertion of a nasogastric tube to achieve decompression of the gastric lumen.

Similar to our patients, delayed perforation may extensively involve the ulcer floor, and the muscular layer may already be necrotic. Closure of a perforation by endoscopic clipping may therefore be challenging. Moreover, insufflation at the time of endoscope insertion can increase the size of the perforation and thus have a negative effect. Even if the perforation site can be successfully closed by endoscopic clipping, re-perforation accompanied by the intraperitoneal leakage of gastric juice or bile has been reported in postoperative patients with a remnant stomach not surrounded by the greater omentum^[3]. Therefore, if delayed perforation is diagnosed on the basis of postoperative abdominal findings and the presence of free air on plain radiographs, surgeons should immediately be consulted about the need for surgical intervention. Performing surgery before the exacerbation of peritonitis will also most likely contribute to a better postoperative course.

Delayed perforation is a serious complication of ESD for early gastric cancer^[11,12]. A diagnosis of delayed perforation requires prompt action, including surgical intervention when required.

COMMENTS

Case characteristics

Among 1984 lesions of early gastric cancer treated in the authors' hospital by endoscopic submucosal dissection (ESD) in 1588 patients from September 2002 through March 2015, delayed perforation developed in 4 patients.

Differential diagnosis

Gastrointestinal perforation.

Imaging diagnosis

Chest radiography and abdominal computed tomography (CT) on the day after ESD showed the presence of free air. They diagnosed delayed perforation.

Pathological diagnosis

At the ulcer floor, the muscular layer was exposed, and all layers had become necrosis.

Treatment

Chest radiography and abdominal CT on the day after ESD showed the presence of free air, and emergency surgery was performed on the same day.

Related reports

Few studies have reported on delayed perforation, and its management remains controversial.

Experiences and lessons

Delayed perforation is a serious complication of ESD for early gastric cancer. A diagnosis of delayed perforation requires prompt action, including surgical intervention when required.

Peer-review

The authors have reported good study for "Delayed perforation after endoscopic submucosal dissection for early gastric cancer" and have submitted a well-written manuscript.

REFERENCES

- 1 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]
- 2 **Minami S**, Gotoda T, Ono H, Oda I, Hamanaka H. Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery (with video). *Gastrointest Endosc* 2006; **63**: 602-605 [DOI: 10.1016/j.gie.2005.07.029]
- 3 **Sekiguchi M**, Suzuki H, Oda I, Yoshinaga S, Nonaka S, Saka M, Katai H, Taniguchi H, Kushima R, Saito Y. Dehiscence following successful endoscopic closure of gastric perforation during endoscopic submucosal dissection. *World J Gastroenterol* 2012; **18**: 4224-4227 [PMID: 22919258 DOI: 10.3748/wjg.v18.i31.4224]
- 4 **Ikezawa K**, Michida T, Iwahashi K, Maeda K, Naito M, Ito T, Katayama K. Delayed perforation occurring after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2012; **15**: 111-114 [PMID: 21948482 DOI: 10.1007/s10120-011-0089-2]
- 5 **Hanaoka N**, Uedo N, Ishihara R, Higashino K, Takeuchi Y, Inoue T, Chatani R, Hanafusa M, Tsujii Y, Kanzaki H, Kawada N, Iishi H, Tatsuta M, Tomita Y, Miyashiro I, Yano M. Clinical features and outcomes of delayed perforation after endoscopic submucosal dissection for early gastric cancer. *Endoscopy* 2010; **42**: 1112-1115 [PMID: 21120780 DOI: 10.1055/s-0030-1255932]
- 6 **Ohkuwa M**, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221-226 [PMID: 11293753 DOI: 10.1055/s-2001-12805]
- 7 **Ono H**, Hasuike N, Inui T, Takizawa K, Ikehara H, Yamaguchi Y, Otake Y, Matsubayashi H. Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. *Gastric Cancer* 2008; **11**: 47-52 [PMID: 18373177 DOI: 10.1007/s10120-008-0452-0]
- 8 **Sumie H**, Rikitake Y, Matsuo T, Mukasa M, Yoshida H, Ushijima T, Kizaki J, Nagata S, Noda T, Maeyama Y, Tsuruta O, Sata M. Successful conservative management of a case of panperitonitis and intra-abdominal abscess in a patient with delayed perforation after ESD for early gastric cancer. *Jpn J Clin Exp Med* 2014; **91**: 105-110
- 9 **Stadaas J**, Aune S, Haffner JF. Effects of proximal gastric vagotomy on intragastric pressure and adaptation in pigs. *Scand J Gastroenterol* 1974; **9**: 479-485 [PMID: 4851772]
- 10 **Saul SH**, Dekker A, Watson CG. Acute gastric dilatation with infarction and perforation. Report of fatal outcome in patient with anorexia nervosa. *Gut* 1981; **22**: 978-983 [PMID: 7308853]
- 11 **Takizawa K**, Hasuike N, Ikehara H, Inui T, Ono H. Management and prevention during endoscopic submucosal dissection (ESD). *Endosc Dig* 2008; **20**: 373-378
- 12 **Onozato Y**, Iizuka H, Sagawa T, Yoshimura S, Sakamoto I, Arai H, Ishihara H, Tomizawa N, Ogawa T, Takayama H, Abe H, Motegi A, Ito H. A case report of delayed perforation due to endoscopic submucosal dissection (ESD) for early gastric cancer. *Progr Dig Endosc* 2006; **68**: 114-115 [DOI: 10.11641/pde.68.2_114]
- 13 **Hirasawa T**, Yamamoto Y, Okada K, Hayashi Y, Nego M, Kishihara T, Yshimoto K, Ishiyama A, Ueki N, Ogawa T, Chino A, Tsuchida T, Fujisaki J, Hoshino E, Igarashi M, Takahashi H. A case of the delayed perforation due to endoscopic submucosal dissection for the early gastric cancer of the residual stomach. *Progr Dig Endosc* 2009; **74**: 52-53 [DOI: 10.11641/pde.74.2_52]
- 14 **Akamatsu M**, Yokoyama N, Maeda C, Katayanagi N, Nagahama M, Nshimaki T. A Patient of Late Gastric Perforation Caused by Gastric Endoscopic Submucosal Dissection Repaired with SILS Technique. *J Japanese College Surg* 2012; **37**: 951-954 [DOI: 10.4030/jjcs.37.951]
- 15 **Kato K**, Tominaga K, Nagami Y, Machida H, Okazaki H, Tanigawa W, Watanabe T, Fujiwara Y, Ohsawa M, Arakawa T. A Patient of Delayed Perforation of a Gastric Ulcer Induced by Endoscopic Submucosal Dissection for Early Gastric Cancer. *Gastroenterol Endosc* 2011; **53**: 3280-3285 [DOI: 10.11280/gee.53.3280]
- 16 **Tanabe S**, Koizumi W, Mitomi H, Nakai H, Murakami S, Nagaba S, Kida M, Oida M, Saigenji K. Clinical outcome of endoscopic aspiration mucosectomy for early stage gastric cancer. *Gastrointest Endosc* 2002; **56**: 708-713 [PMID: 12397280 DOI: 10.1016/S0016-5107(04)00803-X]

P- Reviewer: Park WS S- Editor: Qi Y

L- Editor: A E- Editor: Liu SQ



Diagnosis of a submucosal mass at the staple line after sigmoid colon cancer resection by endoscopic cutting-mucosa biopsy

Mitsuaki Morimoto, Koji Koinuma, Alan K Lefor, Hisanaga Horie, Homare Ito, Naohiro Sata, Yoshikazu Hayashi, Keijiro Sunada, Hironori Yamamoto

Mitsuaki Morimoto, Koji Koinuma, Alan K Lefor, Hisanaga Horie, Homare Ito, Naohiro Sata, Department of Surgery, Jichi Medical University, Tochigi 329-0498, Japan

Yoshikazu Hayashi, Keijiro Sunada, Hironori Yamamoto, Department of Gastroenterology, Jichi Medical University, Tochigi 329-0498, Japan

Author contributions: Koinuma K revised the manuscript, and is the article guarantor; Lefor AK, Hayashi Y, Sunada K and Yamamoto H revised the manuscript; Sata N approved the final version of the manuscript; all authors contributed to this manuscript.

Institutional review board statement: The patient was treated with approved diagnostic and therapeutic procedures according to generally accepted standards of care.

Informed consent statement: Informed consent was not required in our facility but obtained from the patient for this case report.

Conflict-of-interest statement: None to report.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Koji Koinuma, MD, Department of Surgery, Jichi Medical University, 3311-1 Yakushiji Shimotsuke, Tochigi 329-0498, Japan. kjkoinum@jichi.ac.jp
Telephone: +81-285-587371
Fax: +81-285-443234

Received: November 11, 2015
Peer-review started: November 12, 2015

First decision: December 7, 2015

Revised: January 16, 2016

Accepted: February 14, 2016

Article in press: February 16, 2016

Published online: April 25, 2016

Abstract

A 48-year-old man underwent laparoscopic sigmoid colon resection for cancer and surveillance colonoscopy was performed annually thereafter. Five years after the resection, a submucosal mass was found at the anastomotic staple line, 15 cm from the anal verge. Computed tomography scan and endoscopic ultrasound were not consistent with tumor recurrence. Endoscopic mucosa biopsy was performed to obtain a definitive diagnosis. Mucosal incision over the lesion with the cutting needle knife technique revealed a creamy white material, which was completely removed. Histologic examination showed fibrotic tissue without caseous necrosis or tumor cells. No bacteria, including mycobacterium, were found on culture. The patient remains free of recurrence at five years since the resection. Endoscopic biopsy with a cutting mucosal incision is an important technique for evaluation of submucosal lesions after rectal resection.

Key words: Submucosal tumor; Staple line; Endoscopic cutting-mucosa biopsy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This case report demonstrates the importance of endoscopic biopsy using a cutting mucosal incision as a diagnostic tool for a submucosal mass that develops next to the staple line after sigmoid colon resection

with a double-stapled anastomosis. We feel that these findings will be of special interest to the readers.

Morimoto M, Koinuma K, Lefor AK, Horie H, Ito H, Sata N, Hayashi Y, Sunada K, Yamamoto H. Diagnosis of a submucosal mass at the staple line after sigmoid colon cancer resection by endoscopic cutting-mucosa biopsy. *World J Gastrointest Endosc* 2016; 8(8): 374-377 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i8/374.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i8.374>

INTRODUCTION

Submucosal tumors, such as neuroendocrine tumors (NET) or gastrointestinal stromal tumors (GIST), are occasionally encountered in the rectum, and are categorized based on the tissue of origin as muscular or neural derived. The differential diagnosis of a submucosal mass adjacent to the staple line after colon resection is extensive, and includes NET, GIST, and tumor recurrence. We report a patient with a submucosal mass at the site of a stapled anastomosis that developed five years after initial resection of a tumor.

CASE REPORT

A 48-year-old male was referred for treatment of sigmoid colon cancer six years previously. He had a past medical history of allergic dermatitis at 26 years of age. Laboratory data showed that both serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were within the normal limits. Enhanced computed tomography (CT) scan showed a sigmoid colon cancer with no evidence of distant metastases. Laparoscopic sigmoid colon resection with a double stapled anastomosis was performed. Macroscopic pathology showed 0-Ip tumor 30 mm in diameter. Microscopic pathology showing a well-differentiated tubular adenocarcinoma invading the muscularis propria with no regional lymph node metastases (UICC category; T2 N0 M0), classified as pathologic stage I disease. The patient remained asymptomatic with no signs of recurrence for four years. Five years postoperatively, a submucosal mass measuring 10 mm in size was detected at the staple line located 15 cm from the anal verge during an annual surveillance colonoscopy (Figure 1). Endoscopic ultrasonography (EUS) showed a well-demarcated and circumscribed homogeneous high echoic lesion in the submucosal layer (Figure 2). The surface of the lesion was covered with normal-appearing mucosa. The submucosal tumor showed no deformity with application of air pressure during the colonoscopy and was negative for the "cushion sign". Abdominal CT scan revealed a small, high-density well-demarcated mass without contrast-enhancement in the colonic wall (Figure 3). No metastatic lesions were seen on CT scan. In retrospect, the small high intensity

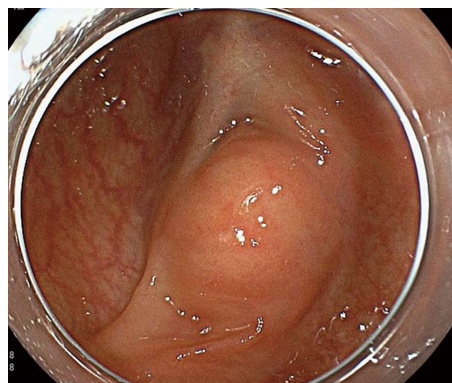


Figure 1 Endoscopic view of a 10 mm submucosal mass in the lower rectum located 15 cm from the anal verge at the staple line of a previous anastomosis.

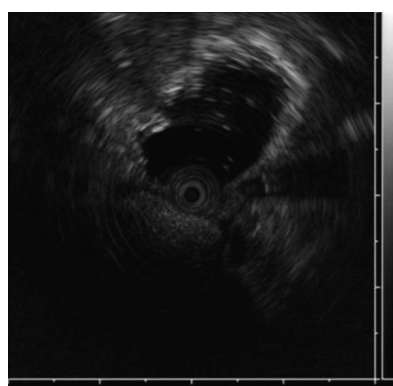


Figure 2 Endoscopic ultrasonography showed a well-circumscribed submucosal tumor with a hyper-echoic appearance.

area near the anastomosis had been evident on a CT scan performed four years after resection, and was gradually increasing in size. Tumor markers, including CEA and CA 19-9, remained within normal limits. It was felt unlikely that the mass was malignant based on its appearance and behavior. However, the mass showed slow growth and there was no definitive diagnosis. Routine endoscopic biopsy was thought to be difficult to establish a diagnosis because most of the target lesion was located in the submucosal layer. Endoscopic cutting mucosal biopsy of the lesion was planned. A precutting needle knife (KD-10Q-1, Olympus Corp, Tokyo, Japan) and an electrosurgical generator (VIO 300D; ERBE Elektromedizin Ltd, Tübingen, Germany) in endocut mode (effect, 1; duration, 4; interval, 1) were used. A mucosal incision was made over the lesion with the cutting needle knife technique after submucosal injection of saline containing 0.001% epinephrine and 0.004% indigocarmine. A pale, orange nodule covered by fibrotic material was seen in the submucosal tissue stained with the blue dye of the indigocarmine, compatible with the EUS results. The nodule was easily distinguished from the muscularis propria by its color because the muscularis propria is white. The fibrotic tissue above the lesion was incised using biopsy forceps (Radial Jaw™ 4, Boston Scientific Corp, Marlborough, MA), revealing a



Figure 3 Un-enhanced and intravenous contrast-enhanced computed tomography scans of the abdomen show a slightly hyperdense mass in the rectal wall without contract enhancement (white arrow). A: Unenhanced CT; B: Contrast enhanced CT. CT: Computed tomography.

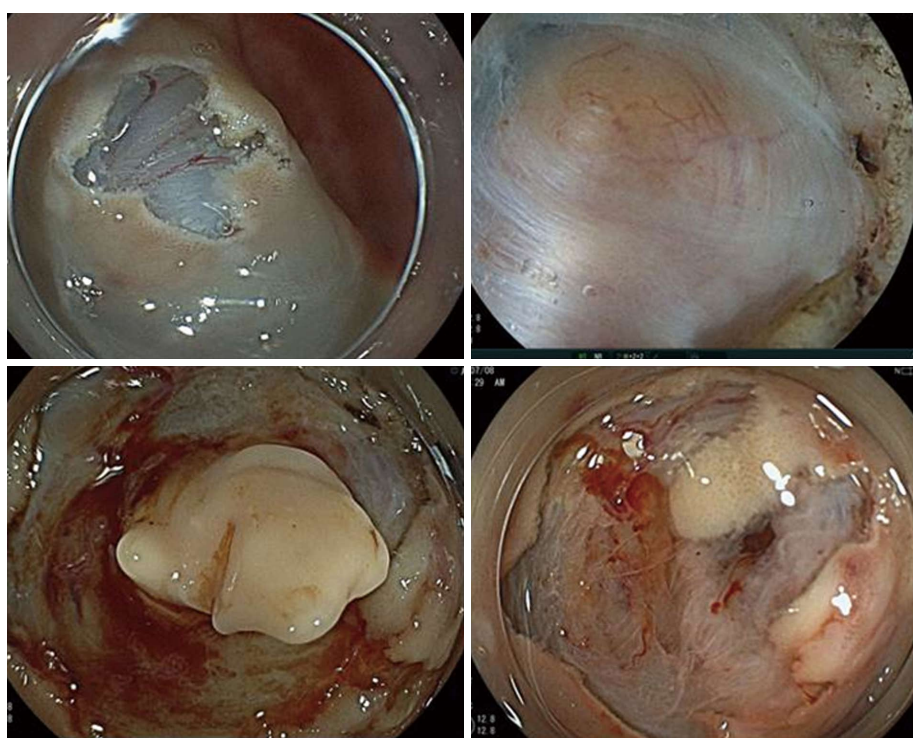


Figure 4 A cruciate incision over the lesion with the cutting needle knife technique revealed soft, white submucosal tissue. The wall of the cavity was left intact.

creamy white material, which was completely removed using the forceps. The wall of the remaining cavity was not resected. The specimen was gray-white and soft (Figure 4). The creamy appearance of the material led to the consideration of caseous necrosis associated with tuberculosis. However, pathological examination showed fibrotic tissues with necrotic material and no signs of caseous necrosis associated with tuberculosis, Crohn's disease or malignancy. The patient remains free of recurrence, five years after the initial resection.

DISCUSSION

The differential diagnosis of submucosal tumors of the colon and rectum includes GIST, NET, inflammatory polyps, desmoid-type fibromatosis, and local recur-

rence^[1]. Submucosal masses due to intestinal tuberculosis are rare^[2]. In this patient, a submucosal mass was located next to the anastomotic staple line, with both CT scan and EUS showing no typical signs of GIST, NET or local recurrence. Local recurrence is rare in patients with T1-2 colorectal cancers^[3]. However, we could not rule out the possibility of tumor recurrence because the lesion showed slow growth on annual CT scans. Thus, an endoscopic biopsy is a reasonable method to obtain a tissue diagnosis. Endoscopic mucosal cutting biopsy is a safe and effective method to establish the diagnosis of submucosal masses^[4]. This technique can be used in institutions where endoscopic submucosal dissection (ESD) is routinely performed for T1 colorectal cancers^[5]. ESD of superficial colorectal neoplasms has become well-accepted over the past

decade, with a low complication rate (delayed bleeding 2%, perforation 1.3%, emergency surgical operation 0.2%)^[6,7]. In this patient, endoscopic biopsy with mucosal incision avoided the need for a second surgical resection.

The double stapling technique for colorectal anastomoses is commonly used after sigmoid colon resection. Surgical procedures that include partial or total transection of the digestive tract evoke considerable physiological morphological, functional, and metabolic changes in adjacent intestinal tissue^[8]. The inflamed area of a fibrotic scar decreases after postoperative day seven with a minimal amount of fibrosis by postoperative day 90^[9]. Luijendijk *et al.*^[10] reported that suture granulomas were seen in 25% of patients with a past history of abdominal surgery. Inflammatory and foreign body reactions to such material can produce lesions mimicking cancer, clinically and radiologically^[11]. There are reports of patients who underwent repeat surgical resection to rule out tumor recurrence^[10,12]. It is unknown whether the fibrotic lesion was associated with the anastomotic stapler and adjacent tissue inflammation in the present patient. The persistent production of cytokines by inflammatory stimulation associated with the fibrotic process may lead to submucosal fibrosis.

Endoscopic biopsy using a cutting mucosal incision is a useful diagnostic tool for submucosal masses that develop next to a staple line after rectal resection and anastomosis using the double stapling technique.

COMMENTS

Clinical diagnosis

Submucosal tumor.

Differential diagnosis

Gastrointestinal stromal tumors (GIST), neuroendocrine tumors (NEC), local recurrence.

Laboratory diagnosis

All tumor markers were within normal limits.

Imaging diagnosis

A malignant tumor was not expected based on computed tomography and endoscopic ultrasonography results.

Pathological diagnosis

Tissue fibrosis.

Treatment

Endoscopic repeat biopsy.

Related reports

References 10 and 12.

Experience and lessons

There is a possibility of developing a granulomatous mass (fibrotic tissue) at the staple line in future patients. This lesion mimics a submucosal tumor such as a GIST or NEC. Some surgeons may initially plan a second resection, similar to another low anterior resection. This case report reminds surgeons of the possibility of a benign lesion.

Peer-review

This is an interesting case report.

REFERENCES

- Miettinen M, Lasota J. Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. *Pol J Pathol* 2003; **54**: 3-24 [PMID: 12817876]
- Yanagida T, Oya M, Iwase N, Okuyama T, Terada H, Sasaki K, Akao S, Ishikawa H, Satoh H. Rectal submucosal tumor-like lesion originating from intestinal tuberculosis. *J Gastroenterol* 1997; **32**: 822-825 [PMID: 9430024]
- Lee W, Lee D, Choi S, Chun H. Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer. *Surg Endosc* 2003; **17**: 1283-1287 [PMID: 12739119]
- Kataoka M, Kawai T, Yagi K, Sugimoto H, Yamamoto K, Hayama Y, Nonaka M, Aoki T, Fukuzawa M, Fukuzawa M, Itoi T, Moriyasu F. Mucosal cutting biopsy technique for histological diagnosis of suspected gastrointestinal stromal tumors of the stomach. *Dig Endosc* 2013; **25**: 274-280 [PMID: 23369082]
- Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Kudo SE, Tsuruta O, Sugihara K, Watanabe T, Saitoh Y, Igarashi M, Toyonaga T, Ajioka Y, Ichinose M, Matsui T, Sugita A, Sugano K, Fujimoto K, Tajiri H. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2015; **27**: 417-434 [PMID: 25652022 DOI: 10.1111/den.12456]
- Nakajima T, Saito Y, Tanaka S, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Matsuda T, Ishikawa H, Sugihara K. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. *Surg Endosc* 2013; **27**: 3262-3270 [PMID: 23508817 DOI: 10.1007/s00464-013-2903-x]
- Yamamoto H. Endoscopic submucosal dissection--current success and future directions. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 519-529 [PMID: 22664591 DOI: 10.1038/nrgastro.2012.97]
- Nandakumar G, Stein SL, Michelassi F. Anastomoses of the lower gastrointestinal tract. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 709-716 [PMID: 19884894 DOI: 10.1038/nrgastro.2009.185]
- Berho M, Wexner SD, Botero-Anug AM, Pelled D, Fleshman JW. Histopathologic advantages of compression ring anastomosis healing as compared with stapled anastomosis in a porcine model: a blinded comparative study. *Dis Colon Rectum* 2014; **57**: 506-513 [PMID: 24608308 DOI: 10.1097/DCR.000000000000009]
- Luijendijk RW, de Lange DC, Wauters CC, Hop WC, Duron JJ, Pajlter JL, Camprodon BR, Holmdahl L, van Geldorp HJ, Jeekel J. Foreign material in postoperative adhesions. *Ann Surg* 1996; **223**: 242-248 [PMID: 8604903]
- Tripathi PB, Kini S, Amarapurkar AD. Foreign body giant cell reaction mimicking recurrence of colon cancer. *Trop Gastroenterol* 2009; **30**: 219-220 [PMID: 20426282]
- Dickinson J. Foreign body granuloma following anastomosis with the anastomotic stapler. *J Pediatr Surg* 1971; **6**: 489 [PMID: 5563893]

P- Reviewer: Battal B, Friedland S S- Editor: Ji FF
L- Editor: A E- Editor: Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 May 10; 8(9): 378-394





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmänn, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



FIELD OF VISION

- 378 Western view of the management of gastroesophageal foreign bodies

Burgos A, Rábago L, Triana P

ORIGINAL ARTICLE

Retrospective Cohort Study

- 385 Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma

Kawakubo K, Kawakami H, Kuwatani M, Haba S, Kudo T, Taya YA, Kawahata S, Kubota Y, Kubo K, Eto K, Ehira N, Yamato H, Onodera M, Sakamoto N

CASE REPORT

- 391 First report of splenic rupture following deep enteroscopy

Girelli CM, Pometta R, Facciotto C, Mella R, Bernasconi G

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 9 May 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Salvatore Maria Antonio Campo, MD, Director, Department of Gastroenterology, Nuovo Regina Margherita Hospital, 00153 Rome, Italy

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerías Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE
May 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Western view of the management of gastroesophageal foreign bodies

Aurora Burgos, Luis Rábago, Paloma Triana

Aurora Burgos, Division of Gastroenterology, La Paz University Hospital, 28046 Madrid, Spain

Aurora Burgos, Luis Rábago, Division of Gastroenterology, San Rafael Hospital, 28016 Madrid, Spain

Paloma Triana, Division of Pediatric Surgery, La Paz University Hospital, 28046 Madrid, Spain

Author contributions: Burgos A collected the material and wrote the manuscript; Rábago L discussed the topic with the experience of a senior endoscopist and also supervised this report; Triana P discussed the topic and collaborated by adding the pediatric surgical experience.

Conflict-of-interest statement: None to be declared by any of the authors.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Aurora Burgos, Division of Gastroenterology, La Paz University Hospital, Paseo de la Castellana 261, 28046 Madrid, Spain. burgos.aurora@gmail.com
Telephone: +34-91-7277158

Received: January 2, 2016

Peer-review started: January 3, 2016

First decision: February 2, 2016

Revised: February 25, 2016

Accepted: March 17, 2016

Article in press: March 18, 2016

Published online: May 10, 2016

Abstract

The best modality for foreign body removal has been

the subject of much controversy over the years. We have read with great interest the recent article by Souza Aguiar Municipal Hospital, Rio de Janeiro, Brazil, describing their experience with the management of esophageal foreign bodies in children. Non-endoscopic methods of removing foreign bodies (such as a Foley catheter guided or not by fluoroscopy) have been successfully used at this center. These methods could be an attractive option because of the following advantages: Shorter hospitalization time; easy to perform; no need for anesthesia; avoids esophagoscopy; and lower costs. However, the complications of these procedures can be severe and potentially fatal if not performed correctly, such as bronchoaspiration, perforation, and acute airway obstruction. In addition, it has some disadvantages, such as the inability to directly view the esophagus and the inability to always retrieve foreign bodies. Therefore, in Western countries clinical practice usually recommends endoscopic removal of foreign bodies under direct vision and with airway protection whenever possible.

Key words: Foreign bodies; Children; Foley catheter; Flexible endoscopy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The best modality for foreign body removal has been the subject of much controversy over the years. Non-endoscopic methods such as a Foley catheter technique have a lot of advantages, such as their simplicity and cost savings, particularly for proximally located coins. However, their complications can be potentially serious regarding airway obstruction or perforation. This article will discuss the point of view of the European and Western countries, which usually recommend endoscopic removal of foreign bodies under direct vision and with airway protection whenever possible.

Burgos A, Rábago L, Triana P. Western view of the management of gastroesophageal foreign bodies. *World J Gastrointest Endosc* 2016; 8(9): 378-384 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i9/378.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i9.378>

COMMENTARY ON HOT TOPICS

We have read with great interest the recent article by Souza Aguiar Municipal Hospital, describing their management of esophageal foreign bodies in children. This is a relevant experience and we understand the authors' point of view regarding the benefits gained from using non-endoscopic methods for the removal of foreign bodies due to their simplicity and cost savings. However, we would like to point out that the management strategy is different in most of the medical hospitals in Western countries. Generally, it is recommended that endoscopic removal of foreign bodies is carried out under direct vision; in addition, among the child population it is also recommended to protect the airway with an endotracheal tube during foreign body removal. In our opinion, this should be considered as a more effective and safer practice in children.

The aim of this article is to describe a comprehensive approach towards children presenting with foreign body ingestion, and to discuss the difference between endoscopic methods and non-endoscopic methods of removing foreign bodies.

INTRODUCTION

The ingestion of foreign bodies is a frequent complaint in Pediatric Emergency services^[1]. Fortunately, only 10%-20% will require removal^[2] because most of them (80%) spontaneously advance distally. The primary location of lodged esophageal foreign bodies is the proximal esophagus and coins are the most prevalent foreign bodies. Other esophageal locations include: The aortic arch and the lower esophageal sphincter^[1,3]. Only 1% of cases will require a surgical removal^[4].

INITIAL EVALUATION/DIAGNOSIS

If the foreign body ingestion is suspected (ingestion witnessed by a caretaker, or the child has respiratory or digestive symptoms), we firstly recommend to perform simple chest and abdomen X-ray studies in all children. These X-ray studies sometimes allow us to detect the object (although not all foreign bodies are radiopaque), or complications (such as air in the mediastinum and subcutaneous emphysema, indicating esophageal perforation)^[5]. Also, it allows to distinguish between different types of foreign bodies (for instance button batteries can be distinguished from coins because of a double contour from a lateral view)^[6]. Although radiographic contrast could be used for foreign bodies

which are not radiopaque, it generally should be avoided due to aspiration risk^[5]. Computed tomography scan may be performed in selected cases if a complication is suspected. If perforation, peritonitis or small-bowel obstruction are confirmed, endoscopy is contraindicated and, in most cases, surgery is required^[5].

TREATMENT

The type of object, its location, the child's symptoms, the skills of the physician, and the usual institutional practice in relation to their available means will dictate the treatment of gastrointestinal foreign bodies.

NON-ENDOSCOPIC TREATMENT

Many non-endoscopic techniques have been described in the article by Souza Aguiar Municipal Hospital, including Foley catheter balloons.

In experienced hands, particularly for proximally located coins, a Foley catheter under fluoroscopic guidance can be inserted into the esophagus to a depth distal to the site of the impacted object. Then, the balloon is inflated symmetrically and traction is applied until the foreign body is removed. Before the catheter is withdrawn, the child is placed in a prone oblique position with mild cervical extension^[6].

Advantages of the Foley catheter method are: Efficacy (83%-90%), quick treatment (20 min), no need for anesthesia, available to be performed on an outpatient basis, and cost-effective with a reported savings of \$5027.31 per patient^[2,7].

Complications after Foley balloon extraction are rare and generally minor^[8-10] but some of them could be potentially serious because the procedure is performed blindly and depends on the physician's skill. Schunk *et al*^[9] reported a rate of 2% minor and 1% major complications. Minor complications included vomiting and nasal bleeding; major complications are transient airway compromise, mucosal erosion, esophageal mucosal laceration that required extensive surgical repair, respiratory distress and hypoxia^[11]. To date, only one case has reportedly led to death, caused by bronchoaspiration of a coin during the Foley catheter removal^[12].

Careful patient selection is critical in preventing complications. The use of Foley balloon extraction is contraindicated in the following situations^[7,13]: (1) impactions of more than 72 h (or more than 24 h in some centers); (2) three unsuccessful removal attempts; (3) complete obstruction of the esophagus; (4) esophageal perforation; (5) multiple foreign body impaction; (6) signs of airway distress or obstruction; (7) children younger than 1.5 years; (8) sharp-edged foreign bodies; and (9) button batteries that have been impacted for more than 2 h. From our point of view, button batteries should always be removed endoscopically as early as possible because of the likelihood of tissue liquefaction-necrosis and perforation.

Foley catheter extraction could only be an acceptable alternative in the first two hours post-impaction if endoscopy is not available^[13].

Esophageal bougienage has also been used successfully in different centers^[14]. An esophageal dilator is easily and quickly passed down through the esophagus to the estimated depth of the foreign body in order to push it into the stomach. This technique is efficient (success rate of 94%-95% vs 100% endoscopic success rate)^[14-16], can be performed quickly without anesthesia in the emergency department, and is available to perform on an outpatient basis. It has been considered to be the most cost-effective strategy in an analysis comparison of 4 management strategies for coins (endoscopy, esophageal bougienage, an outpatient observation period or an inpatient observation period)^[17]. Arms *et al.*^[15] found a payment difference of \$4200 between non-endoscopic and endoscopic techniques.

However, the esophageal bougienage method has some significant additional disadvantages^[14]. On one hand, bougienage does not retrieve the foreign body and it may be contraindicated in children with potential intestinal inflammatory or fibrotic conditions, such as Crohn's disease or a personal history of duodenal or small bowel surgery with intestinal anastomosis due to the risk of gastric or intestinal obstruction requiring further invasive procedures^[16]. On the other hand, it is imperative to discard the presence of multiple coins, a battery or a foreign body with a complex configuration because the identification of these foreign bodies requires urgent endoscopic removal^[16]. It is unclear whether children under one year of age should be excluded from bougienage, but it may be advisable, particularly since most ingestions by infants are also not witnessed. An additional disadvantage is that a second radiography is always needed to determine coin passage into the stomach or the small bowel^[16]. Other disadvantages and contraindications are the same as previously pointed out concerning the use of a Foley balloon (see above): No airway protection, lack of direct visualization of the esophagus, patient discomfort and exposure to radiation.

Minor complications of esophageal bougienage are vomiting, discomfort and gagging. To date, there have been no reports of major complications associated with selected bougienage of esophageal coins in children^[16] but it is still an uncommon management technique.

A third non-endoscopic uncommon procedure is the penny-pincher technique: A grasping endoscopic forceps is inserted through a soft rubber catheter and is then inserted like an orogastric tube under fluoroscopy. After the forceps reaches the object, the object is grasped and removed. The technique does not require sedation or placement of an advanced airway device^[18].

So, in summary, there is still a great grade of controversy regarding non-endoscopic methods, mainly regarding patient safety. Although the complications of these procedures are reported as "low" as shown by the Souza Aguiar Municipal Hospital study, they can be

severe and potentially fatal (e.g., airway obstruction, perforation)^[9,10], so their performance should be limited to physicians experienced in the procedures and in airway management, with suction apparatus, and oxygen supply readily available^[7,15,19]. Therefore, in our opinion, endoscopic approaches are recommended in most cases^[1,3,5,6,20,21] when adequate resources are available.

ENDOSCOPIC TREATMENT

Both, rigid endoscopy and flexible endoscopy procedures are safe and effective for food impaction and foreign bodies^[22], allowing excellent visualization and biopsy of the esophagus if required.

Flexible endoscopy is considered as the "first line" approach with a success rate of between 80%-100% and a less than 1% risk of perforation^[16,22-24]. Rigid endoscopy is considered as a "second line" when flexible endoscopy is not effective (6.6%) and possibly for those foreign bodies located in the upper esophagus^[23]. This technique allows having a wider lumen that is a great help for the removal of foreign bodies^[12]. Rigid endoscopy success rate is 87%-98% and perforation rate is 3%.

Compared with the standard practice of endoscopy in adults, it is generally recommended in children that foreign-body removal should be performed under general anesthesia with endotracheal intubation to protect the airway from aspiration^[1,20,21,23,25].

Most flexible endoscopy complications are considered minor^[26]. Regarding anesthesia, minor complications are described in 1.5% of patients^[27] and the most frequent are bronchospasm, delayed extubation and fever^[26]. Regarding endoscopy, complications are reported in 2%-3% of patients and decrease with age^[28], the most common being hypoxia (1.5%) and bleeding (0.3%). Also, it has been published that a long duration between the ingestion until the endoscopy is performed, and the finding of initial mucosal injury are well-known risk factors related with complications after endoscopic foreign body removal^[29].

There are few contraindications to perform an endoscopic procedure in children such as unstable airways, cardiovascular collapse, gastrointestinal perforation or peritonitis. The children's weight is rarely a contraindication, and upper endoscopic examination can be safely performed in neonates as small as 1.5 to 2 kg^[21,30]. Relative contraindications include coagulopathy, thrombocytopenia, recent abdominal surgery, unstable cardiopulmonary disease, and recent oral intake^[21,26].

Endoscopic treatment has a lot of advantages. As already mentioned, the greatest advantage is the capability of direct evaluation of esophageal mucosa because esophageal abnormalities in children range between 6% and 13% in different foreign bodies studies^[22,23]. Endoscopic examination allows biopsy if required (e.g., eosinophilic esophagitis), and also allows more complex techniques such as stricture-dilation, as

Table 1 Classifications of foreign bodies

Objects shape
Short-blunt: Coins, rings
Long: Utensils for eating, string, cord, toothbrush
Sharp-pointed: Nails, pins, tacks, toothpicks, chicken, fish bones
Objects including poisons
Button cell and disk batteries
Cylindrical batteries (these batteries do not typically discharge electrical current the way button batteries do)
Narcotic packets
Objects inducing esophageal or gastrointestinal obstruction
Magnets
Food bolus impaction
Superabsorbent polymers

well as the possibility to perform a push enteroscopy in selected cases. It can be used not only for proximally located coins, but also for different types and multiple objects in any location (upper, medium or lower esophagus and also stomach or duodenum), as will be described later.

In addition, various retrieval devices can be used to remove the object (polypectomy snares, rat-tooth and alligator forceps, Dormier baskets, magnetic probes polyp graspers, retrieval nets, and friction-fit adaptors or banding caps)^[6]. The most appropriate device according to the characteristics of the foreign body should be chosen. However, the type of the device can be changed depending on the success with the previous one.

We agree with the authors regarding Magill forceps. Magill forceps are angled forceps commonly used in anesthesia. They can remove some objects located in the oropharynx or upper esophagus, with the help of a laryngoscope or rigid esophagoscopy under general anesthesia^[31,32]. A 96% success rate is described with this method^[33].

An overtube may be used to provide airway protection in adults. In children its use has not been generally recommended due to its diameter, except in selected cases^[34]. A protector hood or a transparent distal cap^[6,20] can also help to avoid mucosal injury during endoscopic removal procedure of sharp objects.

ENDOSCOPIC TREATMENT: SPECIAL SITUATIONS

The risk and the timing of the endoscopic intervention depend on: The shape, size and content of the foreign body, anatomic location, and the time since their ingestion. Classifications of foreign bodies and timing of the endoscopic intervention are described in Tables 1 and 2. In the case of esophageal obstruction, button cell batteries, magnets or sharp-pointed objects in the esophagus, emergent removal is always required.

Regarding object shape, short-blunt objects (coins) are the most prevalent foreign bodies in children. If the patient is asymptomatic, coins placed especially in the

Table 2 Timing of endoscopy for ingested foreign bodies

Emergent endoscopy
Esophageal obstruction (patient unable to manage secretions)
Sharp-pointed objects in the esophagus (or in the stomach/small bowel if symptomatic)
Disk or button cell batteries in the esophagus (or in the stomach/small bowel if symptomatic)
Magnets in the esophagus (or in the stomach/small bowel if symptomatic)
Urgent endoscopy
Esophageal foreign objects that are not sharp-pointed
Esophageal food impaction in patients without complete obstruction
Sharp-pointed objects in the stomach or duodenum (if asymptomatic)
Objects > 6 cm in length at or above the proximal duodenum in adults
Disk and button cell batteries in the stomach (if age < 5 and button battery > 20 mm)
Magnets within endoscopic reach (if asymptomatic)
Absorptive object
Nonurgent (elective) endoscopy
Objects in the stomach with diameter 2.5 cm in adults
Objects > 2 cm and longer than 5 cm in older children
Objects longer than 3 cm in infants and young children
Coins in the esophagus may be observed for 12-24 h before endoscopic removal in an asymptomatic patient
Disk and button cell batteries and cylindrical batteries that are in the stomach of patients without signs of gastrointestinal injury may be observed for as long as 48 h. Batteries remaining in the stomach longer than 48 h should be removed

Modified from American Society of Gastrointestinal Endoscopy and NASPGHAN Endoscopy Committee.

distal esophagus can be observed for 12 to 24 h (Figure 1). Endoscopy is indicated if the coins remain in the esophagus or if the patient is symptomatic. Endoscopic devices that are most frequently used in this situation are snare, rat-tooth or alligator forceps or retrieval nets^[6].

Long objects can be removed with a snare or basket and, in selected cases in the adult population, with the help of an overtube.

Sharp-pointed objects have risk of perforation (35%) and they must always be removed (Figure 2). We can use forceps, snares or retrieval nets. If the object cannot be reached endoscopically due to deep migration, daily radiographs should be obtained^[6,20].

Regarding object location, 20% of foreign bodies lodged in the esophagus may harbor risk of aspiration and perforation, so we recommend endoscopic removal in the first 24 h of ingestion. The size will be determinant for its removal if the foreign body has already passed to the stomach (60%). In older children, objects wider than 2 cm and longer than 4-6 cm should be removed^[5,35-37]. In infants and young children, the limit could be 3 cm^[3]. If the object has passed the duodenum, conservative treatment is recommended (Table 2).

In relation with the type of foreign body, button cell and disk batteries are very dangerous because of the likelihood of liquefaction necrosis of the tissues and perforation. Therefore, endoscopic emergent removal is always recommended and it can be completed with a rat tooth grasper, a retrieval basket or a net^[20]. In this

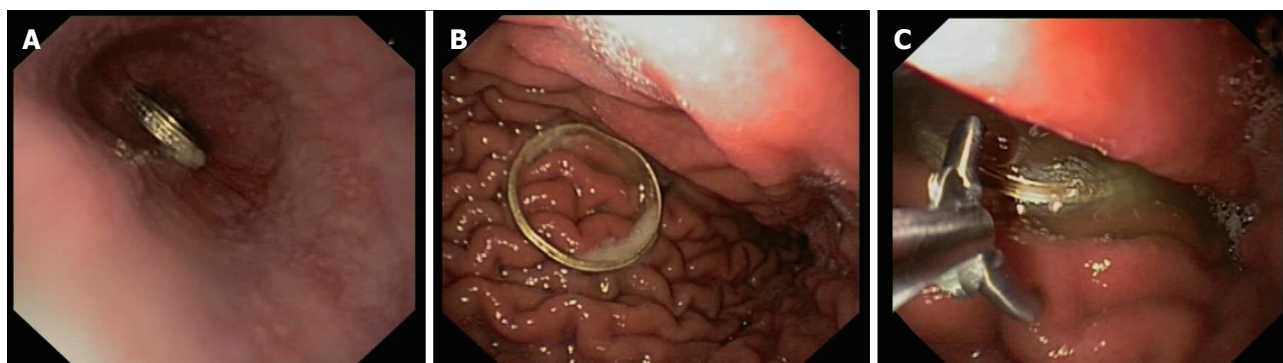


Figure 1 Short-blunt objects: A ring. The ring in the esophagus was observed for 24 h before endoscopic removal. A: Esophagus; B: Stomach; C: Rat-tooth forceps.

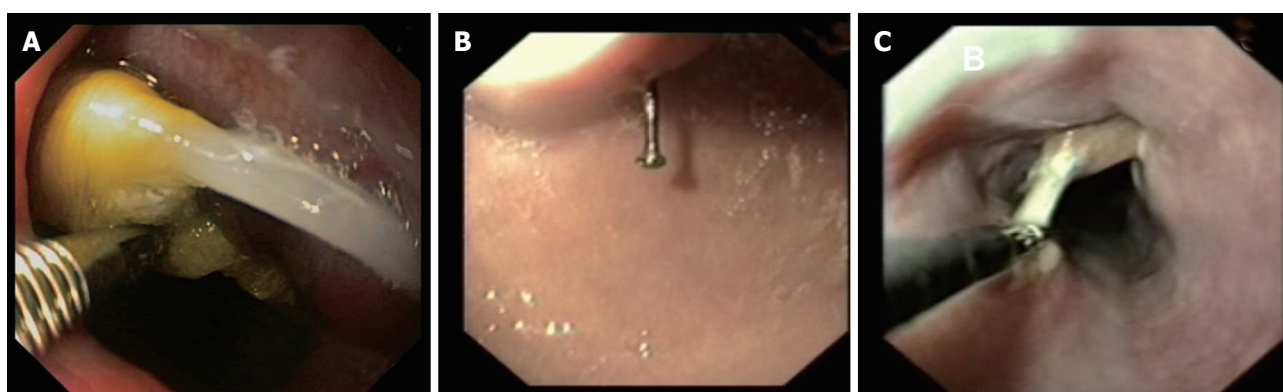


Figure 2 Sharp-pointed objects. A: Fish bone; B: Nail; C: Chicken bone. Removal with alligator forceps.

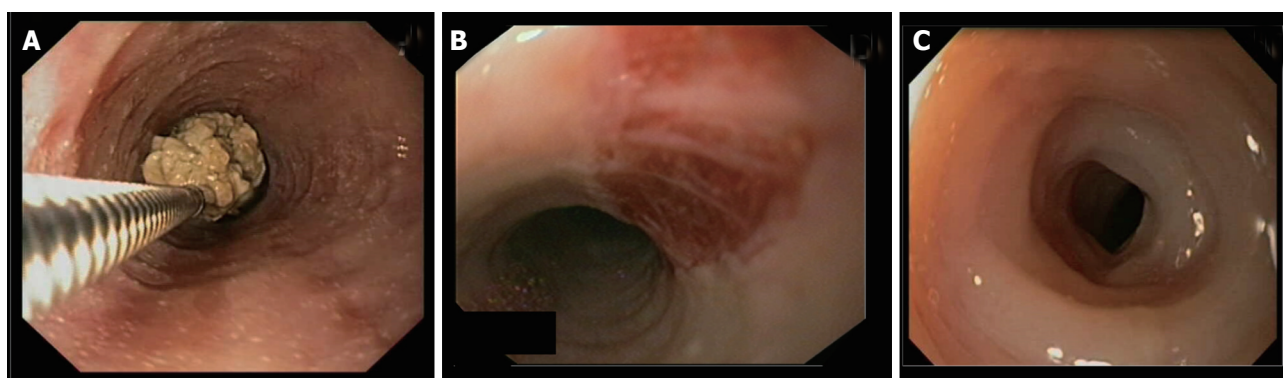


Figure 3 Food bolus impaction in patient with eosinophilic esophagitis. A: Removal with a snare; B: Esophageal rings, linear furrows and mucosal fragility; C: Stricture.

situation, we can also use a through-the-scope (TTS) balloon (Fogarty balloon or Controlled Radial Expansion balloon) to remove the foreign body. This is a similar practice as the authors recommend with the Foley catheter in the article, but with the additional help and safety provided by both, the endoscope and the balloon together, with the importance of adding the airway protection^[6]. Cylindrical batteries lodged in the stomach of an asymptomatic patient may be observed for 48 h; however, batteries that do not pass spontaneously, batteries in a symptomatic patient or multiple gastric cylindrical batteries should be removed^[6,35].

Magnets should also always be removed, even if only one magnet is evident^[6]. If the child ingests two magnets or a magnet and a metal object, these two objects can trap a portion of bowel wall causing necrosis, fistula or perforation.

Food bolus impaction in children can often mean an underlying esophageal pathology (e.g., eosinophilic esophagitis)^[38]. Sometimes intravenous Glucagon is firstly used but its results are equivocal^[39]. Bolus can be “extracted” or “pushed” into the stomach with a snare or retrieval net (Figure 3).

Other completely different types of foreign bodies

are narcotic packets: Unfortunately, children can transport these substances into their stomach like "body packing". In this case, endoscopic removal is contraindicated in order to avoid the rupture of the contents^[6,20].

Finally, superabsorbent polymers in some feminine hygiene products (tampons) and children's toys can absorb and retain large amounts of water causing intestinal obstruction if they are ingested^[40]. In the case of ingestion of superabsorbent objects, emergent or urgent endoscopy should be recommended with a retrieval net or basket for round objects and a polyp snare for larger and irregular shaped objects.

CONCLUSION

The best modality for foreign body removal has been the subject of much controversy over the years. Non-endoscopic methods such as a Foley catheter or an esophageal bougienage have many advantages, such as their simplicity and cost savings, particularly for proximally located coins. However, their complications can be potentially serious regarding airway obstruction or perforation. Only experienced hands should perform both techniques and they should be avoided if there has been previous esophageal surgery or the object has been impacted for more than 24 h. Endoscopic procedures allow direct examination of the esophagus and more complex techniques with airway control; in addition, they can be used not only for proximally coins, but also for different types and multiple objects in any location (esophagus, stomach or duodenum). Therefore, in Western countries clinical practice usually recommends endoscopic removal of foreign bodies under direct vision and with airway protection whenever possible.

REFERENCES

- Rahman I**, Patel P, Boger P, Rasheed S, Thomson M, Afzal NA. Therapeutic upper gastrointestinal tract endoscopy in Paediatric Gastroenterology. *World J Gastrointest Endosc* 2015; **7**: 169-182 [PMID: 25789087 DOI: 10.4253/wjge.v7.i3.169]
- Little DC**, Shah SR, St Peter SD, Calkins CM, Morrow SE, Murphy JP, Sharp RJ, Andrews WS, Holcomb GW, Ostlie DJ, Snyder CL. Esophageal foreign bodies in the pediatric population: our first 500 cases. *J Pediatr Surg* 2006; **41**: 914-918 [PMID: 16677882 DOI: 10.1016/j.jpedsurg.2006.01.022]
- Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition**. Spanish Association of Pediatrics (SEGHPN-AEP). Ingestion of foreign bodies. Diagnostic-therapeutic protocols of Gastroenterology, Hepatology and Pediatric Nutrition. 2nd ed. Spain: Editorial Ergón, 2010: 131-134
- Kay M**, Wyllie R. Pediatric foreign bodies and their management. *Curr Gastroenterol Rep* 2005; **7**: 212-218 [PMID: 15913481]
- Ikenberry SO**, Jue TL, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, Decker GA, Fanelli RD, Fisher LR, Fukami N, Harrison ME, Jain R, Khan KM, Krinsky ML, Maple JT, Sharaf R, Strohmeier L, Dominitz JA. Management of ingested foreign bodies and food impactions. *Gastrointest Endosc* 2011; **73**: 1085-1091 [PMID: 21628009 DOI: 10.1016/j.gie.2010.11.010]
- Louie MC**, Bradin S. Foreign body ingestion and aspiration. *Pediatr Rev* 2009; **30**: 295-301, quiz 301 [PMID: 19648260 DOI: 10.1542/pir.30-8-295]
- Abdurehim Y**, Yasin Y, Yaming Q, Hua Z. Value and efficacy of foley catheter removal of blunt pediatric esophageal foreign bodies. *ISRN Otolaryngol* 2014; **2014**: 679378 [PMID: 24634788 DOI: 10.1155/2014/679378]
- Campbell JB**, Condon VR. Catheter removal of blunt esophageal foreign bodies in children. Survey of the Society for Pediatric Radiology. *Pediatr Radiol* 1989; **19**: 361-365 [PMID: 2771474]
- Schunk JE**, Harrison AM, Corneli HM, Nixon GW. Fluoroscopic foley catheter removal of esophageal foreign bodies in children: experience with 415 episodes. *Pediatrics* 1994; **94**: 709-714 [PMID: 7936900]
- Wang J**, Wang P. Clinical analysis on 138 cases of removing esophageal foreign bodies in children by utilizing foley catheter. *CJEBM* 2010; **10**: 1118-1119
- McGuirt WF**. Use of Foley catheter for removal of esophageal foreign bodies. A survey. *Ann Otol Rhinol Laryngol* 1982; **91**: 599-601 [PMID: 7149541]
- Hawkins DB**. Removal of blunt foreign bodies from the esophagus. *Ann Otol Rhinol Laryngol* 1990; **99**: 935-940 [PMID: 2244725 DOI: 10.1177/000348949009901201]
- Gasior AC**, Knott EM, Sharp SW, Snyder CL, St Peter SD. Predictive factors for successful balloon catheter extraction of esophageal foreign bodies. *Pediatr Surg Int* 2013; **29**: 791-794 [PMID: 23793986 DOI: 10.1007/s00383-013-3331-7]
- Allie EH**, Blackshaw AM, Losek JD, Tuuri RE. Clinical effectiveness of bougienage for esophageal coins in a pediatric ED. *Am J Emerg Med* 2014; **32**: 1263-1269 [PMID: 25178851 DOI: 10.1016/j.ajem.2014.08.007]
- Arms JL**, Mackenberg-Mohn MD, Bowen MV, Chamberlain MC, Skrypek TM, Madhok M, Jimenez-Vega JM, Bonadio WA. Safety and efficacy of a protocol using bougienage or endoscopy for the management of coins acutely lodged in the esophagus: a large case series. *Ann Emerg Med* 2008; **51**: 367-372 [PMID: 17933426 DOI: 10.1016/j.annemergmed.2007.09.001]
- Heinzerling NP**, Christensen MA, Swedler R, Cassidy LD, Calkins CM, Sato TT. Safe and effective management of esophageal coins in children with bougienage. *Surgery* 2015; **158**: 1065-1070; discussion 1071-1072 [PMID: 26239181 DOI: 10.1016/j.surg.2015.06.025]
- Soprano JV**, Mandl KD. Four strategies for the management of esophageal coins in children. *Pediatrics* 2000; **105**: e5 [PMID: 10617742 DOI: 10.1542/peds.105.1.e5]
- Gauderer MW**, DeCou JM, Abrams RS, Thomason MA. The 'penny pincher': a new technique for fast and safe removal of esophageal coins. *J Pediatr Surg* 2000; **35**: 276-278 [PMID: 10693680]
- Dahshan AH**, Kevin Donovan G. Bougienage versus endoscopy for esophageal coin removal in children. *J Clin Gastroenterol* 2007; **41**: 454-456 [PMID: 17450025 DOI: 10.1097/01.mcg.00000225]
- Kramer RE**, Lerner DG, Lin T, Manfredi M, Shah M, Stephen TC, Gibbons TE, Pall H, Sahn B, McOmber M, Zacur G, Friedlander J, Quiros AJ, Fishman DS, Mamula P. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN Endoscopy Committee. *J Pediatr Gastroenterol Nutr* 2015; **60**: 562-574 [PMID: 25611037 DOI: 10.1097/MPG.0000000000000729]
- Lightdale JR**, Acosta R, Shergill AK, Chandrasekhara V, Chathadi K, Early D, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Hwang JH, Kashab M, Muthusamy VR, Pasha S, Saltzman JR, Cash BD. Modifications in endoscopic practice for pediatric patients. *Gastrointest Endosc* 2014; **79**: 699-710 [PMID: 24593951 DOI: 10.1016/j.gie.2013.08.014]
- Russell R**, Lucas A, Johnson J, Yannam G, Griffin R, Beierle E, Anderson S, Chen M, Harmon C. Extraction of esophageal foreign bodies in children: rigid versus flexible endoscopy. *Pediatr Surg Int* 2014; **30**: 417-422 [PMID: 24549805 DOI: 10.1007/s00383-014-3481-2]
- Gmeiner D**, von Rahden BH, Meco C, Hutter J, Oberascher G, Stein HJ. Flexible versus rigid endoscopy for treatment of foreign body impaction in the esophagus. *Surg Endosc* 2007; **21**: 2026-2029 [PMID: 17393244 DOI: 10.1007/s00464-007-9252-6]

- 24 **Popel J**, El-Hakim H, El-Matary W. Esophageal foreign body extraction in children: flexible versus rigid endoscopy. *Surg Endosc* 2011; **25**: 919-922 [PMID: 20734073 DOI: 10.1007/s00464-010-1299-0]
- 25 **Katsinelos P**, Kountouras J, Paroutoglou G, Zavos C, Mimidis K, Chatzimavroudis G. Endoscopic techniques and management of foreign body ingestion and food bolus impaction in the upper gastrointestinal tract: a retrospective analysis of 139 cases. *J Clin Gastroenterol* 2006; **40**: 784-789 [PMID: 17016132 DOI: 10.1097/01.mcg.0000225602.25858.2c]
- 26 **Temiz A**. Efficiency of upper gastrointestinal endoscopy in pediatric surgical practice. *World J Clin Pediatr* 2015; **4**: 113-119 [PMID: 26566483 DOI: 10.5409/wjcp.v4.i4.113]
- 27 **Lee WS**, Zainuddin H, Boey CC, Chai PF. Appropriateness, endoscopic findings and contributive yield of pediatric gastrointestinal endoscopy. *World J Gastroenterol* 2013; **19**: 9077-9083 [PMID: 24379634 DOI: 10.3748/wjg.v19.i47.9077]
- 28 **Thakkar K**, El-Serag HB, Mattek N, Gilger MA. Complications of pediatric EGD: a 4-year experience in PEDS-CORI. *Gastrointest Endosc* 2007; **65**: 213-221 [PMID: 17258979 DOI: 10.1016/j.gie.2006.03.015]
- 29 **Park YK**, Kim KO, Yang JH, Lee SH, Jang BI. Factors associated with development of complications after endoscopic foreign body removal. *Saudi J Gastroenterol* 2013; **19**: 230-234 [PMID: 24045597 DOI: 10.4103/1319-3767.118136]
- 30 **Volonaki E**, Sebire NJ, Borrelli O, Lindley KJ, Elawad M, Thapar N, Shah N. Gastrointestinal endoscopy and mucosal biopsy in the first year of life: indications and outcome. *J Pediatr Gastroenterol Nutr* 2012; **55**: 62-65 [PMID: 22210413 DOI: 10.1097/MPG.0b013e3182478f83]
- 31 **Crysdale WS**, Sendi KS, Yoo J. Esophageal foreign bodies in children. 15-year review of 484 cases. *Ann Otol Rhinol Laryngol* 1991; **100**: 320-324 [PMID: 2018291 DOI: 10.1177/000348949110000410]
- 32 **Kessler E**, Chappell JS. Upper gastro-intestinal endoscopy in children. *S Afr Med J* 1979; **56**: 591-593 [PMID: 550408]
- 33 **Cetinkursun S**, Sayan A, Demirbag S, Surer I, Ozdemir T, Arikan A. Safe removal of upper esophageal coins by using Magill forceps: two centers' experience. *Clin Pediatr (Phila)* 2006; **45**: 71-73 [PMID: 16429219 DOI: 10.1177/000992280604500111]
- 34 **Barth BA**, Banerjee S, Bhat YM, Desilets DJ, Gottlieb KT, Maple JT, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Wang A, Song LM, Rodriguez SA. Equipment for pediatric endoscopy. *Gastrointest Endosc* 2012; **76**: 8-17 [PMID: 22579260 DOI: 10.1016/j.gie.2012.02.023]
- 35 **Sahn B**, Mamula P, Ford CA. Review of foreign body ingestion and esophageal food impaction management in adolescents. *J Adolesc Health* 2014; **55**: 260-266 [PMID: 24686070 DOI: 10.1016/j.jadohe.2014.01.022]
- 36 **Smith MT**, Wong RK. Foreign bodies. *Gastrointest Endosc Clin N Am* 2007; **17**: 361-382, vii [PMID: 17556153]
- 37 **Paul RI**, Jaffe DM. Sharp object ingestions in children: illustrative cases and literature review. *Pediatr Emerg Care* 1988; **4**: 245-248 [PMID: 3068636]
- 38 **Lao J**, Bostwick HE, Berezin S, Halata MS, Newman LJ, Medow MS. Esophageal food impaction in children. *Pediatr Emerg Care* 2003; **19**: 402-407 [PMID: 14676489 DOI: 10.1097/01.ped.0000101581.65509.17]
- 39 **Weant KA**, Weant MP. Safety and efficacy of glucagon for the relief of acute esophageal food impaction. *Am J Health Syst Pharm* 2012; **69**: 573-577 [PMID: 22441787 DOI: 10.2146/ajhp100587]
- 40 **Mirza B**, Sheikh A. Mortality in a case of crystal gel ball ingestion: an alert for parents. *APSP J Case Rep* 2012; **3**: 6 [PMID: 22953300]

P- Reviewer: Chen JQ, Lee CL, Menten O, Xiao Q

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL



Retrospective Cohort Study

Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma

Kazumichi Kawakubo, Hiroshi Kawakami, Masaki Kuwatani, Shin Haba, Taiki Kudo, Yoko A Taya, Shuhei Kawahata, Yoshimasa Kubota, Kimitoshi Kubo, Kazunori Eto, Nobuyuki Ehira, Hiroaki Yamato, Manabu Onodera, Naoya Sakamoto

Kazumichi Kawakubo, Hiroshi Kawakami, Masaki Kuwatani, Shin Haba, Taiki Kudo, Yoko A Taya, Shuhei Kawahata, Yoshimasa Kubota, Kimitoshi Kubo, Kazunori Eto, Nobuyuki Ehira, Hiroaki Yamato, Manabu Onodera, Naoya Sakamoto, Department of Gastroenterology and Hepatology, Hokkaido University Graduate School of Medicine, Sapporo 0608638, Japan

Author contributions: Kawakubo K designed and performed the study and wrote the paper; Kawakami H and Kuwatani M designed the study and supervised the writing of the report; Haba S, Kudo T, Taya YA, Kawahata S, Kubota Y, Kubo K, Eto K, Ehira N, Yamato H and Onodera M collected and analyzed the data; and Sakamoto N approved the final version of the manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of Hokkaido University Hospital.

Informed consent statement: Patients were not required to give informed consent to participate in the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Hokkaido University Hospital.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Kazumichi Kawakubo, MD, PhD, Assistant Professor, Department of Gastroenterology and Hepatology, Hokkaido University Graduate School of Medicine, Kita 15 Nishi 7, Kita-ku, Sapporo 0608638, Japan. kkawakubo-gi@umin.ac.jp
Telephone: +81-11-7161161
Fax: +81-11-7067867

Received: December 21, 2015

Peer-review started: December 22, 2015

First decision: January 30, 2016

Revised: February 15, 2016

Accepted: March 14, 2016

Article in press: March 16, 2016

Published online: May 10, 2016

Abstract

AIM: To identify the most effective endoscopic biliary drainage technique for patients with hilar cholangiocarcinoma.

METHODS: In total, 118 patients with hilar cholangiocarcinoma underwent endoscopic management [endoscopic nasobiliary drainage (ENBD) or endoscopic biliary stenting] as a temporary drainage in our institution between 2009 and 2014. We retrospectively evaluated all complications from initial endoscopic drainage to surgery or palliative treatment. The risk factors for biliary reintervention, post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis, and percutaneous transhepatic biliary drainage (PTBD) were also analyzed using patient- and procedure-related characteristics. The risk factors for bilateral drainage were examined in a subgroup analysis of patients who underwent initial unilateral drainage.

RESULTS: In total, 137 complications were observed in 92 (78%) patients. Biliary reintervention was required in 83 (70%) patients. ENBD was significantly associated with a low risk of biliary reintervention [odds ratio (OR) = 0.26, 95%CI: 0.08-0.76, $P = 0.012$]. Post-ERCP pancreatitis was observed in 19 (16%) patients. An absence of endoscopic sphincterotomy was significantly associated with post-ERCP pancreatitis (OR = 3.46, 95%CI: 1.19-10.87, $P = 0.023$). PTBD was required in 16 (14%) patients, and Bismuth type III or IV cholangiocarcinoma was a significant risk factor (OR = 7.88, 95%CI: 1.33-155.0, $P = 0.010$). Of 102 patients with initial unilateral drainage, 49 (48%) required bilateral drainage. Endoscopic sphincterotomy (OR = 3.24, 95%CI: 1.27-8.78, $P = 0.004$) and Bismuth II, III, or IV cholangiocarcinoma (OR = 34.69, 95%CI: 4.88-736.7, $P < 0.001$) were significant risk factors for bilateral drainage.

CONCLUSION: The endoscopic management of hilar cholangiocarcinoma is challenging. ENBD should be selected as a temporary drainage method because of its low risk of complications.

Key words: Hilar cholangiocarcinoma; Endoscopic nasobiliary drainage; Endoscopic biliary stenting; Endoscopic sphincterotomy; Complications

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This retrospective study evaluated the risk of complications associated with a temporary endoscopic biliary drainage for hilar cholangiocarcinoma. Endoscopic nasobiliary drainage (ENBD) had a significantly lower incidence of biliary complications than biliary stenting. Endoscopic sphincterotomy significantly reduced the rate of post-endoscopic retrograde cholangiopancreatography pancreatitis, but was associated with bilateral drainage. Therefore, ENBD should be selected as a temporary biliary drainage method for patients with hilar cholangiocarcinoma.

Kawakubo K, Kawakami H, Kuwatani M, Haba S, Kudo T, Taya YA, Kawahata S, Kubota Y, Kubo K, Eto K, Ehira N, Yamato H, Onodera M, Sakamoto N. Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma. *World J Gastrointest Endosc* 2016; 8(9): 385-390 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i9/385.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i9.385>

INTRODUCTION

Surgery is the only curative treatment for patients with hilar cholangiocarcinoma, and the routine use of preoperative biliary drainage should be avoided^[1,2]. However, preoperative drainage is mandatory to assess the surgical resectability and obtain pathological

confirmation^[3,4]. In other words, surgical resectability cannot be accurately assessed before biliary drainage.

Endoscopic biliary drainage is widely accepted as the standard therapy for palliation of malignant biliary obstruction^[5,6]. Because of severe complications and tumor seeding, percutaneous transhepatic biliary drainage (PTBD) is not recommended as a routine preoperative drainage method^[7,8]. Therefore, endoscopic nasobiliary drainage (ENBD) is usually selected for temporary biliary drainage in patients with hilar cholangiocarcinoma, especially in high-volume centers. In patients who are not candidates for surgery after a work-up for resectability, endoscopic biliary drainage using a self-expandable metallic stent is often performed because of the long stent patency^[6,9].

No studies have evaluated the safety of endoscopic biliary drainage as a bridge to definitive surgery or palliative treatment in patients with hilar cholangiocarcinoma. The aim of this study was to evaluate the complications associated with temporary endoscopic biliary drainage in patients with hilar cholangiocarcinoma from the initial biliary drainage to the definitive surgery or palliative treatment.

MATERIALS AND METHODS

Study design

This retrospective study was performed at a tertiary care university hospital in which > 50 cases of major hepatectomy are performed every year. The prospectively collected endoscopy database at our department was searched for patients who underwent biliary drainage of hilar cholangiocarcinoma for temporary purpose from 2009 to 2014. We excluded patients who underwent PTBD or self-expandable metallic stent (SEMS) placement as an initial drainage technique. In patients who underwent curative surgery, all complications that occurred from initial drainage to surgery were reviewed. In the remaining patients, all complications that occurred from initial drainage to palliative treatment were assessed. Palliative treatment included SEMS placement, bypass surgery, and permanent PTBD. The severity of each complication was defined by a lexicon from the American Society for Gastrointestinal Endoscopy. The study was approved by the institutional review board of Hokkaido University Hospital (014-044) and complied with the Health Insurance Portability and Accountability Act regulations (UMIN000017178).

Endoscopic management of hilar cholangiocarcinoma

Written informed consent was obtained from each patient before endoscopic retrograde cholangiopancreatography (ERCP). In our institution, the initial drainage technique for patients with hilar cholangiocarcinoma is usually unilateral ENBD to the future remnant liver lobe^[8]. However, in other hospitals, the selection of initial drainage technique depended on each endoscopist. In patients who had previously

Table 1 Patient characteristics (N=118)

Age, yr (mean, SD)	69 (9)
Male/female	74/44
Preoperative bilirubin, mg/dL (median, range)	2.0 (0.5–24.9)
Bismuth I/II/IIIa/IIIb/IV, <i>n</i>	18/25/35/5/35
Initial biliary drainage at our institutions, <i>n</i> (%)	43 (36)
Initial drainage ENBD/EBS, <i>n</i>	85/33
Unilateral/bilateral, <i>n</i>	102/16
Sphincterotomy, <i>n</i> (%)	74 (63)
PTPE, <i>n</i> (%)	54 (46)
Surgery, <i>n</i> (%)	71 (60)
Time to surgery, days (median, range)	62 (4–233)

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting; PTPE: Percutaneous transhepatic portal vein embolization.

undergone drainage, biliary reintervention with ENBD was considered in the following situations: Catheter obstruction, segmental cholangitis, spontaneous catheter dislocation, accidental ENBD tube removal, and/or ENBD-induced duodenal ulcer formation. Catheter obstruction was diagnosed in patients with a high fever ($> 38^{\circ}\text{C}$) and elevated serum hepatobiliary enzyme concentrations. Segmental cholangitis was defined as cholangitis that occurred in an undrained area. In patients with catheter obstruction, the previous endoscopic biliary stent (EBS) or ENBD tube was exchanged for an ENBD tube in the same segment. In patients with segmental cholangitis, an additional ENBD tube was placed in the segment in which cholangitis was suspected. PTBD was performed in patients with segmental cholangitis if ENBD failed or after severe post-ERCP pancreatitis.

Resectability assessment

The criteria for surgical resectability were basically determined according to our previous study^[10,11], and some patients with advanced age or comorbid diseases did not undergo surgery. Portal vein embolization was performed as necessary^[12]. If the patient was determined to have unresectable disease, endoscopic SEMS placement, PTBD, or bypass surgery was performed as a palliative treatment.

Statistical analysis

Results are reported as mean \pm SD for quantitative variables and as percentage for categorical variables. We analyzed the risk factors for all complications, biliary reintervention, and PTBD using age, sex, Bismuth type I/II/III or IV cholangiocarcinoma, total bilirubin concentration before initial drainage, EBS placement/ENBD, unilateral/bilateral disease, and sphincterotomy. Risk factors for post-ERCP pancreatitis were evaluated using age, sex, EBS placement/ENBD, unilateral/bilateral disease, and sphincterotomy. In patients who underwent unilateral initial drainage, we evaluated risk factors for bilateral drainage using these factors.

Table 2 Complications

Initial drainage	ENBD (<i>n</i> = 85)	EBS (<i>n</i> = 33)
ENBD dislocation	20	6
EBS occlusion	8	14
ENBD occlusion	14	7
Contralateral cholangitis	25	12
Accidental ENBD extubation	2	2
Cholecystitis	0	3
Liver abscess	0	2
ENBD induced ulcer	0	1
Inappropriate location	1	1
Pancreatitis	12	7
(Mild/moderate/severe)	(5/2/5)	(3/2/2)

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

Statistical analysis was performed by JMP version 11 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Patient characteristics

During the study period, 125 patients underwent endoscopic biliary evaluation and drainage for temporary purpose at our institution. Two patients were excluded because of previous PTBD placement at the previous hospital. Five patients who underwent SEMS placement at the time of initial drainage were also excluded. Therefore, 118 patients were included and evaluated in this study. The patients' baseline characteristics are shown in Table 1. Eighty-five patients underwent ENBD for initial drainage, while the remaining underwent EBS placement. One hundred and two patients underwent unilateral initial drainage and 16 underwent bilateral drainage. Seventy-four patients underwent endoscopic sphincterotomy at the time of the initial drainage. The initial drainage was performed at other hospitals in 75 patients. Seventy-one patients underwent definitive surgery, while the remaining underwent palliative treatment. Palliative treatment included SEMS placement or PTBD. The median time to the final treatment was 64 d (range: 4–233 d).

Complications

Between the initial drainage and final treatment, 118 complications in 92 patients were observed (Table 2). Biliary reintervention was required in 83 (70%) patients; the incidence was 35%, 53%, and 63% within 30, 60, and 90 d, respectively. The reasons for biliary reintervention were contralateral cholangitis ($n = 37$), ENBD dislocation ($n = 26$), EBS occlusion ($n = 22$), ENBD occlusion ($n = 21$), accidental ENBD removal ($n = 4$), inappropriate tube location ($n = 2$), and ENBD-induced duodenal ulcer formation ($n = 1$). PTBD was required in 16 (14%) patients with contralateral cholangitis but who underwent failed endoscopic drainage. Post-ERCP pancreatitis was observed in 19 patients; the severity was mild in eight, moderate in four, and severe in seven.

Table 3 Risk factors for biliary reintervention

	OR	95%CI	P value
Age (+1 yr)	1.01	0.96-1.06	0.626
Female/male	1.23	0.50-3.14	0.650
Bismuth I	1		
Bismuth II	1.53	0.38-9.19	0.555
Bismuth IIIa/b/IV	2.06	0.68-6.11	0.195
Preoperative Bil (+ 1 mg/dL)	0.97	0.91-1.05	0.492
EBS/ENBD	3.80	1.32-13.02	0.012
Unilateral/bilateral	2.62	0.74-9.20	0.132
Sphincterotomy	1.32	0.53-3.25	0.551

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

Table 4 Risk factors for percutaneous transhepatic biliary drainage

	OR	95%CI	P value
Age (+1 yr)	0.96	0.92-1.08	0.220
Female/male	2.48	0.73-8.71	0.143
Bismuth I	1		
Bismuth II	0.54	0.02-15.15	0.683
Bismuth IIIa/b/IV	10.15	1.62-214.7	0.010
Sphincterotomy	2.36	0.69- 9.43	0.178
EBS/ENBD	2.63	0.70-9.89	0.149
Unilateral/bilateral	8.77	1.09-214.7	0.040
Preoperative bilirubin (+ 1 mg/dL)	1.02	0.93-1.12	0.604

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

In 102 patients who underwent initial unilateral drainage, 49 (48%) required bilateral drainage.

Risk factors for biliary reintervention

Multivariate analysis showed that EBS placement was a significant risk factor for biliary reintervention (OR = 3.80, 95%CI: 1.32-13.02, $P = 0.012$). ENBD was significantly associated with a low risk of biliary reintervention (OR = 0.26, 95%CI: 0.08-0.76, $P = 0.012$) and *vice versa* (Table 3).

Risk factors for PTBD

Multivariate analysis showed that patients with Bismuth III and IV cholangiocarcinoma (OR = 10.15, 95%CI: 1.62-214.7, $P = 0.010$) and initial unilateral drainage (OR = 8.77, 95%CI: 1.09-214.7, $P = 0.040$) were significant risk factors for PTBD (Table 4).

Risk factors for post-ERCP pancreatitis

Multivariate analysis showed that absence of endoscopic sphincterotomy was significantly associated with post-ERCP pancreatitis (OR = 3.46, 95%CI: 1.19-10.87, $P = 0.023$) (Table 5).

Risk factors for bilateral drainage

In the multivariate analysis of 102 patients, those with Bismuth II/III/IV cholangiocarcinoma (OR = 34.69, 95%CI: 4.88-736.7, $P < 0.001$) and the presence of endoscopic sphincterotomy (OR = 4.43, 95%CI:

Table 5 Risk factors for post-endoscopic retrograde cholangio-pancreatography pancreatitis

	OR	95%CI	P value
Age (+1 yr)	0.95	0.89-1.01	0.078
Female/male	1.45	0.48-4.36	0.501
EBS/ENBD	2.24	0.70-7.09	0.171
Unilateral/bilateral	1.46	0.31-11.24	0.661
No sphincterotomy	3.46	1.19-10.87	0.023

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

Table 6 Risk factors for bilateral drainage ($n = 102$)

	OR	95%CI	P value
Age (+1 yr)	0.95	0.89-1.01	0.077
Female/male	1.76	0.66-4.91	0.259
EBS/ENBD	3.12	0.97-11.26	0.056
Bismuth I	1		
Bismuth II	34.69	4.88-736.7	< 0.001
Bismuth IIIa/b/IV	1.12	0.36-3.53	0.843
Sphincterotomy	4.43	1.61-13.51	0.004
Preoperative bilirubin	1.07	0.98-1.17	0.156

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

1.61-13.51, $P = 0.004$) were significant risk factors for bilateral drainage (Table 3).

DISCUSSION

In this study, endoscopic biliary drainage of hilar cholangiocarcinoma for temporary purpose had a high morbidity rate. However, ENBD was associated with a significantly lower risk of biliary reintervention than EBS placement. Endoscopic sphincterotomy reduced the risk of post-ERCP pancreatitis, but was significantly associated with bilateral drainage.

The treatment strategy for hilar cholangiocarcinoma depends on the surgical resectability. Surgical resectability was determined not only by the tumor itself but also the presence of jaundice, liver function test results, performance status, and/or comorbid diseases. Endoscopic biliary drainage is usually necessary after endoscopic biopsy of the bile duct to prevent post-ERCP cholangitis. We previously demonstrated that ENBD is the most suitable preoperative drainage method for hilar cholangiocarcinoma because it is associated with a lower complication rate than are EBS and PTBD^[8]. Preoperative drainage did not affect the mortality rate among jaundiced patients with hilar cholangiocarcinoma^[13,14]. In a recent study, surgeons preferred endoscopic biliary drainage to PTBD to avoid tumor seeding and severe complications^[7,15]. Actually, during the study period, only two patients underwent PTBD as the initial biliary drainage method. This study showed that ENBD is still the most suitable initial temporary drainage method for the management of hilar cholangiocarcinoma. This means that ENBD should be selected as a tem-

porary drainage method in jaundiced patients with hilar cholangiocarcinoma regardless of the surgical resectability. In previous studies involving patients who were not candidates for surgical resection, an endoscopic SEMS was deployed in place of an ENBD tube because of the longer patency duration than a plastic stent^[9,16].

Post-ERCP pancreatitis is an unresolved problem in endoscopic biliary drainage^[17,18]. Prophylactic pancreatic stenting and rectal indomethacin has been recommended to prevent post-ERCP pancreatitis^[19]. This study showed that endoscopic sphincterotomy can reduce the incidence of post-ERCP pancreatitis without prophylactic pancreatic stenting or rectal indomethacin, which is consistent with the findings of previous retrospective studies^[15,20]. However, endoscopic sphincterotomy did not reduce the incidence of post-ERCP pancreatitis in patients with distal malignant biliary obstruction before ENBD^[21,22]. The risk of post-ERCP pancreatitis was higher in patients with hilar cholangiocarcinoma than in patients with pancreatic cancer^[22]. The effect of endoscopic sphincterotomy before endoscopic biliary drainage for hilar cholangiocarcinoma on post-ERCP pancreatitis should be clarified in a randomized prospective study.

PTBD was historically a standard preoperative management technique for hilar cholangiocarcinoma^[23]. However, the development of endoscopic biliary drainage and the high risk of severe complications rendered it salvage therapy^[4]. In the present study, 14% of patients required PTBD for the management of contralateral cholangitis, and highly advanced biliary stricture was significantly associated with PTBD. This is consistent with previous reports^[24]. Although multiple ENBD is possible, surgeons and endoscopists should understand the limitations of ENBD, especially for highly advanced hilar cholangiocarcinoma^[4].

There is still controversy regarding the superiority of unilateral or bilateral drainage for management of hilar malignant biliary obstruction. In the present study, 49% of patients who underwent unilateral initial drainage required bilateral drainage until the surgery or palliative treatment because of contralateral cholangitis. In patients with unresectable malignant hilar biliary obstruction, bilateral drainage was associated with a longer stent patency time than was unilateral drainage. However, bilateral drainage was sometimes technically difficult, especially in patients with highly advanced biliary strictures^[25]. Additional studies are required to compare unilateral and bilateral endoscopic biliary drainage for temporary biliary drainage.

This study had several limitations. This was a retrospective nonrandomized study. Each endoscopist chose the endoscopic biliary drainage method and necessity of endoscopic sphincterotomy. The usefulness of inside stent placement for temporary preoperative drainage was recently reported^[26]. The superiority of ENBD to inside stent placement requires clarification in future studies. Furthermore, few patients in this study underwent preoperative neoadjuvant therapy, in which

the preoperative period was much longer. The safety of surgery after SEMS placement was reported, and temporary SEMS placement should be evaluated^[27].

Endoscopic biliary drainage for temporary purpose in patients with hilar cholangiocarcinoma has a high morbidity rate. Until surgical resectability is determined, ENBD should be selected for temporary endoscopic biliary drainage because of its low reintervention rate. Endoscopic sphincterotomy should be considered to prevent post-ERCP pancreatitis. Further studies are required to identify a more suitable management technique for patients with hilar cholangiocarcinoma.

COMMENTS

Background

Surgery is the only curative treatment for patients with hilar cholangiocarcinoma, and the routine use of preoperative biliary drainage should be avoided. However, surgical resectability cannot be always accurately assessed before biliary drainage. No studies have evaluated the safety of endoscopic biliary drainage as a bridge to definitive surgery or palliative treatment in patients with hilar cholangiocarcinoma.

Research frontiers

The authors previously reported endoscopic nasobiliary drainage (ENBD) is the most suitable for preoperative biliary drainage in patients with hilar cholangiocarcinoma. The authors provide support to the preference of ENBD for both preoperative and palliative biliary drainage in patients with hilar cholangiocarcinoma.

Innovations and breakthroughs

ENBD had a significantly lower incidence of biliary complications than biliary stenting in patients with hilar cholangiocarcinoma.

Applications

Endoscopic biliary drainage for temporary purpose in patients with hilar cholangiocarcinoma has a high morbidity rate. Until surgical resectability is determined, ENBD should be selected for temporary endoscopic biliary drainage because of its low reintervention rate.

Terminology

ENBD is one of the biliary drainage methods. The advantage of ENBD over biliary stenting is the monitoring of bile, cholangiography, bile cytology, and removability. The disadvantage is the discomfort of the patients.

Peer-review

In this retrospective study, the authors end up into some conclusions, the majority of which are well known from previous studies. What is new is that according to their findings ENBD was a better approach and with lower complications.

REFERENCES

- 1 **Kondo S**, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T, Yamamoto M, Kayahara M, Kimura F, Yoshitomi H, Nozawa S, Yoshida M, Wada K, Hirano S, Amano H, Miura F. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. *J Hepatobiliary Pancreat Surg* 2008; **15**: 41-54 [PMID: 18274843 DOI: 10.1007/s00534-007-1279-5]
- 2 **Khan SA**, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, Rosenberg WM, Tait P, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Wasan H. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 2012; **61**:

- 1657-1669 [PMID: 22895392 DOI: 10.1136/gutjnl-2011-301748]
- 3 **Nagino M**, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Kondo S, Furuse J, Saito H, Tsuyuguchi T, Yoshikawa T, Ohta T, Kimura F, Ohta T, Yoshitomi H, Nozawa S, Yoshida M, Wada K, Amano H, Miura F. Preoperative biliary drainage for biliary tract and ampullary carcinomas. *J Hepatobiliary Pancreat Surg* 2008; **15**: 25-30 [PMID: 18274841 DOI: 10.1007/s00534-007-1277-7]
- 4 **Kawakami H**, Kondo S, Kuwatani M, Yamato H, Ehira N, Kudo T, Eto K, Haba S, Matsumoto J, Kato K, Tsuchikawa T, Tanaka E, Hirano S, Asaka M. Preoperative biliary drainage for hilar cholangiocarcinoma: which stent should be selected? *J Hepatobiliary Pancreat Sci* 2011; **18**: 630-635 [PMID: 21655974 DOI: 10.1007/s00534-011-0404-7]
- 5 **Isayama H**, Nakai Y, Kawakubo K, Kogure H, Hamada T, Togawa O, Sasahira N, Hirano K, Tsujino T, Koike K. Endoscopic retrograde cholangiopancreatography for distal malignant biliary stricture. *Gastrointest Endosc Clin N Am* 2012; **22**: 479-490 [PMID: 22748244 DOI: 10.1016/j.giec.2012.04.024]
- 6 **Kawakami H**, Itoi T, Kuwatani M, Kawakubo K, Kubota Y, Sakamoto N. Technical tips and troubleshooting of endoscopic biliary drainage for unresectable malignant hilar biliary obstruction. *J Hepatobiliary Pancreat Sci* 2015; **22**: E12-E21 [PMID: 25379788 DOI: 10.1002/jhbp.186]
- 7 **Takahashi Y**, Nagino M, Nishio H, Ebata T, Igami T, Nimura Y. Percutaneous transhepatic biliary drainage catheter tract recurrence in cholangiocarcinoma. *Br J Surg* 2010; **97**: 1860-1866 [PMID: 20799295 DOI: 10.1002/bjs.7228]
- 8 **Kawakami H**, Kuwatani M, Onodera M, Haba S, Eto K, Ehira N, Yamato H, Kudo T, Tanaka E, Hirano S, Kondo S, Asaka M. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. *J Gastroenterol* 2011; **46**: 242-248 [PMID: 20700608 DOI: 10.1007/s00535-010-0298-1]
- 9 **Mukai T**, Yasuda I, Nakashima M, Doi S, Iwashita T, Iwata K, Kato T, Tomita E, Moriwaki H. Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. *J Hepatobiliary Pancreat Sci* 2013; **20**: 214-222 [PMID: 22415652 DOI: 10.1007/s00534-012-0508-8]
- 10 **Kondo S**, Hirano S, Ambo Y, Tanaka E, Okushiba S, Morikawa T, Katoh H. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. *Ann Surg* 2004; **240**: 95-101 [PMID: 15213624 DOI: 10.1097/01.sla.0000129491.43855.6b]
- 11 **Kawakami H**, Kuwatani M, Etoh K, Haba S, Yamato H, Shinada K, Nakanishi Y, Tanaka E, Hirano S, Kondo S, Kubota K, Asaka M. Endoscopic retrograde cholangiography versus peroral cholangioscopy to evaluate intraepithelial tumor spread in biliary cancer. *Endoscopy* 2009; **41**: 959-964 [PMID: 19802775 DOI: 10.1055/s-0029-1215178]
- 12 **Hirano S**, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, Matsumoto J, Kawasaki R. Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. *J Hepatobiliary Pancreat Sci* 2010; **17**: 455-462 [PMID: 19820891 DOI: 10.1007/s00534-009-0208-1]
- 13 **Farges O**, Regimbeau JM, Fuks D, Le Treut YP, Cherqui D, Bachellier P, Mabrut JY, Adham M, Pruvot FR, Gigot JF. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 2013; **100**: 274-283 [PMID: 23124720 DOI: 10.1002/bjs.8950]
- 14 **Sugawara G**, Ebata T, Yokoyama Y, Igami T, Takahashi Y, Takara D, Nagino M. The effect of preoperative biliary drainage on infectious complications after hepatobiliary resection with cholangiojejunostomy. *Surgery* 2013; **153**: 200-210 [PMID: 23044266 DOI: 10.1016/j.surg.2012.07.032]
- 15 **Kawashima H**, Itoh A, Ohno E, Itoh Y, Ebata T, Nagino M, Goto H, Hirooka Y. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. *Ann Surg* 2013; **257**: 121-127 [PMID: 22895398 DOI: 10.1097/SLA.0b013e318262b2e9]
- 16 **Kawakubo K**, Kawakami H, Kuwatani M, Kudo T, Abe Y, Kawahata S, Kubo K, Kubota Y, Sakamoto N. Single-step simultaneous side-by-side placement of a self-expandable metallic stent with a 6-Fr delivery system for unresectable malignant hilar biliary obstruction: a feasibility study. *J Hepatobiliary Pancreat Sci* 2015; **22**: 151-155 [PMID: 25345586 DOI: 10.1002/jhbp.173]
- 17 **Coté GA**, Kumar N, Ansstas M, Edmundowicz SA, Jonnalagadda S, Mullady DK, Azar RR. Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. *Gastrointest Endosc* 2010; **72**: 748-754 [PMID: 20630513 DOI: 10.1016/j.gie.2010.05.023]
- 18 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]
- 19 **Dumonceau JM**, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, Marek T, Baron TH, Hassan C, Testoni PA, Kapral C. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. *Endoscopy* 2014; **46**: 799-815 [PMID: 25148137 DOI: 10.1055/s-0034-1377875]
- 20 **Matsubayashi H**, Fukutomi A, Kanemoto H, Maeda A, Matsunaga K, Uesaka K, Otake Y, Hasuike N, Yamaguchi Y, Ikehara H, Takizawa K, Yamazaki K, Ono H. Risk of pancreatitis after endoscopic retrograde cholangiopancreatography and endoscopic biliary drainage. *HPB (Oxford)* 2009; **11**: 222-228 [PMID: 19590651 DOI: 10.1111/j.1477-2574.2008.00020.x]
- 21 **Hayashi T**, Kawakami H, Osanai M, Ishiwatari H, Naruse H, Hisai H, Yanagawa N, Kaneto H, Koizumi K, Sakurai T, Sonoda T. No benefit of endoscopic sphincterotomy before biliary placement of self-expandable metal stents for unresectable pancreatic cancer. *Clin Gastroenterol Hepatol* 2015; **13**: 1151-8.e2 [PMID: 25632802 DOI: 10.1016/j.cgh.2015.01.008]
- 22 **Kawakubo K**, Isayama H, Nakai Y, Togawa O, Sasahira N, Kogure H, Sasaki T, Matsubara S, Yamamoto N, Hirano K, Tsujino T, Toda N, Tada M, Omata M, Koike K. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. *Surg Endosc* 2012; **26**: 771-776 [PMID: 22011943 DOI: 10.1007/s00464-011-1950-4]
- 23 **Nimura Y**, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda K, Sano T, Yamamoto H, Hayakawa N. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. *J Hepatobiliary Pancreat Surg* 2000; **7**: 155-162 [PMID: 10982608 DOI: 10.1007/s005340000070155.534]
- 24 **Berknimitz R**, Kladcharoen N, Mahachai V, Kullavanijaya P. Result of endoscopic biliary drainage in hilar cholangiocarcinoma. *J Clin Gastroenterol* 2004; **38**: 518-523 [PMID: 15220688 DOI: 10.1097/01.mcg.0000123204.36471.be]
- 25 **Kawakubo K**, Kawakami H, Toyokawa Y, Otani K, Kuwatani M, Abe Y, Kawahata S, Kubo K, Kubota Y, Sakamoto N. Risk factors for technical failure of endoscopic double self-expandable metallic stent placement by partial stent-in-stent method. *J Hepatobiliary Pancreat Sci* 2015; **22**: 79-85 [PMID: 25308061 DOI: 10.1002/jhbp.170]
- 26 **Kobayashi N**, Watanabe S, Hosono K, Kubota K, Nakajima A, Kaneko T, Sugimori K, Tokuhisa M, Goto A, Mori R, Taniguchi K, Matsuyama R, Endo I, Maeda S, Ichikawa Y. Endoscopic inside stent placement is suitable as a bridging treatment for preoperative biliary tract cancer. *BMC Gastroenterol* 2015; **15**: 8 [PMID: 25649526 DOI: 10.1186/s12876-015-0233-2]
- 27 **Fukami Y**, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nagino M. Salvage hepatectomy for perihilar malignancy treated initially with biliary self-expanding metallic stents. *Surgery* 2013; **153**: 627-633 [PMID: 23270971 DOI: 10.1016/j.surg.2012.11.008]

P-Reviewer: Buanes TA, Garg P, Thomopoulos KC
S-Editor: Gong ZM **L-Editor:** A **E-Editor:** Wu HL



First report of splenic rupture following deep enteroscopy

Carlo Maria Girelli, Roberta Pometta, Corinna Facciotto, Roberto Mella, Giordano Bernasconi

Carlo Maria Girelli, Giordano Bernasconi, Gastroenterology and Digestive Endoscopy Unit, Hospital of Busto Arsizio, 21052 Busto Arsizio (VA), Italy

Roberta Pometta, Corinna Facciotto, Roberto Mella, Division of Internal Medicine, Hospital of Angera, 21021 Angera (VA), Italy

Author contributions: Girelli CM wrote a section of the manuscript and performed deep enteroscopy; Pometta R wrote a section of the manuscript and performed upper and lower endoscopy; Facciotto C was the referring physician who provided clinical details; Mella R performed capsule endoscopy; Bernasconi G wrote a section of the manuscript; all co-authors read and approved the final version of the manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Hospital of Busto Arsizio (Italy).

Informed consent statement: The patient involved in this study gave his written informed consent authorizing use and disclosure of his protected health information.

Conflict-of-interest statement: All authors have no conflict of interests to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Carlo Maria Girelli, MD, Head of the IBD Unit, Gastroenterology and Digestive Endoscopy Unit, Hospital of Busto Arsizio, Via Arnaldo da Brescia, 1, 21052 Busto Arsizio (VA), Italy. cargirel@gmail.com
Telephone: +39-03-31699261
Fax: +39-03-31699265

Received: January 8, 2016
Peer-review started: January 12, 2016
First decision: February 2, 2016

Revised: February 17, 2016
Accepted: March 7, 2016
Article in press: March 9, 2016
Published online: May 10, 2016

Abstract

Splenic rupture is a rare complication of diagnostic and therapeutic gastrointestinal endoscopy procedures. Herein, we report for the first time a case of splenic rupture following therapeutic retrograde double-balloon enteroscopy, which occurred in an 85-year-old man who was treated for recurrent mid-intestinal bleeding that resulted from ileal angioectasia. This patient promptly underwent an operation and eventually recovered.

Key words: Angioectasia; Artero-venous malformation; Capsule endoscopy; Complication; Deep enteroscopy; Device assisted enteroscopy; Double balloon enteroscopy; Mid gastrointestinal bleeding; Obscure gastrointestinal bleeding; Small bowel; Splenic injury; Splenic rupture

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Splenic rupture is a rare, devastating complication of colonoscopy. For the first time, we report a case of splenic rupture following therapeutic retrograde double-balloon enteroscopy.

Girelli CM, Pometta R, Facciotto C, Mella R, Bernasconi G. First report of splenic rupture following deep enteroscopy. *World J Gastrointest Endosc* 2016; 8(9): 391-394 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i9/391.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i9.391>

INTRODUCTION

Splenic rupture is a rare complication of gastrointestinal

endoscopy. Although very few cases of splenic injuries have been reported following endoscopic retrograde cholangio pancreatography^[1,2], immediate or delayed splenic injury and rupture have mostly been reported following diagnostic and therapeutic colonoscopy. To the best of our knowledge, 102 of such cases have been reported in the English language literature^[3]. Deep enteroscopy (DE) is a relatively new endoscopic technique involving approach of the small bowel from an oral (antegrade DE) or aboral (retrograde DE) route. In contrast to small bowel capsule endoscopy (SBCE), DE is invasive, requires sedation and allows for endoscopic interventions (*i.e.*, biopsy, tattooing, hemostasis, or polypectomy). In accordance with the European Society of Gastrointestinal Endoscopy guidelines^[4], in the clinical setting of recurrent, overt mid-gastrointestinal bleeding, we perform DE to better characterize and/or treat lesions identified by other less invasive means, such as SBCE and/or cross-sectional imaging. DE can be performed with the aid of an overtube; currently, three different instruments are used: A single-balloon enteroscope, a double-balloon enteroscope (DBE) and a spiral enteroscope. To date, no case of splenic rupture has been reported following DE. Herein, we present the first such case, which occurred after a therapeutic retrograde DBE (R-DBE).

CASE REPORT

An 85-year-old Caucasian man was admitted to hospital in March 2015 because of gastrointestinal bleeding (bright red blood in his stools) and anemia (hemoglobin level of 7.7 g/dL). In 1998, he underwent aortic valve replacement with a mechanical prosthesis, with subsequent long-life warfarin (target INR of 3-4.5). Previously, 5 mo before his current admission, he was admitted because of overt gastrointestinal hemorrhage. Although an upper endoscopy was normal, colonoscopy revealed sigmoid diverticula and active bleeding resulting from a Dieulafoy lesion of the right flexure, which was successfully clipped.

During this present instance of hospital admission, two units of packed red blood cells were administered. Urgent esophagogastroduodenoscopy and colonoscopy were performed without evidence of active bleeding. Therefore, the patient underwent SBCE (Pillcam SB3, Covidien, Ireland). At 3 h 30 min after capsule ingestion (81% of the small bowel transit time from the first duodenal image), the capsule showed active ileal oozing and bleeding from an otherwise normal mucosa (Figure 1). With the aim of stopping the bleeding, we performed an R-DBE (instrument: Fuji EN450T5; working length: 2000 mm, and distal end diameter: 9.4 mm) under conscious sedation (pethidine 50 mg, midazolam 5 mg, *i.v.*) up to 180 cm from the ileocecal valve, which we calculated using the May method^[5] without experiencing any technical difficulty. A 5 mm, branched angioectasia (type 1b of the Yano-Yamamoto classification^[6]) was identified that was 150



Figure 1 Capsule endoscopy showing ileal luminal blood (arrow).

cm proximal to the ileocecal valve (Figure 2A), which we treated by argon plasma coagulation (low power, 10 Watt) and then tattooed (Figure 2B). No other lesion was identified. At the end of the procedure (total procedural time: 74 min), the patient was asymptomatic and his vital parameters were stable. Then, 12 h later, he reported a dull, ill-defined abdominal pain and a physical examination was unremarkable. However, laboratory tests showed a decrease of 2 g/dL in the hemoglobin concentration in the absence of overt hematochezia. An urgent contrast enhanced computerized tomography (CT) scan revealed a grade IV splenic injury with active bleeding (Figure 3), according to the American Association for the Surgery of Trauma classification^[7]. Because of the high injury severity score, operative management was performed^[8]. Hemoperitoneum and splenic capsular laceration was confirmed during surgery, and splenectomy and segmental ileal resection of the tattooed ileal region was carried out. The choice to make an ileal resection was dictated based on the high re-bleeding rate after endoscopic thermo-ablation of angioectasia^[9]. The patient was discharged 14 d later in good health and was administered oral warfarin. Then, two months later, he returned to the hospital because of further gastrointestinal bleeding and anemia. Colonoscopy confirmed red blood in the colonic lumen, without any evidence of active bleeding; an upper endoscopy was normal. He was transfused and treated with somatostatin infusion. After confirming that the bleeding had stopped, he was discharged and prescribed subcutaneous long-acting octreotide (20 mg, monthly). No additional transfusions were required during the six-month follow-up period.

DISCUSSION

To date, no case of splenic rupture after DE has been reported in the English language literature. The rate of occurrence of splenic injury following colonoscopy is very low, but it may be underestimated because of a reluctance to report unfavorable outcomes^[10]. In a population-based study, Cooper *et al.*^[11] reported 12 splenic injuries among 165527 procedures. However,

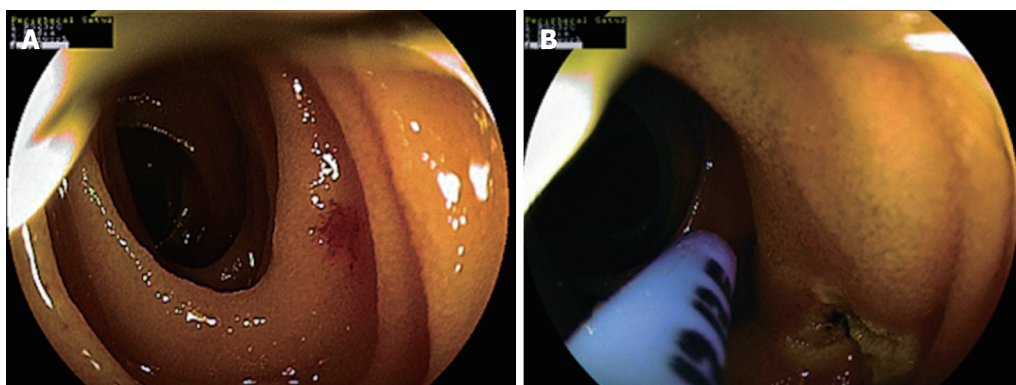


Figure 2 Retrograde double-balloon enteroscopy showing an ileal type 1b lesion before (A) and after (B) thermo-ablative therapy.

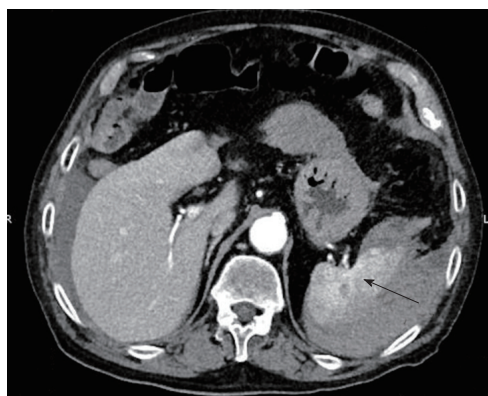


Figure 3 Contrast enhanced abdominal computerized tomography showing peritoneal blood and active bleeding from a ruptured spleen (arrow).

the complication rate with any endoscopic procedure is generally low, so a large number of DE need to be performed to determine the complication rate of such a relatively new invasive procedure. It is conceivable that R-DBE, which is a more invasive and less frequently performed procedure than colonoscopy, may carry a higher risk of splenic injury.

In our unit, beginning in 2006, we have performed a mean of 22 DBE/year, mostly by an antegrade approach; however, a single operator (CMG) recently performed 15 consecutive therapeutic R-DBE procedures without any complications. Although a learning curve has not yet been established for R-DBE, Mehdizadeh *et al.*^[12] suggest a minimum of 20 procedures to learn to maintain ileal access through the ileocecal valve and reduce procedure times.

Splenic injury complicating gastrointestinal endoscopy may result from either direct trauma or excessive traction on the splenocolic ligament that occurs during the maneuvers required for instrument advancement. Several risk factors have been postulated and categorized as endoscopist-dependent (scope straightening, hooking the splenic flexure, alpha maneuver, and excessive hurry) or patient-dependent (female gender, smoking, anticoagulation, splenomegaly, pre-existing spleen disease, and adhesions)^[13-15].

Interestingly, the most predictive diagnostic indicator of splenic injury was found to be an unexplained decrease in hemoglobin greater than 3 g/dL after endoscopy rather than procedural difficulties^[3]. Deep sedation may be related to a delayed diagnosis of this complication^[11]. Nearly all colonoscopic splenic injuries require surgical intervention, with a mortality rate of 5%^[13]. With regard to DBE, two retrospective series of 40 and 41 patients older than 70 and 65 years, respectively, did not show a complication rate that was higher than that seen in younger patients^[16,17]. In our present case, chronic oral anticoagulation, several colonoscopies performed before R-DBE, and mild splenomegaly (resulting from subclinical prosthesis-related mechanical hemolysis) likely contributed to the pathogenesis of this complication.

In conclusion, we have reported the first case of splenic rupture after therapeutic R-DBE. Careful clinical observation after such procedures is strongly advisable to promptly recognize and treat this rare but dreadful endoscopic complication.

COMMENTS

Case characteristic

An 85-year-old man on chronic warfarin underwent successful retrograde double-balloon enteroscopy for bleeding control of an ileal angiodysplasia, diagnosed on a previous capsule endoscopy. Twelve hours following the procedure, the patient complained abdominal pain.

Clinical diagnosis

Acute abdomen following deep enteroscopy (DE).

Differential diagnosis

Intestinal perforation vs splenic injury.

Laboratory diagnosis

Decrease of 2 g/dL of blood hemoglobin level.

Imaging diagnosis

Hemoperitoneum and grade IV splenic injury on contrast enhanced computerized tomography.

Pathological diagnosis

Splenic capsular laceration and rupture of the spleen.

Treatment

Urgent splenectomy and ileal resection.

Related reports

Splenic rupture is a rare devastating complication of gastrointestinal endoscopy. Immediate or delayed splenic injury and rupture have mostly been reported following diagnostic and therapeutic colonoscopy. This is the first reported case of splenic rupture following retrograde DE.

Term explanation

Vascular lesions of the small bowel are classified by the Yano-Yamamoto classification. Type 1a: Punctulate erythema with or without oozing; type 1b: Patchy erythema with or without oozing; type 2a: Punctulate erythema with pulsatile bleeding; type 2b: Pulsatile red protrusion without surrounding venous dilatation; type 3: Pulsatile red protrusion with surrounding venous dilatation; type 4: Other lesions not classified into any of the above categories.

Experiences and lessons

Retrograde double-balloon enteroscopy can cause delayed splenic rupture. Careful clinical patient observation is recommended after this procedure. Abdominal pain along with hemoglobin decrease ≥ 2 g/dL following the procedure mandate urgent contrast enhanced abdominal computerized tomography.

Peer-review

The authors report a case of spleen injury after DE for the first time and underscore the importance of careful clinical observation for a patient, especially complaining of abdominal pain, after endoscopic examination in order to recognize and treat this potentially life-threatening complication as soon as possible. Thus, this report is very unique and instructive for many kinds of clinicians including endoscopists.

REFERENCES

- 1 **Zyromski NJ**, Camp CM. Splenic injury: a rare complication of endoscopic retrograde cholangiopancreatography. *Am Surg* 2004; **70**: 737-739 [PMID: 15328812]
- 2 **Aubrey-Bassler FK**, Sowers N. 613 cases of splenic rupture without risk factors or previously diagnosed disease: a systematic review. *BMC Emerg Med* 2012; **12**: 11 [PMID: 22889306 DOI: 10.1186/1471-227X-12-11]
- 3 **Singla S**, Keller D, Thirunavukarasu P, Tamandl D, Gupta S, Gaughan J, Dempsey D. Splenic injury during colonoscopy--a complication that warrants urgent attention. *J Gastrointest Surg* 2012; **16**: 1225-1234 [PMID: 22450952 DOI: 10.1007/s11605-012-1871-0]
- 4 **Pennazio M**, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for

- diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: 25826168 DOI: 10.1055/s-0034-1391855]
- 5 **May A**, Nachbar L, Schneider M, Neumann M, Ell C. Push-and-pull enteroscopy using the double-balloon technique: method of assessing depth of insertion and training of the enteroscopy technique using the Erlangen Endo-Trainer. *Endoscopy* 2005; **37**: 66-70 [PMID: 15657861]
- 6 **Yano T**, Yamamoto H, Sunada K, Miyata T, Iwamoto M, Hayashi Y, Arashiro M, Sugano K. Endoscopic classification of vascular lesions of the small intestine (with videos). *Gastrointest Endosc* 2008; **67**: 169-172 [PMID: 18155439]
- 7 **Moore EE**, Shackford SR, Pachter HL, McAninch JW, Browner BD, Champion HR, Flint LM, Gennarelli TA, Malangoni MA, Ramenofsky ML. Organ injury scaling: spleen, liver, and kidney. *J Trauma* 1989; **29**: 1664-1666 [PMID: 2593197]
- 8 **Siriratsivawong K**, Zenati M, Watson GA, Harbrecht BG. Nonoperative management of blunt splenic trauma in the elderly: does age play a role? *Am Surg* 2007; **73**: 585-589; discussion 590 [PMID: 17658096]
- 9 **May A**, Friesing-Sosnik T, Manner H, Pohl J, Ell C. Long-term outcome after argon plasma coagulation of small-bowel lesions using double-balloon enteroscopy in patients with mid-gastrointestinal bleeding. *Endoscopy* 2011; **43**: 759-765 [PMID: 21544778 DOI: 10.1055/s-0030-1256388]
- 10 **Lawton R**, Parker D. Barriers to incident reporting in a healthcare system. *Qual Saf Health Care* 2002; **11**: 15-18 [PMID: 12078362]
- 11 **Cooper GS**, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med* 2013; **173**: 551-556 [PMID: 23478904 DOI: 10.1001/jamainternmed.2013.2908]
- 12 **Mehdizadeh S**, Han NJ, Cheng DW, Chen GC, Lo SK. Success rate of retrograde double-balloon enteroscopy. *Gastrointest Endosc* 2007; **65**: 633-639 [PMID: 17383460]
- 13 **Skipworth JR**, Raptis DA, Rawal JS, Olde Damink S, Shankar A, Malago M, Imber C. Splenic injury following colonoscopy--an underdiagnosed, but soon to increase, phenomenon? *Ann R Coll Surg Engl* 2009; **91**: W6-11 [PMID: 19416579 DOI: 10.1308/147870809X400994]
- 14 **Lalor PF**, Mann BD. Splenic rupture after colonoscopy. *JSLs* 2007; **11**: 151-156 [PMID: 17651580]
- 15 **Rao KV**, Beri GD, Sterling MJ, Salen G. Splenic injury as a complication of colonoscopy: a case series. *Am J Gastroenterol* 2009; **104**: 1604-1605 [PMID: 19491881 DOI: 10.1038/ajg.2009.94]
- 16 **Sidhu R**, Sanders DS. Double-balloon enteroscopy in the elderly with obscure gastrointestinal bleeding: safety and feasibility. *Eur J Gastroenterol Hepatol* 2013; **25**: 1230-1234 [PMID: 23751353 DOI: 10.1097/MEG.0b013e3283630f1b]
- 17 **Choi DH**, Jeon SR, Kim JO, Kim HG, Lee TH, Lee WC, Kang BS, Cho JH, Jung Y, Kim WJ, Ko BM, Cho JY, Lee JS, Lee MS. Double-balloon enteroscopy in elderly patients: is it safe and useful? *Intest Res* 2014; **12**: 313-319 [PMID: 25374498 DOI: 10.5217/ir.2014.12.4.313]

P- Reviewer: Akyuz F, Ogata H, Soria F, Tsujikawa T, Urbain D

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 May 25; 8(10): 395-417





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

MINIREVIEWS

- 395 Comparison of endoscopic papillary balloon dilatation and endoscopic sphincterotomy for bile duct stones
Sakai Y, Tsuyuguchi T, Sugiyama H, Hayashi M, Senoo J, Kusakabe Y, Yasui S, Mikata R, Yokosuka O

ORIGINAL ARTICLE

Retrospective Cohort Study

- 402 Safety of direct endoscopic necrosectomy in patients with gastric varices
Storm AC, Thompson CC
- 409 Place of upper endoscopy before and after bariatric surgery: A multicenter experience with 3219 patients
Abd Ellatif ME, Alfalah H, Asker WA, El Nakeeb AE, Magdy A, Thabet W, Gheith MA, Abdallah E, Shahin R, Shoma A, Dawoud IE, Abbas A, Salama AF, Ali Gamal M

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 10 May 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Francis Seow-Choen, FRCS (Ed), Director, Surgeon, Seow-Choen Colorectal Surgery, Fortis Colorectal Hospital, Singapore 238859, Singapore

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Shui Qiu*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerías Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE
May 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Comparison of endoscopic papillary balloon dilatation and endoscopic sphincterotomy for bile duct stones

Yuji Sakai, Toshio Tsuyuguchi, Harutoshi Sugiyama, Masahiro Hayashi, Jun-ichi Senoo, Yuko Kusakabe, Shin Yasui, Rintaro Mikata, Osamu Yokosuka

Yuji Sakai, Toshio Tsuyuguchi, Harutoshi Sugiyama, Masahiro Hayashi, Jun-ichi Senoo, Yuko Kusakabe, Shin Yasui, Rintaro Mikata, Osamu Yokosuka, Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Chiba 260-8670, Japan

Author contributions: Sakai Y, Tsuyuguchi T and Yokosuka O were responsible for manuscript preparation; Sakai Y wrote the paper; Sugiyama H, Hayashi M, Senoo J, Kusakabe Y, Yasui S and Mikata R were responsible for references collection.

Conflict-of-interest statement: The authors have no other disclosures.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Yuji Sakai, MD, Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan. sakai4754@yahoo.co.jp
Telephone: +81-43-2262083
Fax: +81-43-2262088

Received: February 18, 2016
Peer-review started: February 21, 2016
First decision: March 9, 2016
Revised: March 17, 2016
Accepted: April 7, 2016
Article in press: April 11, 2016
Published online: May 25, 2016

Abstract

Endoscopic treatment for bile duct stones is low-invasive

and currently considered as the first choice of the treatment. For the treatment of bile duct stones, papillary treatment is necessary, and the treatments used at the time are broadly classified into two types; endoscopic papillary balloon dilatation where bile duct closing part is dilated with a balloon and endoscopic sphincterotomy (EST) where bile duct closing part is incised. Both procedures have advantages and disadvantages. Golden standard is EST, however, there are patients with difficulty for EST, thus we must select the procedure based on understanding of the characteristics of the procedure, and patient backgrounds.

Key words: Bile duct stones; Endoscopic papillary balloon dilatation; Endoscopic sphincterotomy; Endoscopic retrograde cholangiopancreatography; Post endoscopic retrograde cholangiopancreatography pancreatitis

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: For the treatment of the bile duct stones, it is necessary to perform papillary treatment, and the treatment used at the time are broadly classified into two groups such as endoscopic papillary balloon dilatation and endoscopic sphincterotomy (EST). Golden standard is EST, however, there are patients with difficulty for EST, thus we must select the procedure based on understanding of the characteristics of the procedure, and patient backgrounds.

Sakai Y, Tsuyuguchi T, Sugiyama H, Hayashi M, Senoo J, Kusakabe Y, Yasui S, Mikata R, Yokosuka O. Comparison of endoscopic papillary balloon dilatation and endoscopic sphincterotomy for bile duct stones. *World J Gastrointest Endosc* 2016; 8(10): 395-401 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i10/395.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i10.395>

INTRODUCTION

Currently, the treatment for the bile duct stones are widely conducted with endoscopic treatment as the first choice^[1]. Advantages of endoscopic treatment when compared with the surgery lie in that it can cope with promptly even at the emergent time and it is possible to perform the treatment low-invasively with less human power in a short period of time. Percutaneous transhepatic approach exists, too, but I have long time for treatment and am not performed very much because a maneuver is complicated. The papillary treatment conducted at the time includes endoscopic papillary balloon dilatation (EPBD) and endoscopic sphincterotomy (EST). Although EST is the golden standard procedure, there are patients who are indicated for EPBD. This report describes treatment success rate, procedural accidents, long term prognosis, and indication of EPBD and EST for the bile duct stones.

HISTORY OF EPBD AND EST

EPBD is the procedure reported by Staritz *et al.*^[2] in 1982. Then during 1990's Mac Mathuna *et al.*^[3] and Komatsu *et al.*^[4] have reported. However, it has scarcely been used in Western countries because of problems of postoperative pancreatitis, whereas EST has been used for 40 years or longer after reported by Kawai *et al.*^[5] and Classen *et al.*^[6] in 1974, and currently it has become established as the first choice of endoscopic treatment method for bile duct stones all over the world.

INDICATION OF EPBD AND EST

Based on advantages and disadvantages of EPBD and EST, their respective good indication and points to notice are described. Basically, EST is the first choice, however, patients with liver cirrhosis, blood disease, or patients undergoing anticoagulant therapy or dialysis who have bleeding tendency or patients who are treated with Billroth-II method or gastric bypass with Roux en Y Reconstruction and have anatomical difficulty in undergoing EST are good indications of EPBD^[7,8]. On the other hand, in patients who underwent pancreatography which is considered as high risk factor of post-EPBD pancreatitis, indication must be carefully examined^[9]. In using the mechanical crushing tool for a number of stones or giant stones, it becomes necessary to repeatedly insert the basket balloon catheter into the bile duct for lithotomy. In EPBD, the bile duct opening is not so dilated, thus due to papillary edema, it becomes difficult to insert the treatment tool in the early stage, leading to high frequency of the erroneous insertion into the pancreatic duct. It is considered that incidence of

post-EPBD pancreatitis is high in the younger people, however we hesitate to eliminate the papillary function by conducting EST, considering long term prognosis. There is a report of the study including only 5 patients which describes that bile duct stones in the children were safely and effectively treated with EPBD^[10]. If the treatment can be done more safely by device of safer procedure, indication for EPBD may spread.

ACTUAL PROCEDURE OF EPBD AND EST

The difference between EPBD and EST lies in dilation method of the bile duct closing part of the duodenal papilla, one dilates by dilatating with the balloon and the other dilates by incising with a sphincterotome. In EPBD, once the guidewire can be inserted into the bile duct, the balloon catheter is selected by conforming bile duct diameter through this guidewire, and inserted for dilatation, thus easy by far when compared with EST in terms of the procedure. In EPBD, the bile duct opening of the papilla is not cut and dilated as in EST, thus function of sphincter of Oddi is conserved to some degree. However, on the other hand, insertion of a stone harvesting and crushing tool is more difficult than EST because bile duct opening is small. Furthermore stones around 10 mm in size which can be removed in EST without any treatment cannot be removed in EPBD if they are not crushed with the mechanical lithotripsy tool. In EST, incision is conducted by adjusting the position of the scope with the blade of sphincterotome in the direction of 11-12 o'clock. The procedure must be conducted always paying attention to insertion angle, depth, direction of blade, and incising speed of a sphincterotome into the papilla because risk of perforation and bleeding is high differently from balloon dilatation, thus difficulty level of the procedure is high.

TREATMENT RESULTS OF EPBD AND EST

The results of comparison test on EPBD and EST reported up to the present are described (Table 1)^[11-24]. High complete stone removal rate of 90% or greater is obtained by both methods in a number of reports, and based on these results, it can be determined that final treatment success rate is almost the same. On the other hand, as to procedural accidents, there are reports describing that pancreatitis^[18-20,24] was observed in EPBD, whereas bleeding^[19-21] in EST, and each frequency is high. In particular, in multi-center study conducted in United States, death case due to post-EPBD pancreatitis was observed, which led to that EPBD has been scarcely conducted in Western countries^[20]. As the risk factor of post-EPBD pancreatitis, young people, past history of pancreatitis, no dilated bile duct (9 mm or less), use of the mechanical lithotripsy tool, and pancreatography are reported up to the present^[9,25-28]. As the measure

Table 1 Short term treatment results of endoscopic papillary balloon dilatation and endoscopic sphincterotomy

Ref.	Sample size (EPBD/EST)	Indication	Complete stone removal	Early procedural accident (whole)	Pancreatitis	Mild	Moderate	Severe	Cholecystitis	Cholangitis	Bleeding	Perforation	Basket impaction
Minami <i>et al</i> ^[11]	20/20	No limit	100% /100%	10% /10%	10% /10%	-	-	-	-	-	-	-	-
Bergman <i>et al</i> ^[12]	101/101	No limit	89% /91%	17% /24%	6.9% /6.9%	-	-	-	-	-	0% /4.0%	2.0% /1.0%	-
Ochi <i>et al</i> ^[13]	55/55	Diameter < 15 mm, number < 10	98.1% /92.7%	2.0% /5.6%	0% /3.7%	0% /0%	0% /3.7%	0% /0%	-	-	-	0% /1.9%	-
Yasuda <i>et al</i> ^[14]	35/35	No limit	100% /100%	5.7% /8.6%	5.7% /5.7%	5.7% /5.7%	0% /0%	0% /0%	-	-	0% /2.9%	-	-
Arnold <i>et al</i> ^[15]	30/30	Diameter < 20 mm, number < 5	77% /100% ¹	30.0% /16.7%	20% /10%	13.3% /10%	0% /0%	6.7% /0%	-	10% /0%	0% /6.7%	-	-
Natsui <i>et al</i> ^[16]	70/70	No limit	92.9% /98.6%	10.0% /11.4%	5.7% /4.3%	5.7% /4.3%	-	-	-	2.9% /4.3%	0% /2.9%	-	1.4% /0%
Vlavianos <i>et al</i> ^[17]	103/99	No limit	87.4% /86.9%	6.8% /3.0%	4.9% /1.0%	1.9% /0%	1.9% /1.0%	1.0% /0%	-	1.9% /1.0%	-	-	-
Fujita <i>et al</i> ^[18]	138/144	Diameter < 14 mm	99.3% /100%	14.5% /11.8%	10.9% /2.8% ¹	8.7% /2.1%	2.2% /0.7%	9% /0%	2.2% /4.2%	1.4% /4.2%	0% /1.4%	-	0.7% /0.7%
Baron <i>et al</i> ^[19]	552/554	Meta-analysis	94% /96%	10.4% /10.3%	7.4% /4.3% ¹	-	-	-	2.7% /3.6%	-	0% /2.0% ¹	0.4% /0.4%	-
Disario <i>et al</i> ^[20]	117/120	Diameter < 10 mm, number < 4	97.4% /92.5%	17.9% /3.3% ¹	10.3% /0.8% ¹	-	-	5.1% /0%	0% /0.8%	0.9% /0.8%	10.5% /27.0% ¹	0% /0.8%	-
Lin <i>et al</i> ^[21]	51/ 53	Diameter < 20 mm	94.1% /100%	-	-	-	-	-	-	-	2.0% /26.4% ¹	0% /0.8%	-
Takezawa <i>et al</i> ^[22]	46/45	No limit	100% /100%	0% /0%	-	-	-	-	-	-	-	-	-
Tanaka <i>et al</i> ^[23]	16/16	No limit	100% /100%	18.8% /25.0%	18.8% /18.8%	-	-	-	-	0% /12.5%	-	-	-
Watanabe <i>et al</i> ^[24]	90/90	No limit	86.6% /95.6%	14.4% /3.3% ¹	10.0% /2.2% ¹	8.9% /0%	1.1% /2.2%	-	-	3.3% /0%	1.1% /0%	-	1.1% /0%

¹ *P* < 0.05. EPBD: Endoscopic papillary balloon dilatation; EST: Endoscopic sphincterotomy.

to prevent onset of post-EPBD pancreatitis, intraoperative intravenous drip of isosorbide dinitrate with relaxant effect for the sphincter of Oddi^[29,30], postoperative papillary epinephrine spray to prevent papillary edema^[31], indwelling of pancreatic duct stent^[32] or endoscopic nasobiliary drainage^[33] are attempted and their respective usefulness is reported.

With regard to dilatation pressure and time of the balloon, it has been considered that dilatation at low pressure and short time gives less burden on the papilla and develops less postoperative papillary edema, thus is good for prevention of pancreatitis^[34], however, there appeared a report that longer dilatation time leads to less incidence of pancreatitis^[35,36], which we need to study hereafter.

PAPILLARY FUNCTION OF POST-EPBD AND POST-EST

Sato *et al*^[37] reported after conducting EPBD that significant decrease in bile duct inner pressure, papillary basic pressure, and papillary contraction pressure were observed at 1 wk after EPBD, whereas they were recovered to around the value before EPBD at 1 mo after. Minami *et al*^[11] examined inner pressure and measured papillary function before treatment and at 1 mo after in randomized controlled trial (RCT) comparing EST with EPBD, and reported that a significant decrease was observed in EST, whereas recovery was found without any significant difference in EPBD. Kawabe *et al*^[38] histologically studied the papillary finding of patients who underwent surgery after EPBD

Table 2 Comparison of long term prognosis between endoscopic papillary balloon dilatation and endoscopic sphincterotomy

Ref.	Sample size (EPBD/EST)	Follow-up period	Total	Stone recurrence	Cholangitis	Cholecystitis	Liver abscess	Biliary cancer
Bergman <i>et al</i> ^[12]	101/101	6 mo	18%/23%	7.9%/6.9%	-	1.3%/9.9%	0%/1.0%	-
Ochi <i>et al</i> ^[13]	51/54	Median 23 mo	3.9%/14.8%	3.9%/5.6%	3.9%/3.7%	3.3%/18.5%	-	-
Yasuda <i>et al</i> ^[14]	235/126	Median 37.4/36.3 mo	-	10%/14%	0%/3.2%	2.0%/8.8%	-	-
Natsui <i>et al</i> ^[16]	68/69	Median 30 mo	5.9%/8.7%	4.4%/4.3%	-	3.6%/7.9%	-	-
Vlavianos <i>et al</i> ^[17]	103 /99	12 mo	11.7%/15.2%	1.9%/3.0%	1.9%/1.0%	1.9%/2.0%	-	-
Lin <i>et al</i> ^[21]	51/53	Median 16 mo	-	5.9%/7.5%	-	-	-	-
Yasuda <i>et al</i> ^[51]	138 /144	Median 6.7 yr	10.1%/25.0% ¹	7.8%/17.4% ¹	0%/2.8%	5.5%/8.3%	0%/1.4%	0%/0.7%

¹P < 0.05. EPBD: Endoscopic papillary balloon dilatation; EST: Endoscopic sphincterotomy.

(2-63 wk after EPBD), and reported that breakage of the sphincter was found only in 1 patient at 3 wk after EPBD, and EPBD does not affect the papillary function. According to the above reports, it seems certain that in EPBD the papillary function is recovered in the comparatively early stage in most of patients. On the other hand, as to the report on the papilla and bile duct inner pressure after conducting EST, there are many reports of short term follow up whereas long term follow up is less. Ponce *et al*^[39] reported that papillary basic pressure disappeared immediately after EST, and bile duct inner pressure is also decreased, however, papillary basic pressure partly remains in some patients, which is considered to be related to incision length. Geenen *et al*^[40] conducted papillary inner pressure examination at 1 and 2 years after EST and reported that although bile duct inner pressure and papillary basic pressure disappeared even at 2 years after, height of papillary contracting wave was recovered at 2 years after, showing no significant difference when compared with before EST. According to report of Bergman *et al*^[41] on the study at 15-17 years after conducting EST, papillary basic pressure disappeared and papillary contracting wave disappeared in 75% of patients. Study by Sugiyama *et al*^[42] revealed that incision length by EST is contracted during the course and becomes the length of about 70% at 5 years after, and improvement of papillary function to some degree is expected in the long term. Although papillary basic pressure disappears in a large number of patients after EST, in part of patients with short incision length, it is presumed that remaining or recovery of papillary contracting wave is expected.

LONG TERM PROGNOSIS OF EPBD AND EST

As for long term prognosis after EPBD, Tsujino *et al*^[43] conducted the investigation including 837 patients with mean follow-up period of 4.4 years and reported that

stone recurrence was found in 8.8%, and cholecystitis was in 3.4%, whereas, as to long term prognosis after EST, it is reported that stone recurrence was found in 8.0%-12.3% and cholecystitis in 4.0%-6.7% during mean follow-up period of 6.2-15 years^[44-50]. These are reports by a single procedure. There are some comparative control studies on EPBD and EST (Table 2)^[12-14,16,17,21]. Bergman *et al*^[12] compared late complications until 6 mo after in RCT, and reported that cholecystitis occurred in 1.3% after EPBD, whereas 9.9% after EST, showing significant low rate in EPBD group. Ochi *et al*^[13] also reported that cholecystitis occurred in 3.3% after EPBD and 18.5% after EST during mean follow-up period of 23 mo, and if limited to patients with cholecyst conserved, its frequency was 4.5%, and 29.4%, respectively, showing significant difference^[13]. Yasuda *et al*^[14] conducted retrospective study on late complications in EST and EPBD, and reported that stone recurrence/cholangitis occurred in 10.0% for EPBD, and 17.2% for EST and cholecystitis occurred in 2.0% for EPBD, and 8.8% for EST during median follow-up period of about 3 years (12-67 mo), showing incidence was high in EST with significant difference. Furthermore, Yasuda *et al*^[51] reported the results of long term follow-up in patients of RCT^[18] studying the short term results of EPBD and EST^[51]. According to this, accumulated recurrence rate of stone recurrence/cholangitis was significantly higher after EST during median follow-up period of 6.7 years. These results suggest that whether papillary function can be conserved or not after treatment of the bile duct stones affects long term prognosis, particularly stone recurrence. In considering long term prognosis, a possibility is concerned that inflammation of the bile duct mucosa developed by back-flow of duodenal juice into the bile duct for a long time causes onset of cancer, particularly in patients who underwent EST. However, such a concern is denied by two population-based studies, and actually incidence of biliary cancer is as low as 0%-0.6% in the follow-up of mean 8-14 years after EST. Even in the follow-up of mean 4.4-9.3 years after EPBD, its incidence is

as low as 0%-0.2%, thus the relation between both papillary treatments and onset of biliary cancer may be negative^[52,53].

CONCLUSION

For the treatment of bile duct stones, it is necessary to conduct papillary treatment, and the treatment used at the time is broadly classified into two types; EPBD and EST. Golden standard is EST, however, since there are patients difficult in conducting EST, it is necessary to select the procedure based on understanding of the characteristics of the procedure and patients background.

REFERENCES

- 1 Sakai Y, Tsuyuguchi T, Sugiyama H, Nishikawa T, Tawada K, Saito M, Kurosawa J, Mikata R, Tada M, Ishihara T, Yokosuka O. Current situation of endoscopic treatment for common bile duct stones. *Hepatogastroenterology* 2012; **59**: 1712-1716 [PMID: 22389270 DOI: 10.5754/hge12048]
- 2 Staritz M, Ewe K, Meyer zum Büschenfelde KH. Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy. *Lancet* 1982; **1**: 1306-1307 [PMID: 6123047 DOI: 10.1016/S0140-6736(82)92873-2]
- 3 Mac Mathuna P, White P, Clarke E, Lennon J, Crowe J. Endoscopic sphincteroplasty: a novel and safe alternative to papillotomy in the management of bile duct stones. *Gut* 1994; **35**: 127-129 [PMID: 8307433 DOI: 10.1136/gut.35.1.127]
- 4 Komatsu Y, Kawabe T, Toda N, Ohashi M, Isayama M, Tateishi K, Sato S, Koike Y, Yamagata M, Tada M, Shiratori Y, Yamada H, Ithori M, Kawase T, Omata M. Endoscopic papillary balloon dilation for the management of common bile duct stones: experience of 226 cases. *Endoscopy* 1998; **30**: 12-17 [PMID: 9548037 DOI: 10.1055/s-2007-993721]
- 5 Kawai K, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. *Gastrointest Endosc* 1974; **20**: 148-151 [PMID: 4825160 DOI: 10.1016/S0016-5107(74)73914-1]
- 6 Classen M, Demling L. Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl). *Dtsch Med Wochenschr* 1974; **99**: 496-497 [PMID: 4835515 DOI: 10.1055/s-0028-1107790]
- 7 Kawabe T, Komatsu Y, Tada M, Toda N, Ohashi M, Shiratori Y, Omata M. Endoscopic papillary balloon dilation in cirrhotic patients: removal of common bile duct stones without sphincterotomy. *Endoscopy* 1996; **28**: 694-698 [PMID: 8934088 DOI: 10.1055/s-2007-1005579]
- 8 Takahara N, Isayama H, Sasaki T, Tsujino T, Toda N, Sasahira N, Mizuno S, Kawakubo K, Kogure H, Yamamoto N, Nakai Y, Hirano K, Tada M, Omata M, Koike K. Endoscopic papillary balloon dilation for bile duct stones in patients on hemodialysis. *J Gastroenterol* 2012; **47**: 918-923 [PMID: 22354661 DOI: 10.1007/s00535-012-0551-x]
- 9 Tsujino T, Isayama H, Komatsu Y, Ito Y, Tada M, Minagawa N, Nakata R, Kawabe T, Omata M. Risk factors for pancreatitis in patients with common bile duct stones managed by endoscopic papillary balloon dilation. *Am J Gastroenterol* 2005; **100**: 38-42 [PMID: 15654778 DOI: 10.1111/j.1572-0241.2005.40638.x]
- 10 Osanai M, Maguchi H, Takahashi K, Katanuma A, Yane K, Kaneko M, Hashigo S, Katoh S, Harada R, Katoh R, Tanno S. Safety and long-term outcomes of endoscopic papillary balloon dilation in children with bile duct stones. *Gastrointest Endosc* 2011; **73**: 619-623 [PMID: 21237459 DOI: 10.1016/j.gie.2010.10.051]
- 11 Minami A, Nakatsu T, Uchida N, Hirabayashi S, Fukuma H, Morshed SA, Nishioka M. Papillary dilation vs sphincterotomy in endoscopic removal of bile duct stones. A randomized trial with manometric function. *Dig Dis Sci* 1995; **40**: 2550-2554 [PMID: 8536511 DOI: 10.1007/BF02220440]
- 12 Bergman JJ, Rauws EA, Fockens P, van Berkel AM, Bossuyt PM, Tijssen JG, Tytgat GN, Huibregtse K. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bile duct stones. *Lancet* 1997; **349**: 1124-1129 [PMID: 9113010 DOI: 10.1016/S0140-6736(96)11026-6]
- 13 Ochi Y, Mukawa K, Kiyosawa K, Akamatsu T. Comparing the treatment outcomes of endoscopic papillary dilation and endoscopic sphincterotomy for removal of bile duct stones. *J Gastroenterol Hepatol* 1999; **14**: 90-96 [PMID: 10029284 DOI: 10.1046/j.1440-1746.1999.01798.x]
- 14 Yasuda I, Tomita E, Enya M, Kato T, Moriwaki H. Can endoscopic papillary balloon dilation really preserve sphincter of Oddi function? *Gut* 2001; **49**: 686-691 [PMID: 11600473 DOI: 10.1136/gut.49.5.686]
- 15 Arnold JC, Benz C, Martin WR, Adamek HE, Riemann JF. Endoscopic papillary balloon dilation vs. sphincterotomy for removal of common bile duct stones: a prospective randomized pilot study. *Endoscopy* 2001; **33**: 563-567 [PMID: 11473325 DOI: 10.1055/s-2001-15307]
- 16 Natsui M, Narisawa R, Motoyama H, Hayashi S, Seki K, Wakabayashi H, Itoh S, Asakura H. What is an appropriate indication for endoscopic papillary balloon dilation? *Eur J Gastroenterol Hepatol* 2002; **14**: 635-640 [PMID: 12072597 DOI: 10.1097/00042737-200206000-00008]
- 17 Vlavianos P, Chopra K, Mandalia S, Anderson M, Thompson J, Westaby D. Endoscopic balloon dilatation versus endoscopic sphincterotomy for the removal of bile duct stones: a prospective randomised trial. *Gut* 2003; **52**: 1165-1169 [PMID: 12865276 DOI: 10.1136/gut.52.8.1165]
- 18 Fujita N, Maguchi H, Komatsu Y, Yasuda I, Hasebe O, Igarashi Y, Murakami A, Mukai H, Fujii T, Yamao K, Maeshiro K. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: A prospective randomized controlled multicenter trial. *Gastrointest Endosc* 2003; **57**: 151-155 [PMID: 12556774 DOI: 10.1067/mge.2003.56]
- 19 Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. *Am J Gastroenterol* 2004; **99**: 1455-1460 [PMID: 15307859 DOI: 10.1111/j.1572-0241.2004.30151.x]
- 20 Disario JA, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, Morales TG, Hixson LJ, Sherman S, Lehman GA, Jamal MM, Al-Kawas FH, Khandelwal M, Moore JP, Derfus GA, Jamidar PA, Ramirez FC, Ryan ME, Woods KL, Carr-Locke DL, Alder SC. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004; **127**: 1291-1299 [PMID: 15520997 DOI: 10.1053/j.gastro.2004.07.017]
- 21 Lin CK, Lai KH, Chan HH, Tsai WL, Wang EM, Wei MC, Fu MT, Lo CC, Hsu PI, Lo GH. Endoscopic balloon dilatation is a safe method in the management of common bile duct stones. *Dig Liver Dis* 2004; **36**: 68-72 [PMID: 14971818 DOI: 10.1016/j.dld.2003.09.014]
- 22 Takezawa M, Kida Y, Kida M, Saigenji K. Influence of endoscopic papillary balloon dilation and endoscopic sphincterotomy on sphincter of oddi function: a randomized controlled trial. *Endoscopy* 2004; **36**: 631-637 [PMID: 15243887 DOI: 10.1055/s-2004-814538]
- 23 Tanaka S, Sawayama T, Yoshioka T. Endoscopic papillary balloon dilation and endoscopic sphincterotomy for bile duct stones: long-term outcomes in a prospective randomized controlled trial. *Gastrointest Endosc* 2004; **59**: 614-618 [PMID: 15114302 DOI: 10.1016/S0016-5107(04)00157-9]
- 24 Watanabe H, Yoneda M, Tominaga K, Monma T, Kanke K, Shimada T, Terano A, Hiraishi H. Comparison between endoscopic papillary balloon dilatation and endoscopic sphincterotomy for the treatment of common bile duct stones. *J Gastroenterol* 2007; **42**:

- 56-62 [PMID: 17322994 DOI: 10.1007/s00535-006-1969-9]
- 25 **Sugiyama M**, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for acute pancreatitis and hyperamylasemia after endoscopic papillary balloon dilation. *Gastrointest Endosc* 2003; **57**: 531-535 [PMID: 12665764 DOI: 10.1067/mge.2003.143]
 - 26 **Sugiyama M**, Abe N, Izumisato Y, Masaki T, Mori T, Atomi Y. Risk factors for acute pancreatitis after endoscopic papillary balloon dilation. *Hepatogastroenterology* 2003; **50**: 1796-1798 [PMID: 14696407]
 - 27 **Shin CS**. Endoscopic papillary balloon dilation for removal of common bile duct stones. *Dig Endosc* 2003; **15**: 1-6 [DOI: 10.1046/j.1443-1661.2003.00213.x]
 - 28 **Tsujino T**, Yoshida H, Isayama H, Ito Y, Yashima Y, Yagioka H, Kogure H, Sasaki T, Arizumi T, Togawa O, Matsubara S, Nakai Y, Sasahira N, Hirano K, Tada M, Kawabe T, Omata M, Koike K. Endoscopic papillary balloon dilation for bile duct stone removal in patients 60 years old or younger. *J Gastroenterol* 2010; **45**: 1072-1079 [PMID: 20467759 DOI: 10.1007/s00535-010-0254-0]
 - 29 **Minami A**, Maeta T, Kohi F, Nakatsu T, Morshed SA, Nishioka M. Endoscopic papillary dilation by balloon and isosorbide dinitrate drip infusion for removing bile duct stone. *Scand J Gastroenterol* 1998; **33**: 765-768 [PMID: 9712243 DOI: 10.1080/00365529850171738]
 - 30 **Nakagawa H**. Comparing balloon diameter on performing endoscopic papillary balloon dilation with dinitrate drip infusion for removal of bile duct stones. *Dig Endosc* 2004; **16**: 289-294 [DOI: 10.1111/j.1443-1661.2004.00405.x]
 - 31 **Ohashi A**, Tamada K, Tomiyama T, Wada S, Higashizawa T, Gotoh Y, Satoh Y, Miyata T, Tano S, Ido K, Sugano K. Epinephrine irrigation for the prevention of pancreatic damage after endoscopic balloon sphincteroplasty. *J Gastroenterol Hepatol* 2001; **16**: 568-571 [PMID: 11350556 DOI: 10.1046/j.1440-1746.2001.02483.x]
 - 32 **Aizawa T**, Ueno N. Stent placement in the pancreatic duct prevents pancreatitis after endoscopic sphincter dilation for removal of bile duct stones. *Gastrointest Endosc* 2001; **54**: 209-213 [PMID: 11474392 DOI: 10.1067/mge.2001.115730]
 - 33 **Sato D**, Shibahara T, Miyazaki K, Matsui H, Yanaka A, Nakahara A, Tanaka N. Efficacy of endoscopic nasobiliary drainage for the prevention of pancreatitis after papillary balloon dilatation: a pilot study. *Pancreas* 2005; **31**: 93-97 [PMID: 15968255 DOI: 10.1097/01.mpa.0000163175.52297.a6]
 - 34 **Tsujino T**, Kawabe T, Isayama H, Sasaki T, Kogure H, Togawa O, Arizumi T, Ito Y, Matsubara S, Yamamoto N, Nakai Y, Sasahira N, Hirano K, Toda N, Komatsu Y, Tada M, Yoshida H, Omata M. Efficacy and safety of low-pressured and short-time dilation in endoscopic papillary balloon dilation for bile duct stone removal. *J Gastroenterol Hepatol* 2008; **23**: 867-871 [PMID: 18086110 DOI: 10.1111/j.1440-1746.2007.05267.x]
 - 35 **Liao WC**, Lee CT, Chang CY, Leung JW, Chen JH, Tsai MC, Lin JT, Wu MS, Wang HP. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. *Gastrointest Endosc* 2010; **72**: 1154-1162 [PMID: 20869710 DOI: 10.1016/j.gie.2010.07.009]
 - 36 **Liao WC**, Tu YK, Wu MS, Wang HP, Lin JT, Leung JW, Chien KL. Balloon dilation with adequate duration is safer than sphincterotomy for extracting bile duct stones: a systematic review and meta-analyses. *Clin Gastroenterol Hepatol* 2012; **10**: 1101-1109 [PMID: 22642953 DOI: 10.1016/j.cgh.2012.05.017]
 - 37 **Sato H**, Kodama T, Takaaki J, Tatsumi Y, Maeda T, Fujita S, Fukui Y, Ogasawara H, Mitsufuji S. Endoscopic papillary balloon dilatation may preserve sphincter of Oddi function after common bile duct stone management: evaluation from the viewpoint of endoscopic manometry. *Gut* 1997; **41**: 541-544 [PMID: 9391256 DOI: 10.1136/gut.41.4.541]
 - 38 **Kawabe T**, Komatsu Y, Isayama H, Takemura T, Toda N, Tada M, Imai Y, Shiratori Y, Omata M. Histological analysis of the papilla after endoscopic papillary balloon dilation. *Hepatogastroenterology* 2003; **50**: 919-923 [PMID: 12845950]
 - 39 **Ponce J**, Sala T, Pertejo V, Pina R, Berenguer J. Manometric evaluation of sphincter of Oddi after endoscopic sphincterotomy, and in patients with previous surgical sphincterotomy. *Endoscopy* 1983; **15**: 249-251 [PMID: 6884282 DOI: 10.1055/s-2007-1021524]
 - 40 **Geenen JE**, Toouli J, Hogan WJ, Dodds WJ, Stewart ET, Mavrelis P, Riedel D, Venu R. Endoscopic sphincterotomy: follow-up evaluation of effects on the sphincter of Oddi. *Gastroenterology* 1984; **87**: 754-758 [PMID: 6468866]
 - 41 **Bergman JJ**, van Berkel AM, Groen AK, Schoeman MN, Offerhaus J, Tytgat GN, Huibregtse K. Biliary manometry, bacterial characteristics, bile composition, and histologic changes fifteen to seventeen years after endoscopic sphincterotomy. *Gastrointest Endosc* 1997; **45**: 400-405 [PMID: 9165322 DOI: 10.1016/S0016-5107(97)70151-2]
 - 42 **Sugiyama M**, Atomi Y. Longterm effects of endoscopic sphincterotomy on gall bladder motility. *Gut* 1996; **39**: 856-859 [PMID: 9038669 DOI: 10.1136/gut.39.6.856]
 - 43 **Tsujino T**, Kawabe T, Komatsu Y, Yoshida H, Isayama H, Sasaki T, Kogure H, Togawa O, Arizumi T, Matsubara S, Ito Y, Nakai Y, Yamamoto N, Sasahira N, Hirano K, Toda N, Tada M, Omata M. Endoscopic papillary balloon dilation for bile duct stone: immediate and long-term outcomes in 1000 patients. *Clin Gastroenterol Hepatol* 2007; **5**: 130-137 [PMID: 17234559 DOI: 10.1016/j.cgh.2006.10.013]
 - 44 **Bergman JJ**, van der Mey S, Rauws EA, Tijssen JG, Gouma DJ, Tytgat GN, Huibregtse K. Long-term follow-up after endoscopic sphincterotomy for bile duct stones in patients younger than 60 years of age. *Gastrointest Endosc* 1996; **44**: 643-649 [PMID: 8979051 DOI: 10.1016/S0016-5107(96)70045-7]
 - 45 **Tanaka M**, Takahata S, Konomi H, Matsunaga H, Yokohata K, Takeda T, Utsunomiya N, Ikeda S. Long-term consequence of endoscopic sphincterotomy for bile duct stones. *Gastrointest Endosc* 1998; **48**: 465-469 [PMID: 9831833 DOI: 10.1016/S0016-5107(98)70086-0]
 - 46 **Pereira-Lima JC**, Jakobs R, Winter UH, Benz C, Martin WR, Adamek HE, Riemann JF. Long-term results (7 to 10 years) of endoscopic papillotomy for choledocholithiasis. Multivariate analysis of prognostic factors for the recurrence of biliary symptoms. *Gastrointest Endosc* 1998; **48**: 457-464 [PMID: 9831832 DOI: 10.1016/S0016-5107(98)70085-9]
 - 47 **Saito M**, Tsuyuguchi T, Yamaguchi T, Ishihara T, Saisho H. Long-term outcome of endoscopic papillotomy for choledocholithiasis with cholecystolithiasis. *Gastrointest Endosc* 2000; **51**: 540-545 [PMID: 10805838 DOI: 10.1016/S0016-5107(00)70286-0]
 - 48 **Costamagna G**, Shah SK, Mutignani M, Tringali A, Alevras PP, Vamvakousis V, Racioppi M, D'Addessi A, Perri V. Use of a duodenoscope to manage complications at the ureteroileal anastomotic site after total urinary bladder resection and the Bricker procedure. *Gastrointest Endosc* 2002; **55**: 242-248 [PMID: 11818933 DOI: 10.1067/mge.2002.120888]
 - 49 **Sugiyama M**, Atomi Y. Risk factors predictive of late complications after endoscopic sphincterotomy for bile duct stones: long-term (more than 10 years) follow-up study. *Am J Gastroenterol* 2002; **97**: 2763-2767 [PMID: 12425545 DOI: 10.1111/j.1572-0241.2002.07019.x]
 - 50 **Ando T**, Tsuyuguchi T, Okugawa T, Saito M, Ishihara T, Yamaguchi T, Saisho H. Risk factors for recurrent bile duct stones after endoscopic papillotomy. *Gut* 2003; **52**: 116-121 [PMID: 12477771 DOI: 10.1136/gut.52.1.116]
 - 51 **Yasuda I**, Fujita N, Maguchi H, Hasebe O, Igarashi Y, Murakami A, Mukai H, Fujii T, Yamao K, Maeshiro K, Tada T, Tsujino T, Komatsu Y. Long-term outcomes after endoscopic sphincterotomy versus endoscopic papillary balloon dilation for bile duct stones. *Gastrointest Endosc* 2010; **72**: 1185-1191 [PMID: 20869711 DOI: 10.1016/j.gie.2010.07.006]
 - 52 **Karlson BM**, Ekbohm A, Arvidsson D, Yuen J, Krusemo UB. Population-based study of cancer risk and relative survival following sphincterotomy for stones in the common bile duct. *Br J Surg* 1997; **84**: 1235-1238 [PMID: 9313701 DOI: 10.1002/

- bjs.1800840911]
- 53 **Mortensen FV**, Jepsen P, Tarone RE, Funch-Jensen P, Jensen LS, Sørensen HT. Endoscopic sphincterotomy and long-term risk of

cholangiocarcinoma: a population-based follow-up study. *J Natl Cancer Inst* 2008; **100**: 745-750 [PMID: 18477806 DOI: 10.1093/jnci/djn102]

P- Reviewer: Li YY, Palermo M, Thomopoulos KC
S- Editor: Gong ZM **L- Editor:** A **E- Editor:** Wu HL



Retrospective Cohort Study

Safety of direct endoscopic necrosectomy in patients with gastric varices

Andrew C Storm, Christopher C Thompson

Andrew C Storm, Christopher C Thompson, Department of Medicine, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA 02115, United States

Author contributions: Storm AC collected data and authored the manuscript; Thompson CC devised study and performed critical review of the manuscript.

Institutional review board statement: Internal approval for data collection pertinent to this study was obtained.

Informed consent statement: Retrospectively collected data made informed consent infeasible.

Conflict-of-interest statement: Dr. Storm reports no conflicts of interest, Dr. Thompson is a consultant to Cook, Olympus and Boston Scientific.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Christopher C Thompson, MD, MHES, Department of Medicine, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, United States. ccthompson@partners.org
Telephone: +1-617-5258266
Fax: +1-617-5660338

Received: February 9, 2016

Peer-review started: February 9, 2016

First decision: March 9, 2016

Revised: March 16, 2016

Accepted: April 5, 2016

Article in press: April 6, 2016

Published online: May 25, 2016

Abstract

AIM: To determine the feasibility and safety of transgastric direct endoscopic necrosectomy (DEN) in patients with walled-off necrosis (WON) and gastric varices.

METHODS: A single center retrospective study of consecutive DEN for WON was performed from 2012 to 2015. All DEN cases with gastric fundal varices noted on endoscopy, computed tomography (CT) or magnetic resonance imaging (MRI) during the admission for DEN were collected for analysis. In all cases, external urethral sphincter (EUS) with doppler was used to exclude the presence of intervening gastric varices or other vascular structures prior to 19 gauge fine-needle aspiration (FNA) needle access into the cavity. The tract was serially dilated to 20 mm and was entered with an endoscope for DEN. Pigtail stents were placed to facilitate drainage of the cavity. Procedure details were recorded. Comprehensive chart review was performed to evaluate for complications and WON recurrence.

RESULTS: Fifteen patients who underwent DEN for WON had gastric varices at the time of their procedure. All patients had an INR < 1.5 and platelets > 50. Of these patients, 11 had splenic vein thrombosis and 2 had portal vein thrombosis. Two patients had isolated gastric varices, type 1 and the remaining 13 had > 5 mm gastric submucosal varices on imaging by CT, MRI or EUS. No procedures were terminated without completing the DEN for any reason. One patient had self-limited intraprocedural bleeding related to balloon dilation of the tract. Two patients experienced delayed bleeding at 2 and 5 d post-op respectively. One required no therapy or intervention and the other received 1

unit transfusion and had an EGD which revealed no active bleeding. Resolution rate of WON was 100% (after up to 2 additional DEN in one patient) and no patients required interventional radiology or surgical interventions.

CONCLUSION: In patients with WON and gastric varices, DEN using EUS and doppler guidance may be performed safely. Successful resolution of WON does not appear to be compromised by the presence of gastric varices, with similar rates of resolution and only minor bleeding events. Experienced centers should not consider gastric varices a contraindication to DEN.

Key words: Necrosectomy; Pancreatic necrosis; Endoscopy; Necrotizing pancreatitis; Gastric varices; Varices; Walled off necrosis; Walled-off necrosis; Gastrointestinal hemorrhage; Endoscopic ultrasound

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In this retrospective cohort, 15 out of 90 patients (16.7%) presenting for endoscopic necrosectomy had gastric varices. When performed with best practice technique, direct endoscopic necrosectomy may be safely performed in patients with gastric varices. The best practice technique, from Thompson *et al.* *Pancreatol*, 2015 includes: (1) EUS evaluation with doppler to confirm absence of intervening vessels; (2) injection of contrast to distend collection and create wall tension for access; (3) stiff guidewire looped in cavity to mark access site for duration of the case; (4) entry into the cavity with stiff balloon catheter dilated to 4-8 mm, then 20 mm; (5) exchange for a large-channel endoscope for lavage and debridement of necrosis; (6) placement of pigtail catheters for ongoing drainage of the cavity; and (7) avoid proton pump inhibitor to encourage ongoing digestion of necrotic material.

Storm AC, Thompson CC. Safety of direct endoscopic necrosectomy in patients with gastric varices. *World J Gastrointest Endosc* 2016; 8(10): 402-408 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i10/402.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i10.402>

INTRODUCTION

Pancreatic walled-off necrosis (WON) may result from acute necrotizing pancreatitis. Direct endoscopic necrosectomy (DEN) has emerged as the treatment of choice supported by high resolution and low complication rates for WON^[1-4]. In the patient with WON resulting from acute necrotizing pancreatitis, the presence of gastric varices must be carefully considered, as they may contribute to significant complications including intraprocedural and postprocedural hemorrhage. The prevalence of gastric varices in patients presenting for

DEN is unknown, however bleeding is the most common serious adverse event associated with the procedure^[1-3]. Gastric varices may be present in this patient population for at least two reasons, (1) local inflammation from necrotizing pancreatitis may result in splenic vein thrombosis and/or portal vein thrombosis leading to gastric variceal formation; or (2) a patient with alcoholic pancreatitis may have concomitant alcoholic cirrhosis leading to portal hypertension and development of gastric varices. Portal vein, splenic vein and mesenteric venous thrombosis is reported to occur in up to 53% of patients with severe acute necrotizing pancreatitis^[5,6]. It is therefore possible that the presence and associated procedural risk of gastric varices is underappreciated in this patient population.

Computed tomography (CT) is often used to evaluate the complications of acute pancreatitis and is also used in the pre-procedural evaluation for DEN. CT has been reported to be extremely sensitive at detection of submucosal gastric varices at up to 100%, with good interobserver variability ($\kappa = 0.90$) for both variceal diameter and location^[7]. While endoscopic evaluation outperforms external urethral sphincter (EUS) in detection of esophageal varices, data supports the opposite for detection of gastric varices, where EUS clearly outperforms the eye of the endoscopist^[8].

Non-endoscopic therapies for WON include open and minimally invasive surgical drainage, as well as percutaneous interventional radiology drainage. One randomized control trial comparing endoscopic to surgical necrosectomy found that composite clinical endpoints and inflammatory markers were improved with DEN over surgical drainage^[3]. Complications of surgical drainage may include intra-abdominal hemorrhage, which has been reported in 16%-44% of patients in surgical case series^[9-11]. Percutaneous catheter drainage, with the poorest clinical success rates among the interventional treatment modalities, has reported bleeding complications ranging from 2%-4%^[12,13].

As performance of DEN gains increasing popularity among gastroenterologists managing patients with symptomatic WON, it is important to determine relative and absolute contraindications to the procedure. The aim of this study is to determine the feasibility and safety of transgastric DEN in patients with WON and gastric varices, as this data is previously lacking.

MATERIALS AND METHODS

Population and outcomes

A single center retrospective study of consecutive DEN for WON was performed from 2012 to 2015. Patients were considered for DEN if they met radiographic criteria of a walled-off fluid collection along with presence of symptoms secondary to the collection, including; sepsis, abdominal pain, early satiety, intolerance of full oral diet, nausea and vomiting. All DEN cases with gastric

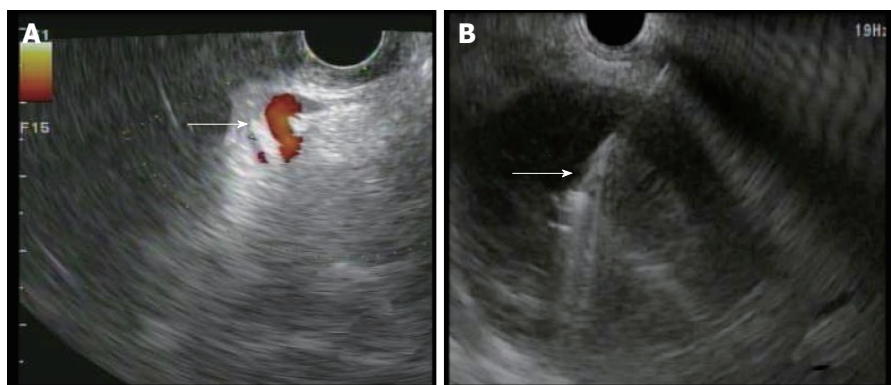


Figure 1 Endoscopic ultrasound of walled off necrosis. A: Doppler used to visualize any intervening vessels (arrow) including varices; B: FNA needle (arrow) seen entering necrotic cyst under EUS guidance. EUS: External urethral sphincter; FNA: Fine-needle aspiration.

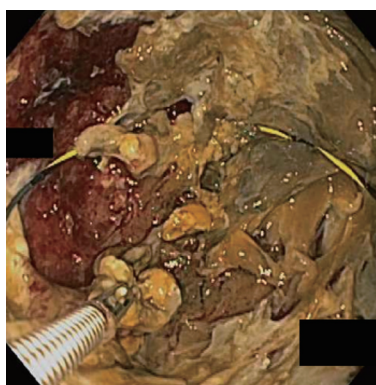


Figure 2 Endoscopic necrosectomy performed with debridement of the cyst cavity. Wire is seen coiled within the cyst to maintain access through the procedure.

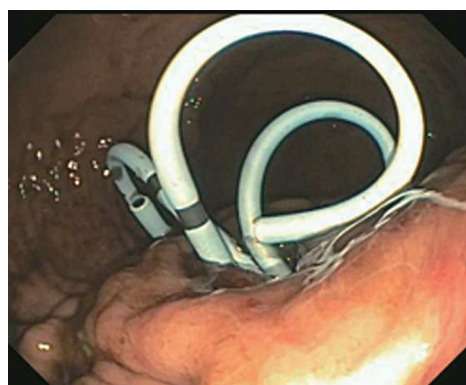


Figure 3 Pigtail stents left in place at the end of endoscopic necrosectomy to encourage ongoing drainage.

varices noted on endoscopy, CT or magnetic resonance imaging (MRI) during the admission for DEN were collected for analysis. Procedure characteristics including patient demographics, procedure characteristics, acute and delayed adverse events and clinical success were recorded. Clinical success was defined as complete resolution of the primary WON symptom leading to DEN, along with absence of any abdominal pain, early satiety, nausea, vomiting, markers of systemic inflammatory response (fever or hypothermia, leukocytosis or severe leukopenia, tachypnea, tachycardia) and bacteremia.

Direct endoscopic necrosectomy

In all cases, patients received general anesthesia and were intubated with endotracheal tube for mechanical ventilation and to provide airway protection. A linear EUS scope with color doppler (GIF-UC240P, Olympus, Tokyo, Japan) was used to exclude the presence of intervening gastric varices or other vascular structures prior to 19 gauge fine-needle aspiration (FNA) needle (Cook, Winston-Salem, NC) access into the cavity (Figure 1). Necrotic fluid was aspirated and sent for culture and gram stain. The cavity was injected with contrast for fluoroscopic visualization and to expand the cavity to compensate for the fluid previously removed. A stiff wire was advanced and coiled into the cavity

and the needle was removed. The tract was serially dilated starting with a 4-mm Hurricane balloon (Boston Scientific, Natick, MA) continuing up to 20 mm with a radially expanding through-the-scope balloon (Boston Scientific). The echoendoscope was then exchanged for a larger channel therapeutic endoscope (GIF XTQ-160 or GIF 2T-160, Olympus) that was used to perform the remaining maneuvers for DEN. This larger channel scope was used to suction out all fluid from the cavity, and then immediate attention was turned to physical debridement of the necrotic material along the cavity walls using various tools including endoscopic retrieval net, forceps and snares until all loose debris was removed (Figure 2). Next 1 to 2L of warmed bacitracin-laden saline solution (25000 UI/L) was used to lavage the cavity. Finally, two to three, 10 French double-pigtail stents (Cook) were placed at the end of the procedure to facilitate ongoing drainage of the cavity (Figure 3). All patients were given two to four weeks of systemic oral antibiotic prophylaxis. Stents, by protocol, were removed at 6-8 wk after placement if they did not spontaneously migrate in that period of time. Follow up procedures for delayed bleeding, repeat DEN or stent retrieval were performed as indicated. Repeat DEN was performed only if patient-reported symptoms of an ongoing fluid collection were present, at which time

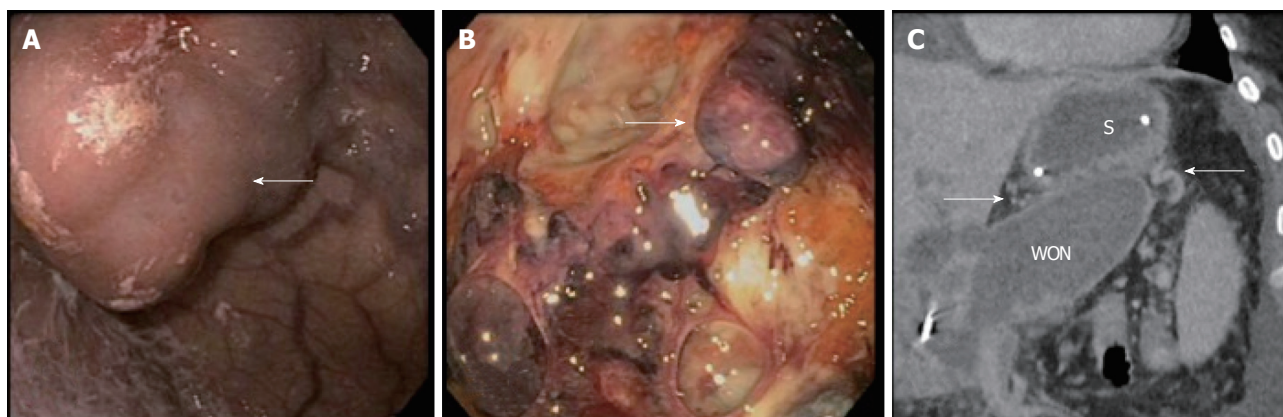


Figure 4 Varices identified through various methods. A: Large gastric varix (arrow) seen endoscopically; B: Peri-gastric varix (arrow) seen within the cyst cavity during endoscopic necrosectomy; C: Computed tomography scan showing gastric varices (arrows) in close proximity to the stomach (S) and walled off necrosis (WON).

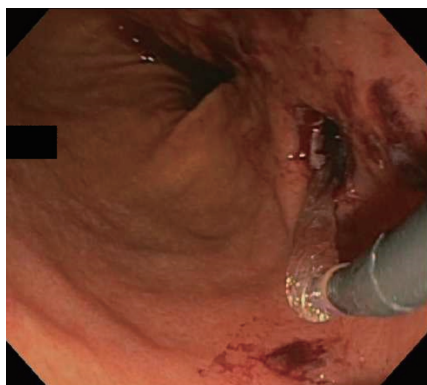


Figure 5 Status-post balloon dilation of the necrosectomy tract, shown with self-limited bleeding.

repeat imaging was used to confirm continued presence of a fluid collection prior to repeating the procedure. Procedure details were recorded retrospectively and comprehensive chart review was performed to evaluate for delayed complications and any recurrence of symptomatic WON occurring after the interval episode of pancreatitis.

RESULTS

Patient characteristics

Out of 90 patients undergoing DEN for WON between 2012 and 2015, a total of 15 patients (16.7%) were determined to have gastric varices at the time of their procedure (Table 1). Mean age was 47.1 years (range 27-62) and six patients (40%) were female. Etiology of pancreatitis leading to WON was alcohol in six patients (40%), gallstone disease in 5 patients (33%) and other/unspecified in four patients (27%). All patients had an INR less than 1.5 (mean 1.16) and platelets greater than 50000/ μ L (mean 237000/ μ L). Of these patients, 11 (73%) had splenic vein thrombosis, 2 (13%) had portal vein thrombosis, and two had no notable thrombosis on imaging. Large endoscopically visualized isolated gastric varices, type 1 were present in two

patients (13%) and the remaining 13 (87%) had 5 mm or greater gastric submucosal varices identified on imaging by CT, MRI or EUS (Figure 4). No procedures were terminated early without fully completing the DEN.

Adverse events

One patient had self-limited intraprocedural bleeding noted upon balloon dilation of the necrosectomy tract (Figure 5). Two patients experienced delayed bleeding at two and five days post-procedure, respectively. One, diagnosed incidentally on the basis of blood seen on CT within the cyst required no therapy or intervention. The other, diagnosed on the basis of hemoglobin and hematocrit drop, received one unit transfusion of packed red blood cells and underwent EGD, which revealed no active bleeding. Some clot material was seen at the entrance to the necrosectomy cavity, suggesting that the source of resolved hemorrhage was within the cavity or emanating from the wall of the endoscopic necrosectomy tract.

Clinical resolution

Clinical success and resolution rate of WON in this patient cohort was 100% after up to two additional DEN procedures. One patient required two additional DEN procedures and four patients required one additional DEN for complete resolution of symptoms. No patients required interventional radiology or surgical interventions for complications of the procedure, or for management of the pancreatic necrosis. No patients required adjunctive endoscopic therapies including nasocystic irrigation or pancreatic duct stenting. A total of five patients underwent follow-up imaging after clinical resolution of WON with thrombosis and varices noted to have dissipated in two out of five patients (40%) over a range of 19-36 mo.

DISCUSSION

Gastric varices are common in patients referred for management of WON. Over 16% of our cohort

Table 1 Patient characteristics

Patient	Age	Sex	Etiology of pancreatitis	Presence of PVT/SVT	Platelet count (normal range 150-450)	INR (normal range 0.9-1.1)	Gastric varices type	Intraprocedural bleeding?	Postprocedural bleeding?	Any variceal bleeding reported?	Repeat therapy required?	Resolution of varices? ¹
1	37	F	Gallstone	SVT	185	1.0	IGV-1	-	-	-	DEN × 2	Unknown
2	44	F	Alcohol	SVT	235	1.3	SMV	-	-	-	DEN × 1	No (24 mo)
3	45	M	Alcohol	-	131	1.1	SMV	-	-	-	-	Unknown
4	39	M	Alcohol	PVT	256	1.4	SMV	-	-	-	DEN × 1	No (14 mo)
5	42	M	Gallstone	SVT	130	1.0	IGV-1	-	-	-	-	Unknown
6	60	F	Unknown	SVT	167	1.2	SMV	Minimal	-	-	-	Yes (36 mo)
7	27	M	Alcohol	SVT	248	1.0	SMV	-	-	-	-	No (32 mo)
8	82	F	Unknown	SVT	145	1.1	SMV	-	-	-	-	Yes (19 mo)
9	41	F	Gallstone	SVT	224	1.0	SMV	-	-	-	DEN × 1	Unknown
10	58	M	Unknown	SVT	252	1.2	SMV	-	Self-limited (seen in cyst on CT 5d later), no transfusion, no EGD	-	-	Unknown
11	62	F	Unknown	SVT	199	1.3	SMV	-	-	-	-	Unknown
12	42	M	Gallstone	SVT	151	1.2	SMV	-	-	-	-	Unknown
13	50	M	Gallstone	SVT	604	1.2	SMV	-	-	-	DEN × 1	Unknown
14	43	M	Alcohol	-	356	1.0	SMV	-	-	-	-	Unknown
15	35	M	Alcohol	PVT	276	1.4	SMV	-	Self-limited, 1u pRBC given. EGD: Clots on pigtail catheters no active bleeding	-	-	Unknown

¹Time interval between procedure and last noted presence of varices. PVT: Portal vein thrombosis; SVT: Splenic vein thrombosis; IGV: Isolated gastric varices; SMV: Submucosal varices; DEN: Direct endoscopic necrosectomy; Male: F; Female.

undergoing DEN had gastric varices^[1,3,10]. The outcomes in this cohort with gastric varices included similarly high clinical resolution rates and similarly low adverse event rates in line with previously reported DEN cohorts. This study suggests that patients with WON and known or suspected gastric varices may safely undergo DEN guided by EUS with doppler. In our cohort, successful resolution of WON using DEN does not appear to be compromised by the presence of gastric varices. A previously reported cohort of 60 patients undergoing DEN at our institution showed a clinical success rate of nearly 90%, with 3.3% major complication rate^[1]. In this cohort of patients undergoing DEN with gastric varices, only minor bleeding events were seen, which did not meet criteria to be listed as a major complication. Importantly, no bleeding events involved puncture or trauma to a gastric varix, likely given the use of EUS doppler guidance when choosing the location of the necrosectomy tract. Furthermore, DEN may be the preferred treatment modality for WON in a population with gastric varices given the ability of EUS to detect submucosal varices, which are not seen when "blindly" accessing the cavity via a surgical or percutaneous route.

Limitations

The retrospective nature of this cohort study is a limitation and the fact that the study was performed in a multidisciplinary center of excellence could limit generalizability. We advocate performing this procedure at a center with DEN-trained endoscopists, and with capable surgical and/or interventional radiology services to manage any procedural complications or therapeutic failures should the need arise. Our single center experience with DEN is relatively robust in numbers, however larger numbers of pooled data would be helpful in making statistically powered clinical observations.

Another limitation to this study population includes the issue that patients should not be subjected to repeat imaging, including the inherent radiation exposure associated with CT, in the absence of symptoms. Because of this, our patients who were asymptomatic on follow up from their initial DEN did not undergo routine repeat

imaging, which limited our ability to comment with confidence on variceal resolution rate as well as radiographic resolution rate of the fluid collections. Instead, resolution of symptoms was used to define clinical success.

Future studies

In our study, 40% of patients who had follow up imaging after DEN had resolution of thrombosis and gastric varices. What role DEN may play in affecting recanalization rates of splanchnic venous thrombosis resulting in portal hypertension and gastric varices is unknown, and is an interesting question. Theoretically, this highly clinically effective procedure, with previously mentioned reductions in inflammatory markers as compared to other treatment modalities, may result in timely reduction of inflammation resulting in reabsorption of thrombosis and vessel recanalization. It is also possible that earlier DEN may reduce thrombotic sequelae of acute pancreatitis. This question should be studied in a larger patient population undergoing DEN.

In conclusion, use of EUS guidance appears to allow the endoscopist to safely avoid intervening gastric varices and bleeding complications, a necessity which both surgical and percutaneous interventional radiology techniques lack. As such, reduction in bleeding complications may be considered one advantage to an endoscopic approach to necrosectomy over other techniques. Experienced centers should not consider gastric varices a contraindication to DEN.

COMMENTS

Background

Increasingly minimally invasive techniques, including both percutaneous and endoscopic, have replaced surgery in the management of infected and symptomatic pancreatic necrosis. Pancreatitis may be associated with portal and splenic thrombosis leading to gastric varices, and is an important consideration in the bleeding risk when performing drainage procedures.

Research frontiers

The role of endoscopic management of pancreatic fluid collections has increased significantly over the past 10 years. The American Society for Gastrointestinal Endoscopy has recently published the first guideline statement regarding the flexible endoscopic management of inflammatory pancreatic fluid collections, available on the web at: [http://www.asge.org/uploadedFiles/Publications_\(public\)/Practice_guidelines/Inflammatory_pancreatic_fluid_collect_ions.pdf](http://www.asge.org/uploadedFiles/Publications_(public)/Practice_guidelines/Inflammatory_pancreatic_fluid_collect_ions.pdf).

Innovations and breakthroughs

This is the first report suggesting a reasonably high prevalence of gastric varices (16.7%) in patients presenting to a tertiary care facility for endoscopic management of walled off pancreatic necrosis. This may have implications regarding the safety and best approach to resolution of these fluid collections in this patient population.

Applications

This study suggests a need for increased awareness of the relevance of gastric varices in the patient with pancreatic necrosis. The presence of varices should be considered when determining the best approach to managing these patients. Endoscopic ultrasound-guided access, with protocol driven debridement appears to be safe and feasible in this patient population.

Terminology

Walled-off necrosis (WON) is an inflammatory collection of debris and fluid that may form and persist after an episode of acute necrotizing pancreatitis. This collection may become infected, leading to sepsis and bacteremia, or may cause symptoms including abdominal pain, early satiety, anorexia, nausea and/or vomiting; direct endoscopic necrosectomy (DEN) is a per-oral procedure using flexible endoscopes to enter WON and provide debridement of non-viable and infected tissue to aid in resolution of the fluid collection and its associated symptoms.

Peer-review

The purpose of this paper is to determine the feasibility and safety of transgastric DEN in patients with WON and gastric varices. The results are feasible, safe and effective.

REFERENCES

- 1 **Thompson CC**, Kumar N, Slattery J, Clancy TE, Ryan MB, Ryou M, Swanson RS, Banks PA, Conwell DL. A standardized method for endoscopic necrosectomy improves complication and mortality rates. *Pancreatol* 2016; **16**: 66-72 [PMID: 26748428 DOI: 10.1016/j.pan.2015.12.001]
- 2 **Kumar N**, Conwell DL, Thompson CC. Direct endoscopic necrosectomy versus step-up approach for walled-off pancreatic necrosis: comparison of clinical outcome and health care utilization. *Pancreas* 2014; **43**: 1334-1339 [PMID: 25083997 DOI: 10.1097/MPA.0000000000000213]
- 3 **Bakker OJ**, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; **307**: 1053-1061 [PMID: 22416101 DOI: 10.1001/jama.2012.276]
- 4 **Muthusamy VR**, Chandrasekhara V, Acosta RD, Bruining DH, Chathadi KV, Eloubeidi MA, Faulx AL, Fonkalsrud L, Gurudu SR, Khashab MA, Kothari S, Lightdale JR, Pasha SF, Saltzman JR, Shaikat A, Wang A, Yang J, Cash BD, DeWitt JM. The role of endoscopy in the diagnosis and treatment of inflammatory pancreatic fluid collections. *Gastrointest Endosc* 2016; **83**: 481-488 [PMID: 26796695 DOI: 10.1016/j.gie.2015.11.027]
- 5 **Easler J**, Muddana V, Furlan A, Dasyam A, Vipplerla K, Slivka A, Whitcomb DC, Papachristou GI, Yadav D. Portosplenomesenteric venous thrombosis in patients with acute pancreatitis is associated with pancreatic necrosis and usually has a benign course. *Clin Gastroenterol Hepatol* 2014; **12**: 854-862 [PMID: 24161350 DOI: 10.1016/j.cgh.2013.09.068]
- 6 **Harris S**, Nadkarni NA, Naina HV, Vege SS. Splanchnic vein thrombosis in acute pancreatitis: a single-center experience. *Pancreas* 2013; **42**: 1251-1254 [PMID: 24152951 DOI: 10.1097/MPA.0b013e3182968ff5]
- 7 **Willmann JK**, Weishaupt D, Böhm T, Pfammatter T, Seifert B, Marincek B, Bauerfeind P. Detection of submucosal gastric fundal varices with multi-detector row CT angiography. *Gut* 2003; **52**: 886-892 [PMID: 12740347]
- 8 **Boustière C**, Dumas O, Jouffré C, Letard JC, Patouillard B, Etai JP, Barthélémy C, Audigier JC. Endoscopic ultrasonography classification of gastric varices in patients with cirrhosis. Comparison with endoscopic findings. *J Hepatol* 1993; **19**: 268-272 [PMID: 8301060]
- 9 **Yang M**, Gou S, Wang C, Wu H, Xiong J, Zhao G, Zhou F, Tao J, Yang Z, Yin T, Peng T, Cui J, Guo Y. [Surgical treatment of necrotizing pancreatitis: 10-year experience at a single center]. *Zhonghua Waik Zazhi* 2015; **53**: 672-675 [PMID: 26654145]
- 10 **Busse MJ**, Ainsworth AP. Ten years of experience with transgastric necrosectomy for walled-off necrosis in acute pancreatitis. *Dan Med J* 2015; **62**: pii: A5131 [PMID: 26324082]
- 11 **Pupelis G**, Fokin V, Zeiza K, Plaudis H, Suhova A, Drozdova N, Boka V. Focused open necrosectomy in necrotizing pancreatitis. *HPB (Oxford)* 2013; **15**: 535-540 [PMID: 23458703 DOI: 10.1111/

- hpb.12004]
- 12 **Baudin G**, Chassang M, Gelsi E, Novellas S, Bernardin G, Hébuterne X, Chevallier P. CT-guided percutaneous catheter drainage of acute infectious necrotizing pancreatitis: assessment of effectiveness and safety. *AJR Am J Roentgenol* 2012; **199**: 192-199 [PMID: 22733912 DOI: 10.2214/AJR.11.6984]
- 13 **Mortelé KJ**, Girshman J, Szejnfeld D, Ashley SW, Erturk SM, Banks PA, Silverman SG. CT-guided percutaneous catheter drainage of acute necrotizing pancreatitis: clinical experience and observations in patients with sterile and infected necrosis. *AJR Am J Roentgenol* 2009; **192**: 110-116 [PMID: 19098188 DOI: 10.2214/AJR.08.1116]

P- Reviewer: Liu QD, Teoh AYB, Tham T, Yan SL **S- Editor:** Qi Y
L- Editor: A **E- Editor:** Wu HL



Retrospective Cohort Study

Place of upper endoscopy before and after bariatric surgery: A multicenter experience with 3219 patients

Mohamed E Abd Ellatif, Haitham Alfalah, Walid A Asker, Ayman E El Nakeeb, Alaa Magdy, Waleed Thabet, Mohamed A Ghaith, Emad Abdallah, Rania Shahin, Asharf Shoma, Ibraheim E Dawoud, Ashraf Abbas, Asaad F Salama, Maged Ali Gamal

Mohamed E Abd Ellatif, Alaa Magdy, Waleed Thabet, Emad Abdallah, Asharf Shoma, Ibraheim E Dawoud, Ashraf Abbas, Department of Surgery, Mansoura University Hospital, Mansoura 35511, Dakahlia, Egypt

Haitham Alfalah, Consultant of Bariatric Surgery, King Saud Medial City (KSMS), Riyadh 12746, Saudi Arabia

Walid A Asker, Ayman E El Nakeeb, Gastroenterology Surgical Center, Mansoura University, Mansoura 35511, Dakahlia, Egypt

Mohamed A Ghaith, Department of Anesthesia, Mansoura University Hospital, Mansoura 35511, Dakahlia, Egypt

Rania Shahin, Department of Clinical Pathology, Benha University Hospital, Benha 13111, Egypt

Asaad F Salama, Maged Ali Gamal, Department of Surgery, Jahra Hospital, Al-Jahra 01753, Kuwait

Author contributions: Abd Ellatif ME, Alfalah H, Asker WA, El Nakeeb AE, Magdy A, Thabet W, Gheith MA, Abdallah E, Shahin R, Shoma A, Dawoud IE, Abbas A, Salama AF and Ali MG contributed equally to this work; Abd Ellatif ME, Asker WA, and El Nakeeb AE designed the research; Abd Ellatif ME, Asker WA, El Nakeeb AE, Magdy A, Thabet W, Gheith MA, Shahin R, Ali Gamal M, Abbas A and Dawoud IE performed the research; Abd Ellatif ME and Gheith MA analyzed the data; Abd Ellatif ME and Shahin R wrote the paper.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer (code No. R/15.08.44).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: The original anonymous dataset is

available on request from the corresponding author at surg_latif@hotmail.com.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Mohamed E Abd Ellatif, Department of Surgery, Mansoura University Hospital, Gihan El Sadat St., Mansoura 35511, Dakahlia, Egypt. surg_latif@hotmail.com
Telephone: +2-0111-5051680

Received: August 24, 2015

Peer-review started: August 28, 2015

First decision: September 28, 2015

Revised: March 12, 2016

Accepted: March 17, 2016

Article in press: March 18, 2016

Published online: May 25, 2016

Abstract

AIM: To study the preoperative and postoperative role of upper esophagogastrroduodenoscopy (EGD) in morbidly obese patients.

METHODS: This is a multicenter retrospective study by reviewing the database of patients who underwent bariatric surgery (laparoscopic sleeve gastrectomy, laparoscopic Roux en Y gastric bypass, or laparoscopic minigastric bypass) in the period between 2001 June and 2015 August (Jahra Hospital-Kuwait, Hafr Elbatin Hospital and King Saud Medical City-KSA, and Mansoura

University Hospital - Egypt). Patients with age 18-65 years, body mass index (BMI) > 40, or > 35 with comorbidities after failure of many dietetic regimen and acceptable levels of surgical risk were included in the study after having an informed signed consent. We retrospectively reviewed the medical charts of all morbidly obese patients. The patients' preoperative data included clinical history including upper digestive symptoms and preoperative full workup including EGD. Only patients whose charts revealed whether they were symptomatic or not were studied. We categorized patients accordingly into two groups; with (group A) or without (group B) upper digestive symptoms. The endoscopic findings were categorized into 4 groups based on predetermined criteria. The medical record of patients who developed stricture, leak or bleeding after bariatric surgery was reviewed. Logistic regression analysis was used to identify preoperative predictors that might be associated with abnormal endoscopic findings.

RESULTS: Three thousand, two hundred and nineteen patients in the study period underwent bariatric surgery (75% LSG, 10% LRYDB, and 15% MGB). Mean BMI was 43 ± 13 , mean age 37 ± 9 years, 79% were female. Twenty eight percent had presented with upper digestive symptoms (group A). EGD was considered normal in 2414 (75%) patients (9% group A *vs* 66% group B, $P = 0.001$). The abnormal endoscopic findings were found high in those patients with upper digestive symptoms. Abnormal findings (one or more) were found in 805 (25%) patients (19% group A *vs* 6% group B, $P = 0.001$). Seven patients had critical events during conscious sedation due to severe hypoxemia (< 60%). Rate of stricture in our study was 2.6%. Success rate of endoscopic dilation was 100%. One point nine percent patients with gastric leak were identified with 75% success rate of endoscopic therapy. Three point seven percent patients developed acute upper bleeding. Seventy-eight point two percent patients were treated by conservative therapy and EGD was performed in 21.8% with 100% success and 0% complications.

CONCLUSION: Our results support the performance of EGD only in patients with upper gastrointestinal symptoms. Endoscopy also offers safe effective tool for anastomotic complications after bariatric surgery.

Key words: Morbid obesity; Obesity surgery; Endoscopy; Complications; Dilation; Stenting

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: It is still a major controversial point to do routine screening endoscopy for obese patients before surgery. Many authors suggest doing upper esophagogastrroduodenoscopy (EGD) for all patients before bariatric procedures because of the lack of correlation between patient symptoms and EGD findings. On the contrary, many other investigators advocate selective approach for asymptomatic patients because of the

relatively weak clinical relevance of the majority of the lesions discovered on routine EGD along with the cost and invasiveness of the EGD. The upper endoscopy is commonly indicated in the postoperative bariatric patient to evaluate post-bariatric symptoms, to detect and manage complications, as well as evaluation of failure of weight loss. Post-bariatric complications prompting upper endoscopy include bleeding, anastomotic or staple line leaks or fistulae, sleeve stricture in laparoscopic sleeve gastrectomy or stomal stenosis in laparoscopic Roux en Y gastric bypass, or laparoscopic minigastric bypass. We aimed in this retrospective study to answer if it is still necessary to do pre-bariatric screening endoscopy and to evaluate the efficacy and safety of the endoscopic therapy for management of post-bariatric complications.

Abd Ellatif ME, Alfalah H, Asker WA, El Nakeeb AE, Magdy A, Thabet W, Gheith MA, Abdallah E, Shahin R, Shoma A, Dawoud IE, Abbas A, Salama AF, Ali Gamal M. Place of upper endoscopy before and after bariatric surgery: A multicenter experience with 3219 patients. *World J Gastrointest Endosc* 2016; 8(10): 409-417 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i10/409.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i10.409>

INTRODUCTION

Obesity represents a serious health problem in nearly the whole world^[1-5]. Obesity surgery is the most effective treatment due to the sustainable and significant weight loss results in addition to the resolution of the comorbidities in up to 80%^[6-8]. Upper digestive diseases are 2-3 times more common in obese then normal weight individuals, including erosive esophagitis, gastroesophageal reflux, hiatal hernia, Barrett's esophagus and *Helicobacter pylori* (*H. pylori*) infection^[9].

It is still a major controversial point to do routine screening endoscopy for those patients before surgery^[10]. There is evidence that some pathologic esophagogastrroduodenoscopy (EGD) findings change the chosen procedure such as a large hiatal hernia or Barrett's esophagus. Many authors suggest doing EGD for all patients before bariatric procedures because of the lack of correlation between patient symptoms and EGD findings^[11-15]. On the contrary, many other investigators advocate selective approach for asymptomatic patients because of the relatively weak clinical relevance of the majority of the lesions discovered on routine EGD along with the cost and invasiveness of the EGD^[16,17]. One of the outmost important points is the risk of conscious sedation at the time of EGD due to hypertension and obstructive sleep apnea^[18].

The upper endoscopy is commonly indicated in the postoperative bariatric patient to evaluate post-bariatric symptoms, to detect and manage complications, as well as evaluation of failure of weight loss. Post-bariatric

complications prompting upper endoscopy include bleeding, anastomotic or staple line leaks or fistulae, sleeve stricture in laparoscopic sleeve gastrectomy (LSG) or stomal stenosis in laparoscopic Roux en Y gastric bypass (LRYGB), or laparoscopic minigastric bypass (MGB). We aimed in this retrospective study to answer if it is still necessary to do pre-bariatric screening endoscopy and to evaluate the efficacy and safety of the endoscopic therapy for management of post-bariatric complications.

MATERIALS AND METHODS

Patients studied

This is a multicenter retrospective study by reviewing the database of 3219 patients who underwent bariatric surgery (LSG, LRYGB, or MGB) in the period between 2001 June and 2015 August (Jahra Hospital-Kuwait, Hafr Elbatin Hospital and King Saud Medical City-KSA, and Mansoura University Hospital - Egypt). The study was reviewed and approved by Mansoura Institutional Review Board. Local ethical committee approval for data base management was obtained at each hospital. Patients with age 18-65 years, body mass index (BMI) > 40, or > 35 with comorbidities after failure of many dietetic regimen and acceptable levels of surgical risk were included in the study after having an informed signed consent. Those patients who underwent routine EGD pre-bariatric and patients' charts revealed whether these patients were actually symptomatic before surgery. We excluded patients with prohibitive surgical risk, indications of lack of compliance with perioperative regimen, uncontrolled alcohol or drug abuse, uncontrolled depression or other mental disorders, and lack of family support or significant discord within the family about the planned surgery.

Preoperative data

All patients underwent detailed clinical history including upper gastrointestinal tract (GIT) symptoms, physical examination, and diagnostic work up including routine upper endoscopy. Only patients whose charts revealed whether they were symptomatic or not were studied. Upper digestive symptoms recorded included heartburn, reflux, acid regurgitation, nausea, vomiting and abdominal pain. We categorized patients accordingly into two groups; with (group A) or without (group B) upper digestive symptoms. The endoscopic findings were categorized into 4 groups based on predetermined criteria suggested by Sharaf *et al*^[11]: (1) group 0: With normal EGD study; (2) group 1: If there were abnormal findings that neither changed the surgical approach nor postponed it; (3) group 2: Abnormal EGD findings that changed or postponed the surgical approach; (4) group 3: The abnormal findings that were absolute contra-indications to surgery. In case if there was more than one endoscopic finding, we considered the most significant lesion was the diagnosis (Table 1).

Table 1 Classification system for endoscopic findings

Group 0: No findings
Normal study
Group 1: Abnormal findings that do not change surgical approach/postpone surgery
Mild esophagitis, gastritis, and/or duodenitis
Esophageal webs
Group 2: Findings that change the surgical approach/postpone surgery
Mass lesions (mucosal/submucosal)
Ulcers (any location)
Severe erosive esophagitis, gastritis, and/or duodenitis
Barrett's esophagus
Bezoar
Hiatal hernia (any size)
Peptic stricture
Zenker's diverticula
Esophageal diverticula
Arteriovenous malformations
Group 3: Absolute contraindications to surgery
Upper GI cancer
Varices

GI: Gastrointestinal.

Preoperative endoscopy was done routinely for all patients. Endoscopy was done by our experienced gastroenterology doctors using local throat anesthesia spray. Conscious sedation was done in some cases (if requested by the patient) with nasal oxygen supply and careful monitoring in presence of an anesthetist. Propofol was the standard sedation used which was extended to midazolam if needed. Esophagitis was graded according to the Savary-Miller classification^[19]. Tissue biopsies for *H. pylori* were taken from the corpus and the antrum of patients following the American College of Gastroenterology guideline^[20] and additional biopsies were taken if other abnormalities were seen. If *H. Pylori* was detected, eradication therapy was given for 1 wk (amoxicillin 750 mg *bid*, clarithromycin 500 mg *bid*, and omeprazole 40 mg once daily); the success of HP eradication was not assessed.

Postoperative data

The medical record of patients who developed stricture after bariatric surgery were reviewed for imaging results, time from surgery until symptoms onset, site of stricture, way of treatment, types gastrointestinal anastomosis in case of LRYGB or MGB (end or linear stapler or hand sewn). If endoscopic management was used; number of dilation sessions, diameter of the balloon used for dilation and duration till patient tolerate soft diet. Sleeves narrowing or stomas less than 10 mm in diameter, or if the scope failed to pass through were considered significant strictures and were treated with balloon dilations.

Data from patients who developed leak included: Methods used to detect and manage leaks, interval between surgery and leak, interval between detection and closure and type of stents used. Acute leaks were defined as those occurring within 7 d of the primary procedure, early leak from 1 to 6 wk of the

Table 2 Patient characteristics

Variable	Summary = 3219
Age	37 ± 9 yr
Female: male	79%:21%
BMI	43 ± 13
Haemoglobin	13 ± 4 g/dL
Upper GI symptoms: 902 (28%) ¹	
Heartburn	19.2%
Acid regurgitation	17.6%
Abdominal pain	7.3%
Nausea with or without vomiting	5.7%
Comorbidities: 1159 (36%) ²	
Obstructive sleep apnea	4.9%
Hypertension	57.8%
Arthritis	56.9%
Diabetes mellitus	40.5%
Hypothyroidism	36.6%
Asthma/COPD	15.1%
Coronary artery disease	9.9%
Type of endoscopy	
Conscious sedation	354 (11%)
Local anesthesia spray	2865 (89%)
Type of bariatric procedure	
Vertical sleeve gastrectomy	2415 (75%)
Roux-en-Y gastric bypass	322 (10%)
Laparoscopic minigastric bypass	482 (15%)

¹Some patients have more than one symptoms; ²Some patients have more than one comorbidity. GI: Gastrointestinal.

primary procedure, late leak after 6 wk of the primary procedure. Post-bariatric hemorrhage was defined as patients who presented with hematemesis and/or melena with significant hemodynamic changes including one or more of increase in heart rate > 20 beat/min, decrease in systolic blood pressure > 20 mmHg, significant drop in hemoglobin > 2 g/dL or endoscopic signs of active or recent bleeding.

Statistical analysis

Continuous variables were compared using a Student *t* test or a nonparametric test, as appropriate. Categorical variables were compared using the χ^2 or Fisher's exact test. A two-tailed *P* < 0.05 was considered statistically significant. All data are expressed as mean (SD). Statistical analysis was performed using a commercially available software package (SPSS version 11.5 for Windows; SPSS Inc, Chicago, IL). Logistic regression analysis was used to identify preoperative predictors that might be associated with abnormal endoscopic findings.

The primary outcome of this study was to compare prevalence of clinically significant lesions found on upper endoscopy before bariatric surgery in patients who have (group A) or do not have (group B) upper digestive symptoms. Secondary outcome was to evaluate the safety and efficacy of upper endoscopy to diagnose and treat post-bariatric surgery complications such as bleeding, leakage and stenosis.

RESULTS

During the study period, 3219 patients underwent

Table 3 Endoscopic findings during routine upper gastrointestinal endoscopy and their prevalence

EGD findings	Group A (n = 902)	Group B (n = 2317)	P value
Esophagus			
Normal = 65%	19%	46%	0.001
Abnormal = 35%	25%	10%	0.001
Hiatal hernia	21.9%	7.9%	
Esophagitis	19%	6%	
Barrett's esophagus	1.1%	0.1%	
Stomach			
Normal = 77%	24%	53%	0.001
Abnormal = 23%	17%	6%	0.001
Spotty gastropathy	4%	1.3%	
Erythematous gastropathy	7%	2.5%	
Erosive gastropathy	8%	1.2%	
Atrophic gastropathy	1%	0.48%	
Multiple polyps	0.1%	0.02%	
Ulcer	2.4%	0.5%	
Duodenum			
Normal = 87%	23%	64%	0.001
Abnormal = 13%	9%	4%	0.001
Erythematous bulbopathy	6%	2.2%	
Erosive bulbopathy	2.6%	1%	
Ulcer	1.4%	0.8%	
+ve biopsy for <i>H. pylori</i> , 407 (14.6%)	10.7%	3.9%	0.001

EGD: Esophagogastroduodenoscopy; *H. pylori*: *Helicobacter pylori*.

bariatric surgery [2415 (75%) LSG, 322 (10%) LRYDB, and 482 (15%) MGB]. Mean BMI was 43 ± 13, mean age 37 ± 9 years, 79% were female and 36% had comorbid diseases (Table 2). Nine hundred and two (28%) had presented with upper digestive symptoms, with the most common symptoms being heartburn (19.2%), acid regurgitation (17.6%), abdominal pain (7.3%), and nausea with or without vomiting (5.7%).

EGD was considered normal in 2414 (75%) patients [9% (group A) vs 66% (group B), *P* = 0.001]. Abnormal findings (one or more) were found in 805 (25%) patients [19% (group A) vs 6% (group B), *P* = 0.001]. Small hiatal hernia was the most common findings (29.7%) followed by gastritis (23%), esophagitis (15%) and Barrett's esophagus (1.2%). Benign polyps and ulcers were detected in (0.12%) and 2.9%, respectively (Table 3). The prevalence of endoscopic findings using Sharaf *et al.*^[11] classification system was as follows: Group 0 (65%), group 1 (18.2%) [9.2% (group A) vs 8.9% (group B), *P* = 0.43], group 2 (6.8%) [5.2% (group A) vs 1.6% (group B), *P* = 0.001], and group 3 (0.0%). In no patients were upper GIT cancers or esophageal varices identified. Thirteen percent underwent EGD in supine position instead of standard left lateral position due to their body weight.

Findings of endoscopy had clinical consequences in 219 (6.8%) patients as showed in (Table 4): Patients with hiatus hernia required crural repair and reduction of the hernia, gastric ulcers, duodenal ulcer operation postponed and medications prescribed till full healing was checked by follow up endoscopy. *H. pylori* was assessed at histopathological examination in 493 (15.3%) patients, and was positive in 407

Table 4 Lesions identified on upper endoscopy and impact on bariatric surgery, $n = 219$ (6.8%)

Lesion	Group A	Group B	Result
Hiatal hernia	25%	10%	Crural repair/reduction of hernia
Gastritis	17%	6%	Medical treatment, postpone surgery
Esophagitis	19%	6%	Medical treatment, postpone surgery
Gastric ulcer	2.4%	0.5%	Await biopsy results, medical treatment, repeat endoscopy
Barrett's esophagus	1.1%	0.1%	Await biopsy results, medical treatment, repeat endoscopy
Duodenal ulcer	1.4%	0.8%	Await <i>Helicobacter pylori</i> results, medical treatment

[14.6% (10.7% in group A vs 3.9% in group B, $P = 0.001$)] of them. Polyps removed from stomach came histopathologically to be hyperplastic polyps. Conscious sedation was used in 354 (11%) on patient request. Those patients were observed for a minimum of 12 h after the endoscopy. Seven (1.97%) patients had critical events during conscious sedation due to severe hypoxemia ($< 60\%$). They received oxygen insufflation via ambu bag, endo-tracheal intubation was necessary in no one. No other critical events, such as aspiration or severe hypotension, occurred. Six hundred and twelve (19%) of our patients, EGD showed presence of esophagitis with GERD symptoms. Of those patients, 307 (9.7%) underwent LSG whose GERD symptoms improved in 217 (70.7%) and worsen in 90 (29.3%). Total number who developed *de novo* GERD was 197 (8.2%) during the 1st year which declined significantly to 48 (2%) after 3 years of their follow up.

Multivariate logistic regression analysis was used to identify clinical predictors that might be associated with abnormal EGD. Univariate analysis demonstrated that 6 independent variables were associated with abnormal endoscopic findings: Age, gender, preoperative BMI, comorbidities, anaemia and GIT symptoms. The upper digestive symptoms were predictive for presence of abnormal endoscopic finding ($P \leq 0.001$). No significant differences were observed in age, gender, preoperative BMI, co-morbidities or anaemia. Univariate (Table 5) and multivariate regression analysis (Table 6) established that presence of GIT symptoms was the only clinical variable associated with abnormal endoscopic findings (OR = 2.649; 95%CI: 1.904-3.684) with $P \leq 0.05$.

Fifty-four (2.2%) patients after sleeve had stricture at the site of incisura (47/54) or at the gastro-esophageal junction (7/54). Stomal stenosis developed in 16 (4.7%) patients after LRYGB and 15 (3.2%) after MGB. They have been diagnosed by contrast study and confirmed and treated by EGD. The Endoscopic dilation was done via through the scope balloon dilation. The mean time from surgery to initial endoscopic dilation was 59 ± 9 d. The mean number of dilations was 1.7, and the median balloon size was 15 mm. The mean

Table 5 Univariate analysis of clinical predictors of abnormal upper endoscopy

Variables	Total population	Normal EGD (65%)	Abnormal EGD (35%)	P value
Age (yr)	37 ± 9	31 ± 9	43 ± 10	0.26
BMI	43 ± 13	43 ± 11	47 ± 16	0.09
Gender (F:M)	79%:21%	64%:36%	69%:31%	0.17
GIT symptoms	13.80%	72%	28%	0.001
Haemoglobin (g/dL)	13 ± 4	13 ± 3.4	11 ± 3.2	0.07
Comorbidities	36%	52%	48%	0.18

F: Female; M: Male; EGD: Esophagogastroduodenoscopy; BMI: Body mass index; GIT: Gastrointestinal tract.

time from the first dilation to toleration of a soft diet was 31 ± 7 d. Success rate for endoscopic intervention was 100% with no complications. None of our patients required operative revision to correct the symptomatic stenosis. One hundred and ninety (3.7%) patients had postoperative GIT bleeding in form of drop of hemoglobin or overt melena and hypotension. Seventy-eight point two percent patients were just treated conservatively. Twenty-one point eight percent patients required endoscopic management in form of adrenaline injection, no one required surgical treatment.

Sixty-one (1.9%) patients had leak; 49 (2.02%) after sleeve (all of them had leakage from gastro-esophageal junction), 5 (1.55%) after LRYGB and 7 (1.45%) after MGB. Twenty-six patients had acute leak; leak site suture was successful in 19/26 patients and gastrostomy tube was placed in 7 patients. All of them were treated by laparoscopic reoperation, thorough washout and drainage. Fourteen cases with early leak were managed successfully with endoscopic wallstent and percutaneous drainage. The other 21 patients had late leak; 11 patients were managed by endoscopic wallstent and percutaneous drainage. One of those patients, gastrograffin study on the 5th day showed leakage which was unsuccessfully treated by one more stent at the same day. His problem has been finished by gastrectomy and oesophagojejunostomy. Ten patients without signs of uncontrolled sepsis were treated non-operatively. Four of these patients required only maintenance of the operatively placed suction tube. Percutaneous drainage was done in 43 patients. Endoscopic clips in 14 patients for chronic leak. A total of 74 stents were placed in our patients (some patients required more than one stent). Success rate was 75%. Forty-three of these were polyester based (Polyflex) and 31 were nitinol based (Alveolus). Migration occurred in 27% stent placements.

One hundred and nineteen (3.7%) patients developed post-operative hemorrhage out of total 3219. Seventy-nine patients had one episode of bleeding, 29 had two episodes and 11 had three episodes, for a total 170 episodes of bleeding. Hematemesis was the predominant manifestation. Table 7 shows the clinical and endoscopic findings of these bleeding episodes. All

Table 6 Multivariate regression analysis of clinical predictors of abnormal esophagogastroduodenoscopy

Variables	OR	95%CI	P value
Age	1.414	0.772-2.59	0.26
BMI	1.092	0.923-1.723	0.38
Gender	0.225	0.028-1.826	0.162
GIT symptoms	2.649	1.904-3.684	0.001
Comorbidities	0.68	0.335-1.381	0.286
Anaemia	0.945	1.241-2.093	0.274

OR: Odds ratio; GIT: Gastrointestinal tract symptoms; BMI: Body mass index.

of these endoscopic procedures have been performed in operative rooms with the patients intubated.

DISCUSSION

The role of routine EGD before bariatric surgery still remains unclear. So far, this study is the largest series trying to find answer for this question. Many authors suggest doing EGD for all patients before bariatric procedures because of the lack of correlation between patient symptoms and EGD findings^[11-15]. On the contrary, many other investigators advocate selective approach for asymptomatic patients because of the relatively weak clinical relevance of the majority of the lesions discovered on routine EGD along with the cost and invasiveness of the EGD^[16,17].

Only patients whose medical charts revealed if upper gastrointestinal (GI) symptoms recorded were enrolled in the study. Prevalence of upper GI symptoms in morbidly obese patients ranges from 10% to 87%^[21-24]. Upper GI symptoms were present in 28% of our patients. We have found, opposite to others^[25,26], strong correlations between patients symptoms and endoscopic findings. EGD was considered normal in 75% patients (9% group A vs 66% group B, $P = 0.001$). Abnormal findings (one or more) were found in 25% patients (19% group A vs 6% group B, $P = 0.001$). Küper *et al*^[14] found that 80% of the patients with pathological findings are asymptomatic.

Our study showed that no EGD findings were absolute contraindications to surgery or changed the decision plans and findings of endoscopy had clinical consequences in 6.8% (5.2% group A vs 1.6%, $P = 0.001$) patients as showed in Table 4: Patients with hiatus hernia required crural repair and reduction of the hernia, gastric ulcers, duodenal ulcer operation postponed and medications prescribed until full healing was checked by follow-up endoscopy. The majority of preoperative EGD findings were benign or mild and of little clinical consequence and the abnormal EGD findings were found to be high in those patients who had upper GIT symptoms. In 93.2% of patients, the EGD findings were either entirely negative or had no effect on the preoperative management or choice of surgery. We found in this study that it might not be wise to expose those morbidly obese patients to

Table 7 Clinical and endoscopic characteristics of bleeding episodes

	1 st episode <i>n</i> = 119	2 nd episode <i>n</i> = 40	3 rd episode <i>n</i> = 11
Presentation			
Hematemesis	93	33	5
Melena	39	19	9
Hypotension	17	3	-
Management			
EGD	28	7	-
Observation	91	33	11
Blood transfusion	43	19	3
Prominent findings on EGD			
Active blood oozing	17/28	7/3	
Bleeding vessel	28/6	7/4	
Adherent clot	28/4	-	
Other findings (visible vessel, red streaks, etc.)	28/4	-	
Endoscopic therapy			
Epinephrine injection	10	5	
Heater probe	9	4	
Clip	7	3	

EGD: Esophagogastroduodenoscopy

routine invasive uncomfortable procedure which carries potential risk although it is minimal. We do not screen the general population for those minor EGD findings; so why should we do it on people planned for bariatric surgery?

EGD was indicated if LSG is planned because of the idea that LSG increases prevalence of GERD. Some showed an increase in prevalence^[27-29] and on opposite, some found reduced prevalence of GERD after sleeve^[30-32]. LSG may promote GERD by reducing LES pressure, reduced gastric compliance and distensibility and increased gastric pressure^[33]. Factors that thought to reduce GERD after LSG include; accelerated gastric emptying, weight loss, reduced acid production and fundal resection which is considered the source of relaxation waves to the lower esophageal sphincter^[32]. Scott *et al*^[34] found that overall GERD symptoms are not more common in patients who have had LSG vs LRYGB. Six hundred and twelve (19%) of our patients, EGD showed presence of esophagitis with GERD symptoms. Of those patients, 307 (9.7%) underwent LSG whose GERD symptoms improved in 217 (70.7%) and worsen in 90 (29.3%). Total number who developed *de novo* GERD was 197 (8.2%) during the 1st year which declined significantly to 48 (2%) after 3 years of their follow up. These data in addition to others^[30-32] confirm that presence of GERD could not be considered as a contraindication for LSG.

In gastric bypass surgery, the EGD was routinely done because the rest of the stomach will be out of reach of endoscopy, for our countries risk of gastric cancer is low and there is no regular screening program for gastric cancer in the normal population; so why would we screen bariatric patients for gastric cancer? Moreover, only the gastric remnant is excluded in gastric bypass, but access to esophagus and possibility

of controlling esophageal abnormalities still remains. We have 1% Barrett's esophagus without dysplasia. Barrett's esophagus can be diagnosed, followed up and even treated after all types of bariatric surgery because for all types the access to the esophagus still remains.

Incidence of gastrointestinal stomal anastomotic stenosis occurs in 5.1%-6.8% of patients following laparoscopic R-Y gastric bypass and most commonly presents within the first year after surgery^[35]. The incidence of this anastomotic stenosis has been found to be technique dependent. The circular stapled anastomoses have been reported to have higher rate anastomotic strictures more than the linear stapled anastomoses^[36]. Hand sewn technique yield the lowest rate of anastomotic stricture^[35]. Endoscopic balloon dilation is the mainstay of treatment of these anastomotic strictures. In our study, rate of success endoscopic dilation of stomal stricture was 100% with no complications. We found stenosis rate after LSG is 1.6% comparable to the previously reported in other studies^[37,38]. We have found, as have others^[37] that the incisura angularis is the place with the greatest potential place for stricture development. The possible reason for this organic stricture could be if stapling has been accidentally performed too close to the incisura creating too tight sleeve in spite of the bougie is in place. Functional stenosis occurs if the gastric tube got twisted due to asymmetrical traction. Symmetrical lateral traction while stapling is of the utmost importance.

Leaks after LSG are reported to occur in 1.4%-5.3% of cases^[38-41] and 1%-5% after LRYGP^[42,43]. In a previous study over 1395 patients who had LSG, we found that neither the distance of the first stapler from the pylorus nor the caliber of the bougie was related to postoperative leak, the same finding we noticed also regarding reinforcement of the suture line^[44]. Management options are varied and dependent on the timing and clinical presentation of the leak. Immediate re-operation is the preferred course of action for the unstable patient, usually with washout, irrigation of the abdominal cavity, wide drainage, and an attempt at suturing of the leak if the tissue condition allows it^[9]. Sound surgical judgment is imperative in deciding whether the tissues are amenable to suturing or whether further intervention will only impose further damage. Endoscopic stent treatment could have a major impact on managing anastomotic complications after bariatric surgery. Standard treatments are time-consuming and can result in substantial morbidity, including patient discomfort and decreased quality of life. It is our impression that stents will shorten hospital stays and reduce complications of specialized feeding. Care will likely be improved as stent manufacturers customize stents for use in bariatric surgery. Our data suggest that the use of covered stents after bariatric surgery can be safe and effective in the treatment of acute leaks, chronic fistulas, and strictures. These stents effectively seal any leak while allowing secretions and food to pass, without compromising healing. We believe

the use of endoscopically placed stents will become the preferred treatment for bariatric patients with staple line complications.

Upper GI hemorrhage occurs in approximately 1%-4% patients after LRYGP^[45]. This hemorrhage usually arises from staple line. We have 3.7% incidence of upper GI hemorrhage. All patients were successfully controlled with observation or endoscopic management, no patient required re-operation for control of bleeding, thus avoiding exposure of these morbidly obese patients for another major surgery with its potential morbidity. Conservative treatment with fluid and blood transfusion is usually effective. Patients who will not respond to conservative therapy will require either endoscopic or surgical management. Some recommend against endoscopy for fear of perforation at the immature anastomotic sites^[46]. The availability of standard hemostatic endoscopic measures, such as epinephrine injection, heater probe, and endoscopic clips, either alone or in combinations, made the success of endoscopic management available in all our patients. The majority of our patients manifested with hematemesis, which may place these patients at a high risk of aspiration. All our patients were managed in the operative room with pre-endoscopy intubation to avoid possibility of aspiration. We have reported, as others have, that endoscopy could be used in controlling postoperative bleeding with good experienced hands and enough precautions^[47-49]. Despite the relatively big number of patients we enrolled in this study, this study is not without limitations. While it is a review of prospectively collected data, it is still retrospective in nature. Additionally, there was no randomization in allocating the patients into either group. We recommend another study to be conducted on a prospective randomized way.

In conclusion, the upper digestive symptoms were predictive for presence of abnormal endoscopic finding. These endoscopic findings were found to be benign and mild. No findings were absolute contraindications to surgery or changed the decision plans. Our results support the performance of EGD only in patients with upper gastrointestinal symptoms. Endoscopy also offer safe effective tool for anastomotic complications after bariatric surgery. Endoscopic dilation of stricture is safe and effective with high success rate. Endoscopic therapy for gastric leak using covered stent is also a good option and should be considered an appropriate intervention. Most post-bariatric bleeding occurs within the first 4 h after the operation and is most commonly arising from the staple line. With experienced hands, EDG is a safe and successful tool in controlling significant post-operative hemorrhage which is best done in operative room with intubation to avoid aspiration.

COMMENTS

Background

Obesity surgery is the most effective treatment due to the sustainable and

significant weight loss results in addition to the resolution of the comorbidities in up to 80%. It is still a major controversial point to do routine screening endoscopy for those patients before surgery. Many authors suggest doing esophagogastroduodenoscopy (EGD) for all patients before bariatric procedures because of the lack of correlation between patient symptoms and EGD findings. Upper endoscopy in those patients is not without risk, one of the outmost important points is the risk of conscious sedation at the time of EGD due to hypertension and obstructive sleep apnea.

Research frontiers

The authors supposed that the upper digestive symptoms were predictive for presence of abnormal endoscopic finding and they provide support to their hypothesis with this paper.

Innovations and breakthroughs

Upper endoscopy was routinely done as a routine preoperative preparation of every obese patient before bariatric operation.

Applications

The upper digestive symptoms were predictive for presence of abnormal endoscopic finding. These endoscopic findings were found to be benign and mild. No findings were absolute contraindications to surgery or changed the decision plans. The results support the performance of EGD only in patients with upper gastrointestinal symptoms. Endoscopy also offer safe effective tool for anastomotic complications after bariatric surgery. Endoscopic dilation of stricture is safe and effective with high success rate. Endoscopic therapy for gastric leak using covered stent is also a good option and should be considered an appropriate intervention. Most post-bariatric bleeding occurs within the first 4 h after the operation and is most commonly arising from the staple line. With experienced hands, EGD is a safe and successful tool in controlling significant post-operative hemorrhage which is best done in operative room with intubation to avoid aspiration.

Terminology

Upper digestive symptoms recorded included heartburn, reflux, acid regurgitation, nausea, vomiting and abdominal pain. Esophagogastroduodenoscopy is a test to examine the lining of the esophagus, stomach and upper part of the duodenum. Laparoscopic sleeve gastrectomy is a safe and effective surgery that can help obese people lose weight. Patients may undergo sleeve gastrectomy as a single surgery or the first stage before a gastric bypass. Laparoscopic R in Y gastric bypass surgery makes the stomach smaller and causes food to bypass part of the small intestine. Mini gastric bypass surgery is a short and relatively simple procedure that has been shown by the available research to have low risk and result in good short and long-term weight loss.

Peer-review

The article is aimed to study the preoperative and postoperative role of upper endoscopy in morbidly obese patients. The clinical application of the study is very important.

REFERENCES

- Mendez MA, Monteiro CA, Popkin BM. Overweight exceeds underweight among women in most developing countries. *Am J Clin Nutr* 2005; **81**: 714-721 [PMID: 15755843]
- Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. *Nat Rev Endocrinol* 2013; **9**: 13-27 [PMID: 23165161 DOI: 10.1038/nrendo.2012.199]
- Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; **1**: 11-25 [PMID: 17902211 DOI: 10.1080/17477160600586747]
- Sturm R. Stemming the global obesity epidemic: what can we learn from data about social and economic trends? *Public Health* 2008; **122**: 739-746 [PMID: 18490037 DOI: 10.1016/j.puhe.2008.01.004]
- James WP. The fundamental drivers of the obesity epidemic. *Obes Rev* 2008; **9** Suppl 1: 6-13 [PMID: 18307693 DOI: 10.1111/j.1467-789X.2007.00432.x]
- Kopelman PG. Obesity as a medical problem. *Nature* 2000; **404**: 635-643 [PMID: 10766250]
- Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrback K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004; **292**: 1724-1737 [PMID: 15479938 DOI: 10.1001/jama.292.14.1724]
- Buchwald H, Estok R, Fahrback K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009; **122**: 248-256.e5 [PMID: 19272486 DOI: 10.1016/j.amjmed.2008.09.041]
- Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998; **6** Suppl 2: 51S-209S [PMID: 9813653]
- Martin M. Routine preoperative endoscopy: necessity or excess? *Surg Obes Relat Dis* 2008; **4**: 713-714 [PMID: 18514582 DOI: 10.1016/j.soard.2008.03.251]
- Sharaf RN, Weinshel EH, Bini EJ, Rosenberg J, Sherman A, Ren CJ. Endoscopy plays an important preoperative role in bariatric surgery. *Obes Surg* 2004; **14**: 1367-1372 [PMID: 15603653 DOI: 10.1381/0960892042583806]
- Muñoz R, Ibáñez L, Salinas J, Escalona A, Pérez G, Pimentel F, Guzmán S, Boza C. Importance of routine preoperative upper GI endoscopy: why all patients should be evaluated? *Obes Surg* 2009; **19**: 427-431 [PMID: 18795381 DOI: 10.1007/s11695-008-9673-x]
- Csendes A, Burgos AM, Smok G, Beltran M. Endoscopic and histologic findings of the foregut in 426 patients with morbid obesity. *Obes Surg* 2007; **17**: 28-34 [PMID: 17355765 DOI: 10.1007/s11695-007-9002-9]
- Küper MA, Kratt T, Kramer KM, Zdechavsky M, Schneider JH, Glatzle J, Stüker D, Königsrainer A, Brütcher BL. Effort, safety, and findings of routine preoperative endoscopic evaluation of morbidly obese patients undergoing bariatric surgery. *Surg Endosc* 2010; **24**: 1996-2001 [PMID: 20135170 DOI: 10.1007/s00464-010-0893-5]
- de Moura Almeida A, Cotrim HP, Santos AS, Bitencourt AG, Barbosa DB, Lobo AP, Rios A, Alves E. Preoperative upper gastrointestinal endoscopy in obese patients undergoing bariatric surgery: is it necessary? *Surg Obes Relat Dis* 2008; **4**: 144-149; discussion 150-151 [PMID: 18294926 DOI: 10.1016/j.soard.2007.12.006]
- Loewen M, Giovanni J, Barba C. Screening endoscopy before bariatric surgery: a series of 448 patients. *Surg Obes Relat Dis* 2008; **4**: 709-712 [PMID: 18514584 DOI: 10.1016/j.soard.2008.02.009]
- Peromaa-Haavisto P, Victorzon M. Is routine preoperative upper GI endoscopy needed prior to gastric bypass? *Obes Surg* 2013; **23**: 736-739 [PMID: 23585025 DOI: 10.1007/s11695-013-0956-5]
- Arrowsmith JB, Gerstman BB, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/ U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. *Gastrointest Endosc* 1991; **37**: 421-427 [PMID: 1833259 DOI: 10.1016/S0016-5107(91)70773-6]
- Miller G, Savary M, Monnier P. Norwendige diagnostik: endoskopie. In: Blum AL, Siewert JR. *Reflux-therapie*. Berlin: Springer-Verlag, 1981: 336-354
- Howden CW, Hunt RH. Guidelines for the management of Helicobacter pylori infection. *Am J Gastroenterol* 1998; **93**: 2330-2338 [DOI: 10.1111/j.1572-0241.1998.00684.x]
- Frigg A, Peterli R, Zynamon A, Lang C, Tondelli P. Radiologic and endoscopic evaluation for laparoscopic adjustable gastric banding: preoperative and follow-up. *Obes Surg* 2001; **11**: 594-599 [PMID: 11594101 DOI: 10.1381/09608920160557075]
- Korenkov M, Köhler L, Yücel N, Grass G, Sauerland S, Lempa M, Trold H. Esophageal motility and reflux symptoms before and after bariatric surgery. *Obes Surg* 2002; **12**: 72-76 [PMID: 11868303 DOI: 10.1381/096089202321144621]
- Frezza EE, Ikramuddin S, Gourash W, Rakitt T, Kingston A, Luketich J, Schauer P. Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. *Surg Endosc* 2002; **16**: 1027-1031 [PMID: 11984683 DOI: 10.1007/

- s00464-001-8313-5]
- 24 **Kral JG**. Morbidity of severe obesity. *Surg Clin North Am* 2001; **81**: 1039-1061 [PMID: 11589244 DOI: 10.1016/S0039-6109(05)70183-3]
 - 25 **Papavramidis ST**, Theocharidis AJ, Zaraboukas TG, Christoforidou BP, Kessissoglou II, Aidonopoulos AP. Upper gastrointestinal endoscopic and histologic findings before and after vertical banded gastroplasty. *Surg Endosc* 1996; **10**: 825-830 [PMID: 8694947 DOI: 10.1007/BF00189543]
 - 26 **Lakdawala MA**, Bhaskar A, Mulchandani D, Goel S, Jain S. Comparison between the results of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass in the Indian population: a retrospective 1 year study. *Obes Surg* 2010; **20**: 1-6 [PMID: 19802646 DOI: 10.1007/s11695-009-9981-9]
 - 27 **Nocca D**, Krawczykowsky D, Bomans B, Noël P, Picot MC, Blanc PM, de Seguin de Hons C, Millat B, Gagner M, Monnier L, Fabre JM. A prospective multicenter study of 163 sleeve gastrectomies: results at 1 and 2 years. *Obes Surg* 2008; **18**: 560-565 [PMID: 18317859 DOI: 10.1007/s11695-007-9288-7]
 - 28 **Frank P**, Crookes P. Management of gastroesophageal reflux after sleeve gastrectomy. Presented at the Second International Consensus Summit for Sleeve Gastrectomy (ICSSG), 2009
 - 29 **Melissas J**, Koukouraki S, Askoxylakis J, Stathaki M, Daskalakis M, Perisinakis K, Karkavitsas N. Sleeve gastrectomy: a restrictive procedure? *Obes Surg* 2007; **17**: 57-62 [PMID: 17355769 DOI: 10.1007/s11695-007-9006-5]
 - 30 **Melissas J**, Daskalakis M, Koukouraki S, Askoxylakis I, Metaxari M, Dimitriadis E, Stathaki M, Papadakis JA. Sleeve gastrectomy-a "food limiting" operation. *Obes Surg* 2008; **18**: 1251-1256 [PMID: 18663545 DOI: 10.1007/s11695-008-9634-4]
 - 31 **Moon Han S**, Kim WW, Oh JH. Results of laparoscopic sleeve gastrectomy (LSG) at 1 year in morbidly obese Korean patients. *Obes Surg* 2005; **15**: 1469-1475 [PMID: 16354529 DOI: 10.1381/096089205774859227]
 - 32 **Himpens J**, Dapri G, Cadière GB. A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: results after 1 and 3 years. *Obes Surg* 2006; **16**: 1450-1456 [PMID: 17132410 DOI: 10.1381/096089206778869933]
 - 33 **Klaus A**, Weiss H. Is preoperative manometry in restrictive bariatric procedures necessary? *Obes Surg* 2008; **18**: 1039-1042 [PMID: 18386106 DOI: 10.1007/s11695-007-9399-1]
 - 34 **Scott JA**, Brochmeyer JR, Johnson RJ, Choi YU. Laparoscopic Sleeve Gastrectomy Does Not Worsen Gastroesophageal Reflux Disease Symptoms in Morbidly Obese Patients. *SAGES* 2012 Meeting, San Diego, March 7-10, 2012
 - 35 **Schreiner MA**, Fennerty MB. Endoscopy in the obese patient. *Gastroenterol Clin North Am* 2010; **39**: 87-97 [PMID: 20202582 DOI: 10.1016/j.gtc.2009.12.009]
 - 36 **Ryskina KL**, Miller KM, Aisenberg J, Herron DM, Kini SU. Routine management of stricture after gastric bypass and predictors of subsequent weight loss. *Surg Endosc* 2010; **24**: 554-560 [PMID: 19585070 DOI: 10.1007/s00464-009-0605-1]
 - 37 **Parikh A**, Alley JB, Peterson RM, Hamisch MC, Pfluke JM, Tapper DM, Fenton SJ. Management options for symptomatic stenosis after laparoscopic vertical sleeve gastrectomy in the morbidly obese. *Surg Endosc* 2012; **26**: 738-746 [PMID: 22044967 DOI: 10.1007/s00464-011-1945-1]
 - 38 **Brethauer SA**, Hammel JP, Schauer PR. Systematic review of sleeve gastrectomy as staging and primary bariatric procedure. *Surg Obes Relat Dis* 2009; **5**: 469-475 [PMID: 19632646 DOI: 10.1016/j.soard.2009.05.011]
 - 39 **Sánchez-Santos R**, Masdevall C, Baltasar A, Martínez-Blázquez C, García Ruiz de Gordejuela A, Ponsi E, Sánchez-Pernaute A, Vesperinas G, Del Castillo D, Bombuy E, Durán-Escribano C, Ortega L, Ruiz de Adana JC, Baltar J, Maruri I, García-Blázquez E, Torres A. Short- and mid-term outcomes of sleeve gastrectomy for morbid obesity: the experience of the Spanish National Registry. *Obes Surg* 2009; **19**: 1203-1210 [PMID: 19572113 DOI: 10.1007/s11695-009-9892-9]
 - 40 **Serra C**, Baltasar A, Andreo L, Pérez N, Bou R, Bengochea M, Chisbert JJ. Treatment of gastric leaks with coated self-expanding stents after sleeve gastrectomy. *Obes Surg* 2007; **17**: 866-872 [PMID: 17894143 DOI: 10.1007/s11695-007-9161-8]
 - 41 **Tan JT**, Kariyawasam S, Wijeratne T, Chandraratna HS. Diagnosis and management of gastric leaks after laparoscopic sleeve gastrectomy for morbid obesity. *Obes Surg* 2010; **20**: 403-409 [PMID: 19936855 DOI: 10.1007/s11695-009-0020-7]
 - 42 **Cucchi SG**, Pories WJ, MacDonald KG, Morgan EJ. Gastrogastric fistulas. A complication of divided gastric bypass surgery. *Ann Surg* 1995; **221**: 387-391 [PMID: 7726674 DOI: 10.1097/0000658-199504000-00009]
 - 43 **Nguyen NT**, Goldman C, Rosenquist CJ, Arango A, Cole CJ, Lee SJ, Wolfe BM. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. *Ann Surg* 2001; **234**: 279-289; discussion 289-291 [PMID: 11524581 DOI: 10.1097/0000658-200109000-00002]
 - 44 **Abd Ellatif ME**, Abdallah E, Askar W, Thabet W, Aboushady M, Abbas AE, El Hadidi A, Elezaby AF, Salama AF, Dawoud IE, Moatamed A, Wahby M. Long term predictors of success after laparoscopic sleeve gastrectomy. *Int J Surg* 2014; **12**: 504-508 [PMID: 24560848 DOI: 10.1016/j.ijsu.2014.02.008]
 - 45 **Jamil LH**, Krause KR, Chengelis DL, Jury RP, Jackson CM, Cannon ME, Duffy MC. Endoscopic management of early upper gastrointestinal hemorrhage following laparoscopic Roux-en-Y gastric bypass. *Am J Gastroenterol* 2008; **103**: 86-91 [PMID: 17941960 DOI: 10.1111/j.1572-0241.2007.01588.x]
 - 46 **Nguyen NT**, Rivers R, Wolfe BM. Early gastrointestinal hemorrhage after laparoscopic gastric bypass. *Obes Surg* 2003; **13**: 62-65 [PMID: 12630615 DOI: 10.1381/096089203321136601]
 - 47 **Moretto M**, Mottin CC, Padoin AV, Berleze D, Repetto G. Endoscopic management of bleeding after gastric bypass -- a therapeutic alternative. *Obes Surg* 2004; **14**: 706 [PMID: 15186645 DOI: 10.1381/096089204323093552]
 - 48 **Steffen R**. Early gastrointestinal hemorrhage after laparoscopic gastric bypass. *Obes Surg* 2003; **13**: 466; author reply 466-467 [PMID: 12841915 DOI: 10.1381/096089203765887877]
 - 49 **Fernández-Esparrach G**, Bordas JM, Pellisé M, Gimeno-García AZ, Lacy A, Delgado S, Cárdenas A, Ginès A, Sendino O, Momblán D, Zabalza M, Llach J. Endoscopic management of early GI hemorrhage after laparoscopic gastric bypass. *Gastrointest Endosc* 2008; **67**: 552-555 [PMID: 18294521 DOI: 10.1016/j.gie.2007.10.024]

P- Reviewer: Amornyotin S, Yan SL **S- Editor:** Kong JX

L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 June 10; 8(11): 418-438





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Izuru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



MINIREVIEWS

- 418 Management of gastric subepithelial tumors: The role of endoscopy
Kim SY, Kim KO

ORIGINAL ARTICLE

Retrospective Study

- 425 Endoscopic retrograde cholangiography for pediatric choledocholithiasis: Assessing the need for endoscopic intervention
Fishman DS, Chumpitazi BP, Rajman I, Tsai CMW, Smith EO, Mazziotti MV, Gilger MA
- 433 Low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate, and clear liquid diet alone prior to small bowel capsule endoscopy
Rayner-Hartley E, Alsahafi M, Cramer P, Chatur N, Donnellan F

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 11 June 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Carlos Robles-Medrand, MD, Head, Professor, Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas (IECED), University Hospital OMNI, Espiritu Santo University, Guayaquil, Guayas 1301266, Ecuador

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jin-Xin Kong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
June 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Management of gastric subepithelial tumors: The role of endoscopy

Su Young Kim, Kyoung Oh Kim

Su Young Kim, Kyoung Oh Kim, Division of Gastroenterology, Department of Internal Medicine, Gachon University, Gil Medical Center, Incheon 405-760, South Korea

Author contributions: Kim SY and Kim KO contributed equally to this work.

Conflict-of-interest statement: No author has any personal or financial conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Kyoung Oh Kim, MD, PhD, Division of Gastroenterology, Department of Internal Medicine, Gachon University, Gil Medical Center, 21, Namdong-daero 774beon-gil, Namdong-gu, Incheon 405-760, South Korea. kkoimge@naver.com
Telephone: +82-32-4603778
Fax: +82-32-4603408

Received: March 26, 2016
Peer-review started: March 27, 2016
First decision: April 19, 2016
Revised: April 28, 2016
Accepted: May 17, 2016
Article in press: May 27, 2016
Published online: June 10, 2016

Abstract

With the wide use of esophagogastroduodenoscopy, the incidence of gastric subepithelial tumor (SET) diagnosis has increased. While the management of large or

symptomatic gastric SETs is obvious, treatment of small (≤ 3 cm) asymptomatic gastric SETs remains inconclusive. Moreover, the presence of gastrointestinal stromal tumors with malignant potential is of concern, and endoscopic treatment of gastric SETs remains a subject of debate. Recently, numerous studies have demonstrated the feasibility of endoscopic treatment of gastric SETs, and have proposed various endoscopic procedures including endoscopic submucosal dissection, endoscopic muscularis dissection, endoscopic enucleation, endoscopic submucosal tunnel dissection, endoscopic full-thickness resection, and a hybrid approach (the combination of endoscopy and laparoscopy). In this review article, we discuss current endoscopic treatments for gastric SETs as well as the advantages and limitations of this type of therapy. Finally, we predict the availability of newly developed endoscopic treatments for gastric SETs.

Key words: Subepithelial tumor; Endoscopy; Stomach; Treatment; Complication

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Recently, technical advances in endoscopic treatment, including diverse endoscopic procedures, have been performed for the resection of gastric subepithelial tumors (SETs). However, the presence of gastrointestinal stromal tumors with malignant potential is of concern and endoscopic treatment of gastric SETs remains of subject of debate. In this review article, we discuss current endoscopic treatments for gastric SETs as well as the advantages and limitations of this type of therapy. The information presented in this review should be taken into consideration when making decisions concerning endoscopic treatment for gastric SETs.

Kim SY, Kim KO. Management of gastric subepithelial tumors: The role of endoscopy. *World J Gastrointest Endosc* 2016; 8(11): 418-424 Available from: URL: <http://www.wjgnet.com>

INTRODUCTION

The majority of subepithelial tumors (SETs) are considered to be benign in origin; however, some lesions may be malignant, especially if they originate in the muscularis propria (MP) layer^[1]. Gastrointestinal stromal tumors (GIST), the most common mesenchymal neoplasms originating in the MP layer of the stomach, are malignant in 10%-30% of cases^[2]. According to the National Comprehensive Cancer Network guidelines, all GISTs larger than 2 cm should be resected. For GISTs smaller than 2 cm without high-risk features on endoscopic ultrasonography (EUS), endoscopic follow-up may be recommended^[3]. However, endoscopic surveillance has limitations, including delayed diagnosis of malignancy, high cost, hazards associated with repeated endoscopic procedures, patient discomfort related with long-term follow up examinations, and concerns associated with missing the optimum treatment window. Therefore, even for small sized gastric SETs originating in the MP layer, histological confirmation should be obtained if the tumor was not definitely differentiated as benign.

In the past, the standard treatment for gastric SETs was surgical resection, including laparotomy or laparoscopic partial gastrectomy^[4], and endoscopy was used for diagnostic purposes, and was rarely used for treatment. However, surgical resection is invasive and associated with possible surgical complications. Recently, numerous reports have proposed that endoscopic resection can be applied to gastric SETs, including GIST^[2,5-11]. The purpose of this article was to examine all practical endoscopic methods that should be taken into consideration when deciding whether to perform endoscopic treatment for gastric SETs. Through this process, we provide orientation for endoscopic treatment of gastric SETs.

WHY IS GASTRIC SET DIFFICULT TO TREAT WITH ENDOSCOPY?

Gastric SETs should be treated using endoscopic procedures; however, they remain challenging to treat. Several factors underlie the difficulties associated with endoscopic treatment. First, determining the possibility of malignancy for gastric SETs is difficult before resection. EUS and computed tomography (CT) can aid in but are by no means satisfactory for accurate diagnosis^[5,12,13], and are limited in their ability to evaluate tumor size, fibrosis, and MP layer invasion. Thus, establishing a treatment strategy with endoscopy may be difficult. Endoscopic treatments alone do not guarantee complete resection and prevention of cancer recurrence for gastric SETs. Secondly, when endoscopic resection was performed in patients with gastric SETs originating from the MP layer,

the complication rate was relatively high, especially for perforation^[2,6]. Furthermore, endoscopic resection removes only the tumor without excision of the surrounding normal tissue; therefore, the tumor is likely to be incompletely resected^[14-16]. Third, it is difficult to eliminate large or predominantly extraluminal growth of SETs by endoscopy alone^[17]. Even the endoscopic full-thickness resection (EFTR) technique that enables treatment of relatively large gastric SETs cannot be used to treat tumors larger than 4 cm with an extraluminal pattern^[18,19]. Lastly, the effectiveness of endoscopic treatment is highly affected by the location of the gastric SET. For instance, endoscope retroflexion should be maintained for gastric SETs located on the fundus or cardiac region, which has been shown to be difficult and to have a high perforation risk^[20].

CONVENTIONAL AND MODIFIED ENDOSCOPIC SUBMUCOSAL DISSECTION FOR TREATMENT OF GASTRIC SETS

Endoscopic submucosal dissection (ESD) is an effective and safe tissue resection method for the treatment of early gastric cancer (EGC)^[7,21]. Although the focus of this technique has been the treatment of EGC, its use has recently been expanded for the treatment of gastric SETs^[7,15]. According to a recent study concerning endoscopic resection of SETs using ESD, the overall rate of R0 resection was 81.1% (30/37) and no recurrence was observed in patients with R0 resections during the follow up period^[7]. In lesions that were incompletely resected, the tissue acquired was sufficient for all immunohistochemistry studies and, as a result, ESD can aid in confirming SET diagnosis. In a large study published in China, ESD was an effective and feasible treatment option for gastric SETs with diameters no greater than 50 mm originating in the MP layer^[6]. The *en bloc* complete resection rate was 92.4% (134/145) and no recurrence was detected during the follow-up period. In our previous study^[2], we discovered that tumors ≤ 2 cm in size or with a positive rolling sign, which indicates that the SET originated from the submucosal layer or has a narrow connection to the MP layer, had high complete resection rates. Moreover, we found that fixed tumor mobility and neurogenic tumors were significantly associated with perforation^[2]. We anticipated that lower tumor mobility was associated with broad muscular connections or intramural-type or subserosal-type tumors, for which it is difficult to dissect the SET from adjacent muscle tissue. To treat gastric SETs, conventional ESD is feasible. However, complete resection rates were inconsistent for the MP layer (68.2%-92.4%), and perforation risk was high^[2,6,7]. Specifically, endoscopic resection without perforation is challenging in the gastric fundus compared with other locations in the stomach. In a prospective study, conventional ESD using the "Resolution clip" was a feasible and easy method to prevent perforation of gastric fundus SETs^[20]. However, this study

Table 1 Publications reporting conventional and modified endoscopic submucosal dissection for upper gastrointestinal subepithelial tumors originating in the muscularis propria

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Lee <i>et al</i> ^[15] (2006)	11	Cardia/body	20.7	60.9	ESD	75.0	0	10.9/N
Jeong <i>et al</i> ^[14] (2011)	64	Cardia/fundus/body/antrum	13.8	34.7	Endoscopic enucleation	92.3	12.3	10.0 ¹ /N
Liu <i>et al</i> ^[22] (2012)	31	Esophagus/cardia/stomach	22.1	76.8	EMD	96.8	12.9	17.7/N
He <i>et al</i> ^[6] (2013)	144	Cardia/fundus/body/antrum	15.1	63.4	ESD	92.4	14.5 ² /4.8 ³	19.1/N
Chu <i>et al</i> ^[8] (2012)	16	Cardia/fundus/body/antrum	26.1	52.0	Modified ESD with enucleation	93.8	0	14.8/N
Li <i>et al</i> ^[20] (2013)	11	Fundus	18.8	81.0	ESD	90.9	27.2	6.4/N
Chun <i>et al</i> ^[2] (2013)	35	Cardia/fundus/body/antrum	18.0	32.3	ESD	74.3	5.7	6.1/N

¹Median follow-up period; ²Perforation; ³Bleeding. ESD: Endoscopic submucosal dissection; N: None; EMD: Endoscopic muscularis dissection.

in a relatively small number of patients showed a high perforation rate of 30%^[20]. Therefore, conventional ESD is limited for removing SETs originating from the MP layer; modified ESD was introduced to solve these problems.

Various modified ESD techniques exist, consisting of a combination of ESD and endoscopic muscularis dissection (EMD). Depending on the degree of connection between the tumor and the muscularis layer, the application ratio of ESD and EMD can be determined. According to Liu *et al*^[22], EMD was effective for treatment of gastric SETs originating in the MP layer. In their study, a longitudinal incision was made to cut the overlying mucosa, and electrical or blunt dissection was then used to dissect the SET from the submucosa and MP layers. Finally, the wound was closed with endoscopic clips^[22]. Using this method, the complete resection rate was as high as 96.8%, but perforation was also high, at 12.9%. Many trials of SET endoscopic resection using conventional and modified ESD exist (Table 1). In a study published in South Korea, in which the mucosa covering the SETs was eliminated using a coagulation snare to reveal the hidden tumors, the successful complete resection rate by endoscopic enucleation was 92.3% (60/65)^[14]; however, the perforation rate was comparatively high (12.3%). The most common location of perforation was the fundus, as it has a thin wall and is difficult to approach endoscopically. Moreover, all perforations occurred in schwannomas and GISTs; these tumors do not have intact tumor capsules and have tight adhesions^[14]. Another study demonstrated the feasibility of modified ESD with enucleation for treatment of gastric SETs^[8]. Two incisions were performed (longitudinal and transverse), which resulted in more obvious exposure of the tumor and its underlying MP layer, and an easier resection^[8]. All tumors were larger than 2 cm, and the complete resection rate was 93.8% (15/16) with no perforation or overt bleeding^[8]. This method demonstrates the beneficial results of endoscopic resection

compared with surgical resection. Open or laparoscopic surgery can lead to late stenosis and gastroesophageal reflux after surgery, resulting in decreased patient satisfaction. Despite the advantages of endoscopic enucleation, several limitations, including the difficulty of complete removal of tissue with a large enough margin around the tumor^[14], are associated with this method. Therefore, if the histologic diagnosis of a SET is highly malignant, clinicians should consider additional treatment. Moreover, in many studies, the follow-up period was short and research was performed at a single center.

ENDOSCOPIC SUBMUCOSAL TUNNEL DISSECTION FOR GASTRIC SETS

Inoue *et al*^[23] (2010) investigated peroral endoscopic myotomy (POEM) for endoscopic treatment of achalasia. This method involves creating a submucosal tunnel to create space for endoscopic treatment under the mucosal layer, and can also be used to remove muscle layer lesions. The POEM procedure was applied to SETs originating in the MP layer, and was named endoscopic submucosal tunnel dissection (ESTD), which was introduced in 2012^[10,24]. A mucosal incision was made proximal to the lesion, and a submucosal tunnel was created to resect the tumor completely using an electrosurgical knife. After removing the tumor, the mucosal layer was sutured using endoscopic clips. Compared with ESD, this method has several benefits, including fast wound healing and maintaining an intact mucosal layer, thus preventing leakage of bowel contents^[10,25]. A Japanese study with a small sample size demonstrated that ESTD resulted in safe resection of SETs without complications^[10]. Since then, other studies have shown the efficacy of ESTD for removal of SETs in the esophagus and the cardia, with complete resection rates of 100% (Table 2)^[26,27]. According to Liu *et al*^[26], esophageal and cardiac SETs originating

Table 2 Publications reporting endoscopic submucosal tunnel dissection for upper gastrointestinal subepithelial tumors originating in the muscularis propria

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Inoue <i>et al</i> ^[10] (2012)	7	Esophagus/cardia	19.0	152	Submucosal endoscopic tumor resection	100	0	5.5/N
Gong <i>et al</i> ^[24] (2012)	12	Esophagus/cardia	19.5	48.3	ESTD	83.3	16.7	NA
Liu <i>et al</i> ^[26] (2013)	12	Esophagus/cardia	18.5	78.3	tEMD	100	66.7	7.1/N
Ye <i>et al</i> ^[25] (2014)	85	Esophagus/cardia/stomach	19.2	57.2	STER	100	9.4	8 ¹ /N
Zhou <i>et al</i> ^[27] (2015)	21	Esophagogastric junction	23.0	62.9	STER	100	42.9	6 ¹ /N

¹Median follow-up period. ESTD: Endoscopic submucosal tunnel dissection; N: None; NA: Not available; tEMD: Tunneling endoscopic muscularis dissection; STER: Submucosal tunneling and endoscopic resection.

in the MP layer were more easily dissected using ESTD than with EMD. Treatment of SET at the esophagogastric junction is difficult due to the interference of esophageal peristalsis and respiration with a detailed endoscopic view and control. ESTD allows for the endoscope to enter into the submucosal tunnel, improving visibility and enabling direct cutting. Moreover, SETs originating from the MP layer can be removed without damage to the mucosa around the lesion, diminishing procedure-related strictures and scars^[27]. In another prospective study, ESTD was successful for the treatment of SETs located in the upper gastrointestinal tract, and revealed GIST and lesions in deeper MP layers as risk factors for complications^[25]. The ESTD method is relatively safe and results in a high rate of complete resection; however, it is not without limitations. In the majority of studies, ESTD was performed for SETs of the esophagogastric junction, while few studies have been performed to determine the effect of ESTD on SETs of the stomach. Because the stomach mucosa is thick and has greater curvature, submucosal tunneling can be challenging in regions including the gastric fundus and the proximal corpus. Therefore, it is difficult to perform consistent tunneling of the stomach. In addition, large SETs (> 3 cm) are difficult to remove with ESTD because confines of tunneling space may give rise to poor endoscopic visualization and insufficient *en bloc* resection^[10,25].

EFTR FOR GASTRIC SETS

Many gastric SETs originate in the deep MP layer. EFTR allows for *en bloc* resection of such SETs, including those tightly connected to the MP layer (Table 3)^[18,19,28], which was first reported in 2001 in Japan^[29]. In the past, EFTR was only applied to small lesions. The usefulness of EFTR with laparoscopy was reported in animals in a 2006 study; however, it also demonstrated the risk for perforation-induced intraperitoneal infections^[30]. In 2011, Zhou *et al*^[28] showed the feasibility of EFTR without

laparoscopy for gastric SETs originating in the MP layer. This strategy was effective in treating deep gastric SETs with a complete resection rate of 100% (26/26) and no severe complications. These results were mirrored in another study published in China, in which EFTR resulted in successful complete resection (98.0%) without severe complications^[18]. However, this study used clip closures and endoloop ligatures as additional closure devices^[18], which may have strengthened the suturing technique to avoid gastric perforation. Moreover, endoloop ligatures are simple and do not require specific equipment. Recently, a new technique was introduced using endoscopic suturing devices in EFTR^[11]; full-thickness sutures were deployed underneath the subepithelial mass and the SET was removed using an endoscopic electrocautery snare. This technique, explained by Schmidt *et al*^[11] as "suture first, cut later", has several advantages including the fact that it is applicable to large tumors (up to 4 cm), it can be applied to tumors at all stomach sites, and it does not require laparoscopic assistance.

While EFTR is effective in treating gastric SETs originating in the MP layer, EFTR without laparoscopy has several limitations, as it is not suitable for the removal of very large tumors, it requires advanced endoscopic skills, and it has a high risk for perforation or peritonitis. Two reports published in Japan investigated the efficacy and feasibility of laparoscopic and endoscopic cooperative surgery (LECS) (Table 3)^[31,32]. In this procedure, three-quarters of the tumor submucosal layer was dissected circumferentially using the ESD technique. Then, laparoscopic seromuscular dissection was performed at the three-quarter cut line around the tumor. Finally, the tumor was raised using laparoscopic forceps, and the resection was performed using laparoscopic stapling devices. This method is applicable to gastric SETs irrespective of tumor dimension and site. Additionally, this procedure only requires a minimal area of the stomach to be resected^[31,32]. To avoid excessive normal gastric tissue removal, Abe *et al*^[33] studied laparoscopy-assisted

Table 3 Publications reporting endoscopic full-thickness resection with or without laparoscopy for gastric subepithelial tumors

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Hiki <i>et al.</i> ^[33] (2008)	7	Esophagogastric junction/stomach	46	169	LECS	100	0	NA
Abe <i>et al.</i> ^[33] (2009)	4	Body	30	201	LAEFR	100	0	8/N
Tsujimoto <i>et al.</i> ^[32] (2012)	20	Esophagogastric junction/body/antrum	37.9	157.5	LECS	100	0	20.7/N
Ye <i>et al.</i> ^[18] (2014)	51	Fundus/body/antrum	24	52	EFTR	98	0	22.4 ¹ /N
Mitsui <i>et al.</i> ^[36] (2014)	6	Body	22.7	273.5	NEWS	100	0	8/N
Schmidt <i>et al.</i> ^[11] (2015)	31	Carida/fundus/body/antrum	20.5	60	EFTR	90.3	9.6 ² /38.7 ³	7 (roughly)/N

¹Median follow up period; ²Perforation; ³Bleeding. LECS: Laparoscopic and endoscopic cooperative surgery; NA: Not available; LAEFR: Laparoscopy-assisted endoscopic full-thickness resection; N: None; EFTR: Endoscopic full-thickness resection; NEWS: Non-exposed endoscopic wall-inversion surgery.

endoscopic full-thickness resection (LAEFR) (Table 3); this technique is a hybrid of natural orifice transluminal surgery. Using the ESD technique, the tissue surrounding the gastric SET was circumferentially incised and the submucosal layer was dissected, and EFTR including the serosal layer was then performed surrounding approximately two-thirds to three-fourths of the tissue surrounding the SET. A laparoscopic full-thickness incision was made to resect and remove the remaining tumor in the peritoneal cavity. Finally, the stomach wall was sutured using laparoscopic hand-sewn closures without linear staples^[33]. Advantages of LAEFR include ease and accuracy, a small resection margin, and it is inexpensive compared to other laparoscopic procedures^[33]. In addition, an important advantage of LECS and LAEFR is that these methods are appropriate for the treatment of intraluminal gastric SETs in the MP layer. Another recent study showed that indications for endoscopic assistance during laparoscopic resection included growing type (intraluminal) tumors and a tumor size ≤ 18 mm^[34]. It is difficult to determine the correct location and proper resection margin of these tumors by laparoscopy, which could result in excessive tissue elimination. Indeed, complications such as stenosis or deformity can occur. LECS or LAEFR could prevent these side effects, as the resection margin is determined through endoscopy^[17].

Some researchers have developed new combinations of endoscopic and laparoscopic treatments for full-thickness resection. A combination of laparoscopic and endoscopic approaches to neoplasia using the non-exposure technique (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS) were developed to avoid malignant tumor dissemination during full-thickness resection^[35,36]. The CLEAN-NET procedure involves mucosal marks made during endoscopy and four full-layer stay sutures to fix the mucosal layer to the seromuscular layer. Following submucosal injection of solution, the seromuscular layer is dissected using a laparoscopic electrocautery knife. Then, the full-layer

specimen is lifted and dissected using a laparoscopic linear stapler. The CLEAN-NET procedure results in no transluminal communication; therefore, it reduces the risk of potential malignant seeding. However, CLEAN-NET has limitations, such as risk of a mucosal tear, and it is difficult to determine the incision line^[35,37-39]. The NEWS procedure is performed as follows. A laparoscopic seromuscular dissection is performed after endoscopic submucosal injection. Then, the seromuscular layer is closed with a laparoscopic suture and the dissected portion is inverted to the luminal side. A circumferential mucosal incision and mucosal layer dissection are made using the ESD technique. The NEWS procedure has various benefits. Similar to CLEAN-NET, the NEWS procedure avoids potential cancer seeding into the peritoneal cavity. Also, it ensures an accurate resection line. The disadvantages of the NEWS procedure are that it is time-consuming and tumor size is limited^[15,36,38-40]. The CLEAN-NET and NEWS procedure are effective novel hybrid techniques. However, these methods are rarely applied to treat gastric SETs. Therefore, further studies of these methods are needed for application to gastric SET treatment.

CONCLUSION

To expand the role of endoscopy for the treatment of gastric SETs, several problems must be resolved. First, it is important to determine ways in which to reduce complications associated with endoscopic treatment, focusing specifically on perforation. Carbon dioxide insufflation during endoscopic procedures could be considered as it may reduce the risk of emphysema and pneumoperitoneum^[9,27]. Several closing devices for the prevention of procedure-induced perforation have been also described^[19,20]. Indeed, methods including OTSC and the "Resolution clip" are efficient in reducing perforation. However, these only apply to a few patients with small perforations and specific lesions sites, and

are not suitable for larger SETs. Thus, the development of new methods to address this limitation is warranted. Secondly, the mean follow-up period of the majority of the studies presented in this review was under 2 years. Although complete resection was preceded by endoscopic treatment, gastric SETs with malignant potential have a risk of recurrence. Therefore, further studies with longer-term follow-up periods and appropriate follow-up duration guidelines after endoscopic SET treatment are required. Next, until now, most studies were performed at a single institute, were retrospective in nature, and only included a small number of participants. Due to the characteristic of SETs, recruitment of a large sample size can be difficult and, thus, may introduce statistical errors including selection bias. Therefore, larger prospective multicenter studies or meta-analyses studying the effects of endoscopic treatment in gastric SETs are warranted. Moreover, the limitations involving large gastric SETs or tumors of the esophagogastric junction or posterior wall must be resolved. As ESTD showed promising results for the treatment of gastric SETs located on the esophagogastric junction, appropriate procedures for other difficult locations should be developed. Finally, a hybrid approach combining endoscopy and laparoscopy should be considered. This method has the advantage of preserving the volume and function of the stomach, and may increase a patient's satisfaction with the procedure. In addition, novel hybrid techniques (CLEAN-NET and NEWS) avoid exposing malignant SETs to the peritoneal cavity. In conclusion, technical modifications and improvements are required to define the role of endoscopy for treating gastric SETs.

REFERENCES

- 1 **Hwang JH**, Rulyak SD, Kimmey MB. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology* 2006; **130**: 2217-2228 [PMID: 16762644 DOI: 10.1053/j.gastro.2006.04.033]
- 2 **Chun SY**, Kim KO, Park DS, Lee IJ, Park JW, Moon SH, Baek IH, Kim JH, Park CK, Kwon MJ. Endoscopic submucosal dissection as a treatment for gastric subepithelial tumors that originate from the muscularis propria layer: a preliminary analysis of appropriate indications. *Surg Endosc* 2013; **27**: 3271-3279 [PMID: 23519491 DOI: 10.1007/s00464-013-2904-9]
- 3 **Demetri GD**, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetz S, Sundar HM, Trent JC, Wayne JD. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 2010; **8** Suppl 2: S1-41; quiz S42-44 [PMID: 20457867]
- 4 **Ponsaing LG**, Hansen MB. Therapeutic procedures for submucosal tumors in the gastrointestinal tract. *World J Gastroenterol* 2007; **13**: 3316-3322 [PMID: 17659670 DOI: 10.3748/wjg.v13.i24.3316]
- 5 **Lee CM**, Kim HH. Minimally invasive surgery for submucosal (subepithelial) tumors of the stomach. *World J Gastroenterol* 2014; **20**: 13035-13043 [PMID: 25278697 DOI: 10.3748/wjg.v20.i36.13035]
- 6 **He Z**, Sun C, Wang J, Zheng Z, Yu Q, Wang T, Chen X, Liu W, Wang B. Efficacy and safety of endoscopic submucosal dissection in treating gastric subepithelial tumors originating in the muscularis propria layer: a single-center study of 144 cases. *Scand J Gastroenterol* 2013; **48**: 1466-1473 [PMID: 24131359 DOI: 10.3109/00365521.2013.845796]
- 7 **Bialek A**, Wiechowska-Kozłowska A, Pertkiewicz J, Polkowski M, Milkiewicz P, Karpińska K, Lawniczak M, Starzyńska T. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). *Gastrointest Endosc* 2012; **75**: 276-286 [PMID: 22032850 DOI: 10.1016/j.gie.2011.08.029]
- 8 **Chu YY**, Lien JM, Tsai MH, Chiu CT, Chen TC, Yang KC, Ng SC. Modified endoscopic submucosal dissection with enucleation for treatment of gastric subepithelial tumors originating from the muscularis propria layer. *BMC Gastroenterol* 2012; **12**: 124 [PMID: 22978826 DOI: 10.1186/1471-230X-12-124]
- 9 **Zhang Y**, Ye LP, Zhou XB, Mao XL, Zhu LH, He BL, Huang Q. Safety and efficacy of endoscopic excavation for gastric subepithelial tumors originating from the muscularis propria layer: results from a large study in China. *J Clin Gastroenterol* 2013; **47**: 689-694 [PMID: 23632361 DOI: 10.1097/MCG.0b013e3182908295]
- 10 **Inoue H**, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Maselli R, Kudo S. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. *Endoscopy* 2012; **44**: 225-230 [PMID: 22354822 DOI: 10.1055/s-0031-1291659]
- 11 **Schmidt A**, Bauder M, Riecken B, von Renteln D, Muehleisen H, Caca K. Endoscopic full-thickness resection of gastric subepithelial tumors: a single-center series. *Endoscopy* 2015; **47**: 154-158 [PMID: 25380509 DOI: 10.1055/s-0034-1390786]
- 12 **Mullady DK**, Tan BR. A multidisciplinary approach to the diagnosis and treatment of gastrointestinal stromal tumor. *J Clin Gastroenterol* 2013; **47**: 578-585 [PMID: 23751846 DOI: 10.1097/MCG.0b013e3182936c87]
- 13 **Faigel DO**, Abulhawa S. Gastrointestinal stromal tumors: the role of the gastroenterologist in diagnosis and risk stratification. *J Clin Gastroenterol* 2012; **46**: 629-636 [PMID: 22858511 DOI: 10.1097/MCG.0b013e3182548f6c]
- 14 **Jeong ID**, Jung SW, Bang SJ, Shin JW, Park NH, Kim do H. Endoscopic enucleation for gastric subepithelial tumors originating in the muscularis propria layer. *Surg Endosc* 2011; **25**: 468-474 [PMID: 20589510 DOI: 10.1007/s00464-010-1195-7]
- 15 **Lee IL**, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. *Endoscopy* 2006; **38**: 1024-1028 [PMID: 17058168 DOI: 10.1055/s-2006-944814]
- 16 **Li QL**, Yao LQ, Zhou PH, Xu MD, Chen SY, Zhong YS, Zhang YQ, Chen WF, Ma LL, Qin WZ. Submucosal tumors of the esophagogastric junction originating from the muscularis propria layer: a large study of endoscopic submucosal dissection (with video). *Gastrointest Endosc* 2012; **75**: 1153-1158 [PMID: 22459663 DOI: 10.1016/j.gie.2012.01.037]
- 17 **Abe N**, Takeuchi H, Ooki A, Nagao G, Masaki T, Mori T, Sugiyama M. Recent developments in gastric endoscopic submucosal dissection: towards the era of endoscopic resection of layers deeper than the submucosa. *Dig Endosc* 2013; **25** Suppl 1: 64-70 [PMID: 23368096 DOI: 10.1111/j.1443-1661.2012.01387.x]
- 18 **Ye LP**, Yu Z, Mao XL, Zhu LH, Zhou XB. Endoscopic full-thickness resection with defect closure using clips and an endoloop for gastric subepithelial tumors arising from the muscularis propria. *Surg Endosc* 2014; **28**: 1978-1983 [PMID: 24619327 DOI: 10.1007/s00464-014-3421-1]
- 19 **Schlag C**, Wilhelm D, von Delius S, Feussner H, Meining A. EndoResect study: endoscopic full-thickness resection of gastric subepithelial tumors. *Endoscopy* 2013; **45**: 4-11 [PMID: 23254401 DOI: 10.1055/s-0032-1325760]
- 20 **Li L**, Wang F, Wu B, Wang Q, Wang C, Liu J. Endoscopic submucosal dissection of gastric fundus subepithelial tumors originating from the muscularis propria. *Exp Ther Med* 2013; **6**: 391-395 [PMID: 24137195 DOI: 10.3892/etm.2013.1181]
- 21 **Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group

- multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]
- 22 **Liu BR**, Song JT, Qu B, Wen JF, Yin JB, Liu W. Endoscopic muscularis dissection for upper gastrointestinal subepithelial tumors originating from the muscularis propria. *Surg Endosc* 2012; **26**: 3141-3148 [PMID: 22580875 DOI: 10.1007/s00464-012-2305-5]
- 23 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
- 24 **Gong W**, Xiong Y, Zhi F, Liu S, Wang A, Jiang B. Preliminary experience of endoscopic submucosal tunnel dissection for upper gastrointestinal submucosal tumors. *Endoscopy* 2012; **44**: 231-235 [PMID: 22354823 DOI: 10.1055/s-0031-1291720]
- 25 **Ye LP**, Zhang Y, Mao XL, Zhu LH, Zhou X, Chen JY. Submucosal tunneling endoscopic resection for small upper gastrointestinal subepithelial tumors originating from the muscularis propria layer. *Surg Endosc* 2014; **28**: 524-530 [PMID: 24013472 DOI: 10.1007/s00464-013-3197-8]
- 26 **Liu BR**, Song JT, Kong LJ, Pei FH, Wang XH, Du YJ. Tunneling endoscopic muscularis dissection for subepithelial tumors originating from the muscularis propria of the esophagus and gastric cardia. *Surg Endosc* 2013; **27**: 4354-4359 [PMID: 23765425 DOI: 10.1007/s00464-013-3023-3]
- 27 **Zhou DJ**, Dai ZB, Wells MM, Yu DL, Zhang J, Zhang L. Submucosal tunneling and endoscopic resection of submucosal tumors at the esophagogastric junction. *World J Gastroenterol* 2015; **21**: 578-583 [PMID: 25593479 DOI: 10.3748/wjg.v21.i2.578]
- 28 **Zhou PH**, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW, Liu JZ. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surg Endosc* 2011; **25**: 2926-2931 [PMID: 21424195 DOI: 10.1007/s00464-011-1644-y]
- 29 **Suzuki H**, Ikeda K. Endoscopic mucosal resection and full thickness resection with complete defect closure for early gastrointestinal malignancies. *Endoscopy* 2001; **33**: 437-439 [PMID: 11396763 DOI: 10.1055/s-2001-14269]
- 30 **Ikeda K**, Mosse CA, Park PO, Fritscher-Ravens A, Bergström M, Mills T, Tajiri H, Swain CP. Endoscopic full-thickness resection: circumferential cutting method. *Gastrointest Endosc* 2006; **64**: 82-89 [PMID: 16813808 DOI: 10.1016/j.gie.2005.12.039]
- 31 **Hiki N**, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Miki A, Ohyama S, Seto Y. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc* 2008; **22**: 1729-1735 [PMID: 18074180 DOI: 10.1007/s00464-007-9696-8]
- 32 **Tsujimoto H**, Yaguchi Y, Kumano I, Takahata R, Ono S, Hase K. Successful gastric submucosal tumor resection using laparoscopic and endoscopic cooperative surgery. *World J Surg* 2012; **36**: 327-330 [PMID: 22187132 DOI: 10.1007/s00268-011-1387-x]
- 33 **Abe N**, Takeuchi H, Yanagida O, Masaki T, Mori T, Sugiyama M, Atomi Y. Endoscopic full-thickness resection with laparoscopic assistance as hybrid NOTES for gastric submucosal tumor. *Surg Endosc* 2009; **23**: 1908-1913 [PMID: 19184206 DOI: 10.1007/s00464-008-0317-y]
- 34 **Dávila JS**, Momblán D, Ginés À, Sánchez-Montes C, Araujo I, Saavedra-Pérez D, Lacy AM, Fernández-Esparrach G. Endoscopic-assisted laparoscopic resection for gastric subepithelial tumors. *Surg Endosc* 2016; **30**: 199-203 [PMID: 25860952 DOI: 10.1007/s00464-015-4183-0]
- 35 **Inoue H**, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Suzuki M, Kudo SE. Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET). *Surg Oncol Clin N Am* 2012; **21**: 129-140 [PMID: 22098836 DOI: 10.1016/j.soc.2011.09.012]
- 36 **Mitsui T**, Niimi K, Yamashita H, Goto O, Aikou S, Hatao F, Wada I, Shimizu N, Fujishiro M, Koike K, Seto Y. Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. *Gastric Cancer* 2014; **17**: 594-599 [PMID: 23974429 DOI: 10.1007/s10120-013-0291-5]
- 37 **Nabeshima K**, Tomioku M, Nakamura K, Yasuda S. Combination of Laparoscopic and Endoscopic Approaches to Neoplasia with Non-exposure Technique (CLEAN-NET) for GIST with Ulceration. *Tokai J Exp Clin Med* 2015; **40**: 115-119 [PMID: 26369265]
- 38 **Ntourakis D**, Mavrogenis G. Cooperative laparoscopic endoscopic and hybrid laparoscopic surgery for upper gastrointestinal tumors: Current status. *World J Gastroenterol* 2015; **21**: 12482-12497 [PMID: 26604655 DOI: 10.3748/wjg.v21.i43.12482]
- 39 **Maehata T**, Goto O, Takeuchi H, Kitagawa Y, Yahagi N. Cutting edge of endoscopic full-thickness resection for gastric tumor. *World J Gastrointest Endosc* 2015; **7**: 1208-1215 [PMID: 26566427 DOI: 10.4253/wjge.v7.i16.1208]
- 40 **Kim DW**, Kim JS, Kim BW, Jung JY, Kim GJ, Kim JJ. Non-Exposed Endoscopic Wall-Inversion Surgery for Gastrointestinal Stromal Tumor of the Stomach: First Case Report in Korea. *Clin Endosc* 2016 Mar 15; Epub ahead of print [PMID: 26975860 DOI: 10.5946/ce.2016.002]

P- Reviewer: Arigami T S- Editor: Ji FF L- Editor: A
E- Editor: Lu YJ



Retrospective Study

Endoscopic retrograde cholangiography for pediatric choledocholithiasis: Assessing the need for endoscopic intervention

Douglas S Fishman, Bruno P Chumpitazi, Isaac Rajiman, Cynthia Man-Wai Tsai, E O'Brian Smith, Mark V Mazziotti, Mark A Gilger

Douglas S Fishman, Bruno P Chumpitazi, Cynthia Man-Wai Tsai, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Texas Children's Hospital, Houston, TX 77030, United States

Isaac Rajiman, Digestive Associates of Houston, Houston, TX 77098, United States

E O'Brian Smith, Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, United States

Mark V Mazziotti, Michael E Debakey, Department of Surgery, Section of Pediatric Surgery, Baylor College of Medicine, Houston, TX 77030, United States

Mark A Gilger, Department of Pediatrics, Baylor College of Medicine, Children's Hospital of San Antonio, San Antonio, TX 78207, United States

Author contributions: Fishman DS designed and performed the research and wrote the manuscript; Chumpitazi BP designed and performed the research, wrote the manuscript and edited and approved the final manuscript; Rajiman I designed the research, supervised the report, contributed to the analysis, edited and approved the final manuscript; Smith EO performed the statistical analysis and supervised the report; Tsai CMW and Mazziotti MV contributed to the analysis, edited and approved the final manuscript; Gilger MA designed and performed the research, supervised the report and contributed to the analysis and final editing and approval of the manuscript.

Institutional review board statement: This study was approved by the Baylor College of Medicine Institutional Review Board.

Informed consent statement: A waiver for informed consent was approved by the Baylor College of Medicine Institutional Review Board. Patients were not required to give informed consent to the study because subjects had previously received standard of care; the study could not be completed without the waiver; and all precautions were taken to prevent loss of private health information.

Conflict-of-interest statement: Dr. Douglas Fishman is on an advisory board for Norgine Pharmaceuticals, and has served as a consultant for Cook Medical. Dr. Rajiman is a speaker and consultant for Boston Scientific. Dr. Chumpitazi has received research support from QOL Medical, Inc. and is a consultant for Mead Johnson Nutrition.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Douglas S Fishman, MD, Associate Professor, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Texas Children's Hospital, Clinical Care Center 1010, 6621 Fannin Street, Houston, TX 77030, United States. dougfishman@gmail.com
Fax: +1-832-8253633

Received: November 13, 2015

Peer-review started: November 16, 2015

First decision: January 4, 2016

Revised: February 16, 2016

Accepted: March 7, 2016

Article in press: March 9, 2016

Published online: June 10, 2016

Abstract

AIM: To assess pediatric patients for choledocholithiasis. We applied current adult guidelines to identify predictive

factors in children.

METHODS: A single-center retrospective analysis was performed at a tertiary children's hospital. We evaluated 44 consecutive pediatric patients who underwent endoscopic retrograde cholangiography (ERCP) for suspected choledocholithiasis. Patients were stratified into those with common bile duct stones (CBDS) at ERCP *vs* those that did not using the American Society of Gastrointestinal Endoscopy (ASGE) guidelines (Very Strong and Strong criteria) for suspected CBDS.

RESULTS: CBDS were identified in 84% at the time of ERCP. Abdominal ultrasound identified CBDS in 36% of patients. Conjugated bilirubin ≥ 0.5 mg/dL was an independent risk factor for CBDS ($P = 0.003$). The Very Strong (59.5%) and Strong (48.6%) ASGE criteria identified the majority of patients ($P = 0.0001$). A modified score using conjugated bilirubin had a higher sensitivity (81.2% *vs* 59.5%) and more likely to identify a stone than the standard criteria, odds ratio of 25.7 compared to 8.8. Alanine aminotransferase and gamma-glutamyl transferase values identified significant differences in a subset of patients with odds ratio of 4.1 and 3.25, respectively.

CONCLUSION: Current adult guidelines identified the majority of pediatric patients with CBDS, but specific pediatric guidelines may improve detection, thus decreasing risks and unnecessary procedures.

Key words: Endoscopic retrograde cholangiography; Pediatric; Endoscopy; Choledocholithiasis; Children; Gallstones; Abdominal ultrasound

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In pediatric patients with gallstones, biliary obstruction has been reported in up to 30% of patients with limited data to predict need for endoscopic retrograde cholangiography for choledocholithiasis. In this single-center retrospective study we evaluated 44 consecutive pediatric patients and used the American Society of Gastrointestinal Endoscopy guidelines for suspected choledocholithiasis. We found that the Very Strong and Strong criteria identified the majority of patients. Conjugated bilirubin was also identified as an important predictor. Current adult guidelines can be used in the majority of patients, but specific pediatric guidelines may improve detection, thus decreasing risks.

Fishman DS, Chumpitazi BP, Raijman I, Tsai CMW, Smith EO, Mazziotti MV, Gilger MA. Endoscopic retrograde cholangiography for pediatric choledocholithiasis: Assessing the need for endoscopic intervention. *World J Gastrointest Endosc* 2016; 8(11): 425-432 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i11/425.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i11.425>

INTRODUCTION

Choledocholithiasis can complicate symptomatic gallstones in up to 10% of adults at cholecystectomy^[1]. Children may be at higher risk with recent studies demonstrating up to 30% of patients evaluated for pediatric gallbladder disease having some form of complicated bile duct obstruction as evidenced by jaundice, pancreatitis, or imaging with a visualized stone or dilated bile duct^[2-4]. As in adult patients with choledocholithiasis, management options in children include both endoscopic and surgical methods. However, normal laboratory value differences and differences in bile duct size between pediatric and adults patients pose further challenges to appropriate patient selection for the management of pediatric choledocholithiasis.

Multiple studies in adult patients have evaluated specific keys in identifying common bile duct stones at endoscopic retrograde cholangiography (ERCP)^[5-9]. Algorithms and scoring systems have been developed in order to identify patients with a high likelihood of having common bile duct stones (CBDS) that would benefit from treatment with ERCP, or other modalities such as laparoscopic cholecystectomy with intraoperative cholangiogram.

Current American Society of Gastrointestinal Endoscopy (ASGE) guidelines stratify adult patients using several predictors^[10]. A probability of stone identification of greater than 50% at ERCP is set as an appropriate level of detection of CBDS. These conditions are met if any of the following were identified: The value of total bilirubin (measured in mg/dL) was greater than 4, a CBDS is visualized by trans-abdominal ultrasound, or the presence of cholangitis. If both the CBD diameter was greater than 6 mm by ultrasound and the total bilirubin was greater than 1.8 mg/dL, ERCP was recommended and considered to meet the 50% threshold. When present these factors were useful for CBDS prediction, while other factors such as age greater than 55 years old, presence of gallstone pancreatitis and abnormal markers of liver and biliary inflammation [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ GT), and alkaline phosphatase] were less likely to predict CBDS. In contrast, limited data and recommendations are available for the management of suspected CBDS or gallstone pancreatitis in children^[11-13]. The aim of our study was to determine the applicability of the current ASGE guidelines in pediatric patients with suspected CBDS and to identify other factors that may be predictive in the pediatric population.

MATERIALS AND METHODS

Retrospective analysis was performed on consecutive ERCPs in children ages 6-18 years of age, performed over 24 mo. Cases were reviewed for patients with suspected common bile duct stones with gallbladder *in situ* evaluated in the hospital or emergency department. Patients were excluded if they were status post-

Table 1 Demographics of patients with suspected choledocholithiasis

Group number	1	2	Total
<i>n</i>	37	7	44
Mean age	14.5 (± 3.8)	14.5 (± 2.0)	14.5 (± 3.5)
Sex			
Male	14	0	14
Female	23	7	30
Ethnicity			
White	4	2	6
African-American	12	0	12
Latino-Hispanic	20	5	25
Other	1	0	1
Imaging			
CBDS on US	16	0	16
No CBDS on US	21	7	28
CBDS on MRCP	6 of 8	3 of 6	9 of 14
Clinical			
Gallstone pancreatitis	11	4	15

CBDS: Common bile duct stone; US: Ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

cholecystectomy, had ERCP for another indication, or ultrasound (US) results were not available. Presence of CBDS by US and bile duct diameter (measured in millimeters) were recorded. Bilirubin (unconjugated and conjugated) and other laboratory values were captured pre-procedure (within 24 h). This study approved by the Institutional Review Board at Baylor College of Medicine, Houston, Texas.

For the purposes of this study, total bilirubin was calculated as the sum of unconjugated and conjugated bilirubin levels. Normal values for unconjugated bilirubin at our institution is 0-1.0 mg/dL, and for conjugated bilirubin is 0-0.3 mg/dL. Biliary cannulation and sphincterotomy was performed in all patients at the time of the procedure. Patients were classified into two groups; Group 1, patients with CBDS found at ERCP and Group 2 those without CBDS at ERCP.

ASGE guidelines to predict the likelihood of detecting CBDS at ERCP were used to classify patients^[10]. Predictors per ASGE guidelines were: Very Strong (VS) if CBDS was identified on abdominal US or total bilirubin > 4 mg/dL or Strong (S) if both CBD diameter ≥ 6 mm on US and bilirubin ≥ 1.8-4 mg/dL.

Patients were assessed on each of the following ASGE factors: (1) Visualized CBDS on ultrasound imaging; (2) CBD diameter > 6 mm on ultrasound imaging; and (3) Total bilirubin level.

For subset analysis, patients were divided into one of two groups: VS: Either CBDS on US or total bilirubin > 4, or those meeting S criteria, with the combination of having both a total bilirubin > 1.8 and a CBD diameter of > 6 mm.

Statistical analysis

SPSS (Statistical Package for the Social Sciences, IBM, Armonk, NY) Version 19.0 was used for statistical calculations. χ^2 with McNemar's test to compare correlated groups was used with interquartile range (IQR) and medians and percentiles calculated for continuous data.

Similarly, Mann-Whitney test was used to compare groups with non-parametric data and the Mantel-Haenszel test was used to calculate a Common Odds Ratio Estimate. A *P*-value of < 0.05 was considered to be statistically significant. Unless otherwise specified, values are presented as median with interquartile range in parentheses. Confidence intervals were calculated using <http://vassarstats.net/clin1.html>. The statistical methods of this study were reviewed by Dr. Smith, biostatistician, Baylor College of Medicine.

RESULTS

Forty-four consecutive children with gallbladder *in situ* hospitalized for evaluation of suspected CBDS were evaluated. The median age was 15.4 years (ages 6-18 years old) (Table 1). Eight of 44 patients (18.2%) had hemolytic disease. Gallstone pancreatitis was the initial presentation in 15 patients (34%). Forty-three/forty-four patients had general anesthesia, and the remaining patients received deep sedation with intravenous midazolam and propofol. Magnetic resonance cholangiopancreatography (MRCP) was performed in 14/44 patients, and identified choledocholithiasis in 9 of 14. ERCP identified stones in 84% (*n* = 37), referred to as Group 1. In Group 2, (*n* = 7) that did not have CBDS at ERCP, common bile duct dilation > 6 mm was evident in 85.7% (*n* = 6), and all had endoscopic or radiographic findings suspicious for papillary stenosis, suprapapillary stricture from stone passage or recent pancreatitis. All patients had a native papilla, and sphincterotomy was performed at time of the procedure. No patients had a clinical picture of cholangitis. Adverse event rates in both groups were similar, with one case of mild pancreatitis in each group.

Use of abdominal US in diagnosis of CBDS

All patients had abdominal ultrasound performed and a portion of the common bile duct was visualized in all but one patient (43/44). CBDS were identified by US in 36% (*n* = 16), and this differed from the 85% (*n* = 37) found to have CBDS by ERCP (*P* = 0.029). Sensitivity of US for CBDS was poor, 43% (95%CI: 28%-60%), with specificity 100% (95%CI: 56%-100%), positive predictive value (PPV) of 100% (95%CI: 76%-100%) and a negative predictive value (NPV) of 25% (95%CI: 11%-45%).

The median CBD diameter in Group 1 was 9.0 mm (7.0, 11.0) and 8.0 mm (6.1-10.0) in Group 2 (Table 1). A CBD greater than 6 millimeters was demonstrated in 36 (81.8%) patients, 30 in Group 1 and 6 in Group 2 (*P* = NS). The combination of ultrasound findings of CBDS and a dilated bile duct > 6 mm was seen in 15 patients (34.1%). Twenty-two patients had one or the other, 16 in Group 1 and 6 in Group 2. Seven patients had a CBD diameter of less than 6 mm or CBDS by ultrasound, and the majority (84%) were in Group 1. Conversely, all 6 patients in Group 2 had a bile duct diameter > 6 mm.

Table 2 Univariate analysis of clinical parameters with interquartile ranges

	Combined group data median (IQR)	Group 1 median (IQR)	Group 2 median (IQR)
Age (yr)	15.8 (12.5, 17.3)	16.1 (12.2, 17.3)	14.8 (12.5, 15.4)
Time to procedure (d)	2 (1.0, 2.3)	2 (1.0, 2.0)	2 (1.0-3.0)
US CBD diameter (mm)	8.8 (6.8, 10.5)	9 (7.0, 11.0)	8 (6.1-10.0)
ERCP CBD diameter (mm)	11 (9.0, 13.0)	11 (9.3, 13)	9 (7.0, 10.0)
Total bilirubin (mg/dL)	2 (0.8, 3.6)	2.5 (0.9, 3.8)	0.9 (0.6-1.5)
Conjugated bilirubin (mg/dL)	1 (0.0-2.1)	1.3 (0.0, 2.4)	0 (0, 0)
ALT (u/L)	242 (142.5, 386.5)	253 (145.0, 403.0)	166 (122.0-166.0)
AST (u/L)	128 (86.0, 188.0)	129 (89.0, 215.0)	119 (53-150)
γGT (u/L)	259 (177.0, 453.5)	259 (181.0, 521.0)	203 (159.0-333)
Alkaline phosphatase (u/L)	252 (179.0, 349.0)	254 (182.0, 405.0)	208 (107.0-256.0)

Combined group data, Group 1 (patients with CBDS) and Group 2 (patients without CBDS). IQR: Interquartile range; CBD: Common bile duct; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γGT: Gamma-glutamyl transferase; US: Ultrasound; ERCP: Endoscopic retrograde cholangiography.

Although it would be expected that in the presence of a larger bile duct, a greater chance for CBDS would be found but this was not the case emphasizing the importance of using multiple parameters in making the clinical assessment.

Serum bilirubin was measured in all patients (Table 2 and Figure 1). There were significant differences between Group 1 and 2 for mean values of total bilirubin ($P = 0.004$) and conjugated bilirubin $P = 0.02$ (0.004 including patients with hemolytic disease). In Group 1, 8 (22%) patients had a total bilirubin greater than 4 mg/dL, while none did in Group 2 ($P = 0.0001$). Twenty-one (58%) patients in Group 1 and 1 patient in Group 2 had total bilirubin > 1.8 mg/dL ($P = 0.0001$). In comparison, 25 (68%) patients in Group 1 had a conjugated bilirubin ≥ 0.5 mg/dL, and none in Group 2 ($P = 0.003$). Sensitivity was also higher using conjugated bilirubin ≥ 0.5 mg/dL than cut-offs of total bilirubin of 4 or 1.8 mg/dL (Table 3). Multivariate logistic regression identified conjugated bilirubin ≥ 0.5 mg/dL as an independent risk factor for detection of CBDS.

Categorization using current ASGE guidelines in management of CBDS

Determinations for each patient were made as to whether patients met the ASGE VS or S criteria (Table 3). As expected, there was a significant difference between patients in Group 1 and 2 using the VS criteria to stratify patients ($P = 0.0001$). The sensitivity for CBDS at the time of ERCP in our population using VS criteria was 59.5%, compared to 48.6% in the patients meeting S criteria (Table 3). Specificity ranged from 86%-100% for each of the VS and S categories.

Development of "modified" pediatric parameters in management of CBDS

Because conjugated bilirubin levels are a prominent finding in obstruction and a component in the liver panel/biochemistries at many pediatric facilities, conjugated bilirubin was substituted for total bilirubin. Thus, ≥ 0.5 mg/dL was substituted into both the VS and S categories. A VS "Pediatric Modified" (VS-PM) criteria

was defined as either a stone visualized on US or a conjugated bilirubin ≥ 0.5 mg/dL. To meet the Strong "Pediatric modified" criteria (S-PM), a patient needed to have a bile duct diameter > 6 mm and a conjugated bilirubin ≥ 0.5 mg/dL. In comparing patients in Group 1 and 2 using the VS-PM there was not a significant difference ($P = 0.07$) but significant using the S-PM criteria, ($P = 0.001$). An imputed odds ratio for a child meeting VS-PM criteria was calculated to be 25.7 times more likely to have a stone at ERCP, and 8.8 times more likely in those meeting S-PM criteria. The VS-PM and S-PM criteria also had improved sensitivity when compared to the respective adult criteria, up to 81.2% for identifying a CBDS at time of ERCP. The S-PM performed as well as the adult VS criteria, both with sensitivities of 59.5% (Table 3).

Use of aminotransferases and γGT in diagnosis of CBDS

Both ALT and AST levels were collected (Table 2 and Figure 1). The mean ALT and AST were not significantly different between Group 1 vs Group 2 ($P = 0.127$ and 0.149 , respectively). When an arbitrary cut-off for ALT of 350 u/L was used, the differences between the two groups was significant ($P = 0.0001$), but not at 300 u/L ($P = 0.052$). Given that aminotransferases are elevated in hemolysis, when patients with hemolytic disease ($n = 7$) were excluded there was still a significant difference between means in Group 1 and 2 ($P = 0.027$).

Additionally, γGT is known to be elevated during biliary obstruction as a surrogate marker of biliary obstruction. The median γGT in patients with CBDS was 259 u/L (181-521) compared to 203 u/L (159-333) in those without CBDS at ERCP ($P = 0.268$). When a γGT cut-off level of 400 u/L was used, a high sensitivity and positive predictive value were seen ($P = 0.0001$). These findings suggest that aminotransferases and γGT may be of value in the prediction of CBDS in children.

DISCUSSION

While several groups have reported their experience using ERCP in pediatric patients, to our knowledge

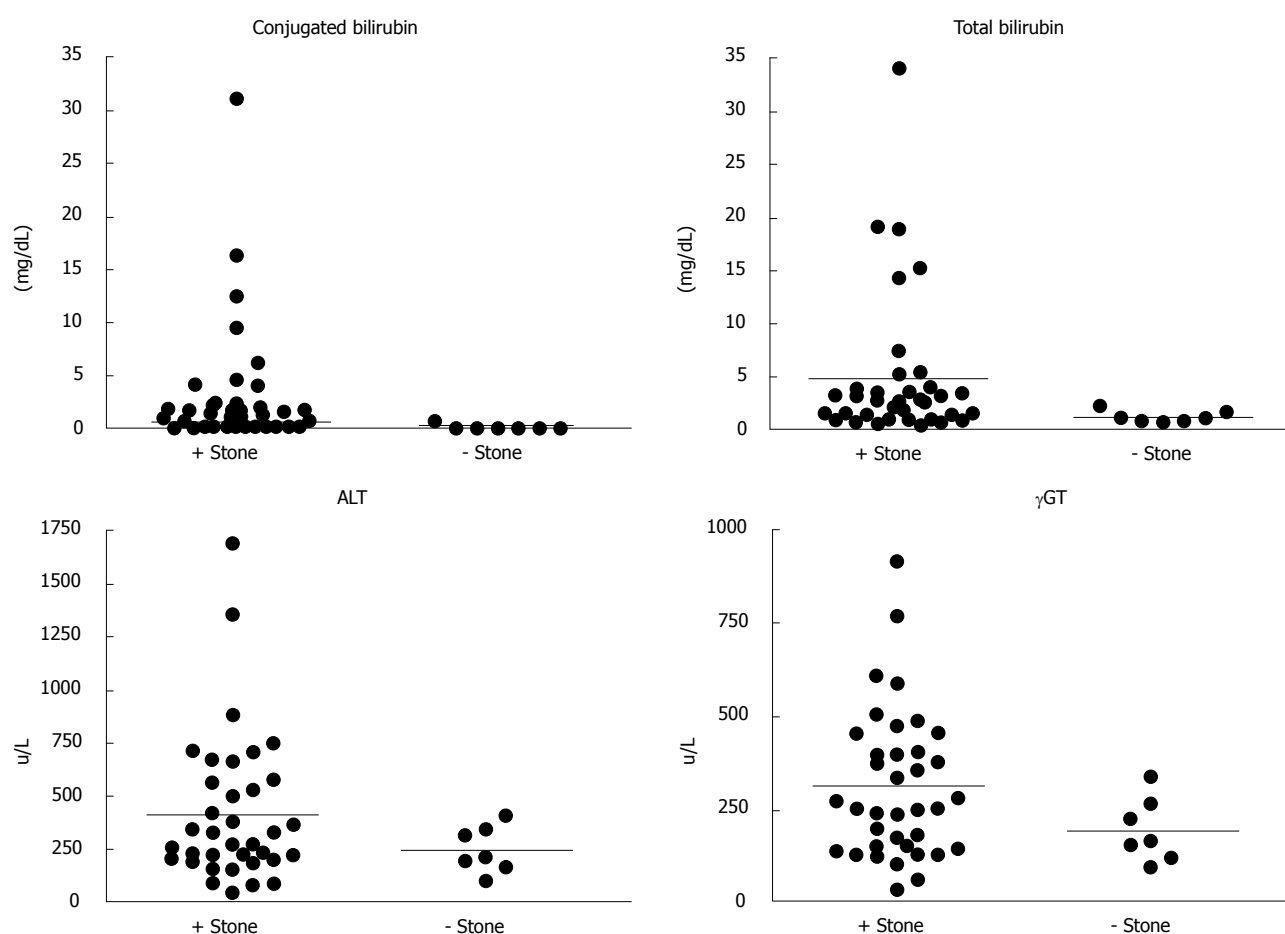


Figure 1 Laboratory comparison of patients with common bile duct stones at endoscopic retrograde cholangiography. Laboratory parameters (conjugated bilirubin, total bilirubin, alanine aminotransferase, and gamma-glutamyl transferase) in patients with and without stones. ERCP: Endoscopic retrograde cholangiography; ALT: Alanine aminotransferase; γ GT: Gamma-glutamyl transferase.

this is the first series to evaluate the management of choledocholithiasis using current clinical practice guidelines^[13-15]. The ASGE guidelines published in 2010 utilize ultrasound findings of CBD stones or common bile duct diameter, total bilirubin, age, and presence of cholangitis to identify patients at highest risk for CBDS^[10]. We classified a series of pediatric patients with suspected choledocholithiasis that underwent ERCP using these criteria at an acceptable sensitivity of 59.5 (VS) and 48.6% (S). However, we found that using conjugated bilirubin instead of total bilirubin improved the sensitivity for CBDS identification to 81%. However in practice, deciding on ERCP in those without a visualized stone on initial imaging and mild elevations or normal bilirubin is quite challenging. In this setting both the standard and modified pediatric strong criteria are important. In our subset of patients, the S-PM had a higher sensitivity than the standard criteria, and the same specificity. These criteria are dependent on both abnormal bilirubin and ductal dilatation, but in both criteria the major driver is the bilirubin level as even in children ductal dilatation is quite common in stone related disease.

The majority of published series and accepted

guidelines in adults use identification of CBDS and bile duct diameter by trans-abdominal ultrasound as critical determinants^[5-10]. The sensitivity of ultrasound for CBDS is reported up to 55% in adults, whereas in our series only 43% of patients had CBDS identified by ultrasound^[16]. Additionally, the sensitivity of the modified VS criteria exceeded the lower limit of sensitivity for CBDS detection by ultrasound. Normal common bile duct diameters in adults are reported to be 4-6 mm, with small increases with advancing age^[17]. A common bile duct diameter greater than 6 mm suggests obstruction and is used in the current ASGE guidelines. Early studies of pediatric common bile duct diameter using intravenous cholangiography, demonstrated an upper limit of 6 to 7 mm in children and that they were more distensible than adult bile ducts^[18,19]. By ultrasound, the common bile duct in early adolescence should not exceed 2.5-3.0 mm, although values for teenagers are largely based on adult normative values^[14,16,18-20]. In our series, patients in Group 2, had a median common bile duct diameter of 8 mm, suggesting some discrepancy in what should be considered abnormal or inflammatory change from a recently passed stone. For this reason and in keeping with current guidelines, a 6 mm cut-off was used for data

Table 3 Univariate characteristics in the evaluation of choledocholithiasis

Criteria	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Odds ratio (95%CI)	P-value
VS-PM	81.2 (64-91)	85.7 (42-99)	96.8 (81-100)	46.2 (20-74)	25.7 (2.65-249)	0.07
S-PM	59.5 (42-75)	85.7 (42-99)	95.7 (76-100)	28.6 (12-52)	8.8 (0.96-80.7)	0.001
VS-Adult	59.5 (42-75)	100 (56-100)	100 (81-100)	31.8 (15-55)	¹ 8.8 (0.96-80.7)	0.0001
S-Adult	48.6 (32-65)	85.7 (42-99)	94.7 (72-100)	24 (10-45)	5.68 (0.62-51.97)	0.0001
CBDS by US	43.2 (28-60)	100 (56-100)	100 (76-100)	25 (11-45)	¹ 4.57 (0.50-41.9)	0.0001
CBD > 6 mm	81.1 (64-91)	14.3 (1-58)	83.3 (67-93)	12.5 (1-33)	0.714 (0.074-6.92)	1
CBD > 8 mm	91.7 (76-98)	28.6 (5-70)	86.8 (71-95)	40 (7-83)	4.4 (0.58-33.2)	0.727
TB > 4.0	21.6 (10-39)	100 (56-100)	100 (60-100)	19.4 (8-37)	11.66 (0.17-15.82)	0.0001
TB ≥ 1.8	56.8 (41-71)	85.7 (49-97)	95.5 (75-100)	27.3 (12-50)	7.88 (0.86-72.12)	0.0001
CB ≥ 0.5	67.6 (50-81)	85.7 (42-99)	96.2 (78-100)	33.3 (14-59)	12.5 (1-115)	0.003
ALT > 300	56.8 (40-72)	14.3 (1-58)	77.8 (57-91)	5.9 (0-31)	0.219 (0.024-2.00)	0.052
ALT > 350	40.5 (26-57)	100 (56-100)	100 (80-100)	24.1 (11-42)	¹ 4.1 (0.45-37.5)	0.0001
AST > 155	43.2 (28-60)	85.7 (42-99)	94 (69-100)	22.2 (9-43)	4.57 (0.499-41.9)	0.0001
γGT > 400	35.1 (21-53)	100 (56-100)	100 (72-100)	22.6 (10-42)	¹ 3.25 (0.352-30.0)	0.0001

¹A zero denominator was substituted with a unit of one for odds ratio only. Includes sensitivity, specificity, positive predictive value, and odds ratio. *P*-values were calculated for each category for differences between patients with and without stones using McNemar's test. PPV: Positive predictive value; NPV: Negative predictive value; VS-PM: Very Strong Pediatric "Modified"; S-PM: Strong Pediatric "Modified"; VS-Adult: Very Strong Adult; S-Adult: Strong Adult; CBDS: Common bile duct stone; CB: Conjugated bilirubin; TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γGT: Gamma-glutamyl transferase; CBD: Common bile duct.

analysis. Using a CBD diameter of 6 mm in the scoring is reasonable for older pediatric patients and likely to improve sensitivity of CBDS detection children compared to adults. However, an 8 mm cut-off compared to 6 mm for CBD diameter had improved sensitivity, with modest increase in PPV, NPV and specificity.

Both MRCP and endoscopic ultrasound (EUS) are commonly used in the pre-procedure management of choledocholithiasis^[21]. MRCP use in pediatrics is common^[22,23]. However, some patients require sedation or anesthesia, and access is sometimes limited. There is an expanding experience and accessibility of EUS in pediatric patients^[24-27]. In a recent study by Adams *et al.*^[28], EUS and MRCP were used along with ERCP to identify the likelihood of CBDS in patients. Specific utilization of EUS and MRCP was not reported, however, using these modalities in addition to available guidelines and laboratory investigations, overall sensitivity and specificity were improved^[28]. Despite the limited use of MRCP and no cases of EUS, in our population, CBDS at the time of ERCP were identified in 84% of patients.

One limitation of our study was the variation in timing of patient presentation to abdominal ultrasound to ERCP from 1 to 6 d. However, the majority of procedures occurred less than 48 h of presentation with a mean of 1.9 (± 1.3) d. Approximately one-fourth of patients had MRCP prior to ERCP, frequently extending time to definitive procedure by 12-24 h. In the patients with a positive MRCP, but negative CBDS, that variability was accentuated and likely contributed to the passage of stones during the interim period. Timing of MRCP and its relationship to ERCP should be considered when planning procedures. Due to restrictions or delays in either of these modalities, it can be expected to have some stone passage, but these should be mitigated by process improvement actions. Based on patient selection completed during routine

clinical practice, and low rate of negative ERCP, our data is likely to represent a reasonable population in which to make predictions. Given the reported rates of stone migration (21% to 80%), we anticipate that data used within 24 h of ERCP, is applicable to optimize patient selection^[14,29]. Another limitation of this study is the limited sample of patients that had ERCP in which CBDS were not identified. Although there was a clinical suspicion for a stone in those cases for which ERCP was considered (*e.g.*, known gallstone disease), a passed stone, suprapapillary stricture or papillary stenosis from a stone was suspected. In the absence of stone this information was identified in the post-procedure note, but based on a normal appearing ampulla or post-sphincterotomy where the dilated bile duct is traced to a stenotic area above the ampulla (suprapapillary stricture) or tactile perception or visibly stenosed ampullary os (papillary stenosis).

Since the primary endpoint was the presence of a stone, this resulted in wide confidence intervals and did not allow for appropriate ROC curve representation. Similarly, due to the zero denominator in several calculations, imputed odds ratios were calculated for the following categories: Total Bilirubin > 4 mg/dL, VS-Adult criteria, and CBDS by US, but likely underestimating these factors.

There are also major differences in normal laboratory values and testing, such as alkaline phosphatase, typically several fold higher in pediatric patients compared to adults^[30]. Similarly, conjugated bilirubin is more often utilized rather than total bilirubin in pediatric laboratory investigations of hepatobiliary inflammation and obstruction. Conjugated bilirubin is thus a more sensitive marker of significant biliary obstruction, even when patients with hemolytic disease were separated from the analysis (*P* < 0.004 vs 0.02 respectively). Cholesterol stone disease is now more common in

pediatric patients compared to pigmented stones from hemolytic disease, but the laboratory examinations in patients with hemolytic disease typically often have marked elevations in both total and conjugated bilirubin.

Our data is probably most applicable when the ASGE criteria are applied to adolescents, as they are more similar in mechanisms of disease and anatomy^[2]. However, when consideration for bile duct size is taken into account, and with increases for advancing age, the use of imaging criteria (e.g., CBD diameter) may require a higher threshold for use in children and adolescents^[18,31,32]. Management algorithms are highly dependent on patient population (e.g., rate of hemolytic disease or obesity), local expertise and availability of ERCP, surgical techniques, and different radiographic modalities. Although the current guidelines for adults use an accepted likelihood of stone identification of greater than fifty percent, a higher cut-off may be more appropriate for children^[10,21,28]. It is our hope that the findings may serve as a clinical framework to pursue multi-center studies to identify optimal lab and imaging criteria in children in the management of CBDS prospectively.

Due to the relative variability in each of the available tests as well as the reported rates of both missed stones at ERCP and rates of stone passage, clinical experience should complement these tools and should take into consideration the inherent risks of the procedure with the risks of a retained stone (e.g., cholangitis, pancreatitis). It is also important to consider the possibility of an alternative diagnosis contributing to intraductal stones such as familial intrahepatic cholestasis or sclerosing cholangitis, both carrying malignancy risks. Intrahepatic stone disease has also been linked to cholangiocarcinoma^[33].

Using ASGE guidelines in a series of pediatric patients with suspected CBDS, stones were appropriately identified in the majority of cases, while US was poorly predictive of a sensitivity of 42%. Modified criteria using conjugated bilirubin ≥ 0.5 mg/dL instead of total bilirubin performed better at identification of CBDS. Conjugated bilirubin, γ GT, ALT and AST may improve specificity in identification of CBDS. Future studies are needed to assess pediatric specific criteria in children including both imaging (US, MRCP and EUS) and laboratory data. In the future, pediatric specific guidelines should be developed to optimize ERCP management in children with suspected CBDS.

COMMENTS

Background

Gallstones are an increasingly reported problem in children and reported rates of choledocholithiasis may be higher in pediatric patients than adults. In patients with suspected choledocholithiasis, criteria have been proposed for adults to help predict the likelihood of identifying and ultimately removing a stone at endoscopic retrograde cholangiography (ERCP). Limited data is available specific to children to guide management for this problem.

Research frontiers

There is great interest in the study of choledocholithiasis and its related

management. It offers opportunity to improve patient care by decreasing risks of a given procedure or related sedation. There is also great variability in the management in these patients despite guidelines due to numerous factors, which may impact both patients and endoscopists.

Innovations and breakthroughs

Using both a standard "adult" scoring system as well as a modified scoring system in a series of pediatric patients, the majority of patients could be identified. Specific laboratory tests such as bilirubin or findings on abdominal ultrasounds can assist in directing care for a pediatric patient with choledocholithiasis.

Applications

Using a combination of labs and imaging as well as clinical experience can help in identifying appropriate patients for ERCP. Utilization of newer applications such as endoscopic ultrasound or magnetic resonance cholangiopancreatography may improve our patient selection for ERCP. Multicenter studies may help to corroborate this data or identify other factors so that pediatric specific guidelines can be created.

Terminology

ERCP: Endoscopic retrograde cholangiography, an endoscopic procedure used with X-ray to evaluate the biliary and pancreatic systems.

Peer-review

This manuscript applied the current adult guidelines from the American Society of Gastrointestinal Endoscopy in pediatric patients with suspected common bile duct stones to identify factors that may be predictive in the pediatric population. It is well designed and performed.

REFERENCES

- 1 **Petelin JB**. Laparoscopic common bile duct exploration. *Surg Endosc* 2003; **17**: 1705-1715 [PMID: 12958681 DOI: 10.1007/s00464-002-8917-4]
- 2 **Mehta S**, Lopez ME, Chumipitazi BP, Mazziotti MV, Brandt ML, Fishman DS. Clinical characteristics and risk factors for symptomatic pediatric gallbladder disease. *Pediatrics* 2012; **129**: e82-e88 [PMID: 22157135 DOI: 10.1542/peds.2011-0579]
- 3 **Herzog D**, Bouchard G. High rate of complicated idiopathic gallstone disease in pediatric patients of a North American tertiary care center. *World J Gastroenterol* 2008; **14**: 1544-1548 [PMID: 18330945 DOI: 10.3748/wjg.14.1544]
- 4 **Bogue CO**, Murphy AJ, Gerstle JT, Moineddin R, Daneman A. Risk factors, complications, and outcomes of gallstones in children: a single-center review. *J Pediatr Gastroenterol Nutr* 2010; **50**: 303-308 [PMID: 20118803 DOI: 10.1097/MPG.0b013e3181b99c72]
- 5 **Tse F**, Barkun JS, Barkun AN. The elective evaluation of patients with suspected choledocholithiasis undergoing laparoscopic cholecystectomy. *Gastrointest Endosc* 2004; **60**: 437-448 [PMID: 15332044 DOI: 10.1016/S0016-5107(04)01457-9]
- 6 **Prat F**, Meduri B, Ducot B, Chiche R, Salimbeni-Bartolini R, Pelletier G. Prediction of common bile duct stones by noninvasive tests. *Ann Surg* 1999; **229**: 362-368 [PMID: 10077048 DOI: 10.1097/0000658-199903000-00009]
- 7 **Abboud PA**, Malet PF, Berlin JA, Starosciak R, Cabana MD, Clarke JR, Shea JA, Schwartz JS, Williams SV. Predictors of common bile duct stones prior to cholecystectomy: a meta-analysis. *Gastrointest Endosc* 1996; **44**: 450-455 [PMID: 8905367 DOI: 10.1016/S0016-5107(96)70098-6]
- 8 **Tham TC**, Lichtenstein DR, Vandervoort J, Wong RC, Brooks D, Van Dam J, Ruymann F, Farraye F, Carr-Locke DL. Role of endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis in patients undergoing laparoscopic cholecystectomy. *Gastrointest Endosc* 1998; **47**: 50-56 [PMID: 9468423 DOI: 10.1016/S0016-5107(98)70298-6]
- 9 **Barkun AN**, Barkun JS, Fried GM, Ghitulescu G, Steinmetz O, Pham C, Meakins JL, Goresky CA. Useful predictors of bile

- duct stones in patients undergoing laparoscopic cholecystectomy. McGill Gallstone Treatment Group. *Ann Surg* 1994; **220**: 32-39 [PMID: 7517657 DOI: 10.1097/0000658-199407000-00006]
- 10 **Maple JT**, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Strohmeier L, Dominitz JA. The role of endoscopy in the evaluation of suspected choledocholithiasis. *Gastrointest Endosc* 2010; **71**: 1-9 [PMID: 20105473 DOI: 10.1016/j.gie.2009.09.041]
 - 11 **Fox VL**, Werlin SL, Heyman MB. Endoscopic retrograde cholangiopancreatography in children. Subcommittee on Endoscopy and Procedures of the Patient Care Committee of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2000; **30**: 335-342 [PMID: 10749424 DOI: 10.1097/00005176-200003000-00025]
 - 12 **Mah D**, Wales P, Njere I, Kortan P, Masiakos P, Kim PC. Management of suspected common bile duct stones in children: role of selective intraoperative cholangiogram and endoscopic retrograde cholangiopancreatography. *J Pediatr Surg* 2004; **39**: 808-812 [PMID: 15185201 DOI: 10.1016/j.jpedsurg.2004.02.019]
 - 13 **Guelrud M**. ERCP in Pediatric Practice: Diagnosis and Management. In: Carr-Locke D, Fox VL, Guelrud M, editors. USA: CRC Press, 1988: 54
 - 14 **Vrochides DV**, Sorrells DL, Kurkchubasche AG, Wesselhoeft CW, Tracy TF, Luks FI. Is there a role for routine preoperative endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis in children? *Arch Surg* 2005; **140**: 359-361 [PMID: 15837886 DOI: 10.1001/archsurg.140.4.359]
 - 15 **Iqbal CW**, Baron TH, Moir CR, Ishitani MB. Post-ERCP pancreatitis in pediatric patients. *J Pediatr Gastroenterol Nutr* 2009; **49**: 430-434 [PMID: 20032630 DOI: 10.1097/MPG.0b013e318186c4a6]
 - 16 **Cronan JJ**. US diagnosis of choledocholithiasis: a reappraisal. *Radiology* 1986; **161**: 133-134 [PMID: 3532178 DOI: 10.1148/radiology.161.1.3532178]
 - 17 **Chawla S**, Trick WE, Gilkey S, Attar BM. Does cholecystectomy status influence the common bile duct diameter? A matched-pair analysis. *Dig Dis Sci* 2010; **55**: 1155-1160 [PMID: 19455421 DOI: 10.1007/s10620-009-0836-y]
 - 18 **Hernanz-Schulman M**, Ambrosino MM, Freeman PC, Quinn CB. Common bile duct in children: sonographic dimensions. *Radiology* 1995; **195**: 193-195 [PMID: 7892467 DOI: 10.1148/radiology.195.1.7892467]
 - 19 **Witcombe JB**, Cremin BJ. The width of the common bile duct in childhood. *Pediatr Radiol* 1978; **7**: 147-149 [PMID: 714527 DOI: 10.1007/BF00975437]
 - 20 **Parulekar SG**. Ultrasound evaluation of common bile duct size. *Radiology* 1979; **133**: 703-707 [PMID: 504652 DOI: 10.1148/133.3.703]
 - 21 **Maple JT**, Ikenberry SO, Anderson MA, Appalaneni V, Decker GA, Early D, Evans JA, Fanelli RD, Fisher D, Fisher L, Fukami N, Hwang JH, Jain R, Jue T, Khan K, Krinsky ML, Malpas P, Ben-Menachem T, Sharaf RN, Dominitz JA. The role of endoscopy in the management of choledocholithiasis. *Gastrointest Endosc* 2011; **74**: 731-744 [PMID: 21951472 DOI: 10.1016/j.gie.2011.04.012]
 - 22 **Tipnis NA**, Dua KS, Werlin SL. A retrospective assessment of magnetic resonance cholangiopancreatography in children. *J Pediatr Gastroenterol Nutr* 2008; **46**: 59-64 [PMID: 18162835 DOI: 10.1097/01.mpg.0000304455.76928.0e]
 - 23 **Fitoz S**, Erden A, Boruban S. Magnetic resonance cholangiopancreatography of biliary system abnormalities in children. *Clin Imaging* 2007; **31**: 93-101 [PMID: 17320775 DOI: 10.1016/j.clinimag.2006.11.002]
 - 24 **Attila T**, Adler DG, Hilden K, Faigel DO. EUS in pediatric patients. *Gastrointest Endosc* 2009; **70**: 892-898 [PMID: 19577744 DOI: 10.1016/j.gie.2009.04.012]
 - 25 **Scheers I**, Ergun M, Aouattah T, Piessevaux H, Borbath I, Stephenne X, De Magnée C, Reding R, Sokal E, Veyckemans F, Weynand B, Deprez PH. Diagnostic and Therapeutic Roles of Endoscopic Ultrasound in Pediatric Pancreaticobiliary Disorders. *J Pediatr Gastroenterol Nutr* 2015; **61**: 238-247 [PMID: 25564818 DOI: 10.1097/MPG.0000000000000692]
 - 26 **Cohen S**, Kalinin M, Yaron A, Givony S, Reif S, Santo E. Endoscopic ultrasonography in pediatric patients with gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2008; **46**: 551-554 [PMID: 18493211 DOI: 10.1097/MPG.0b013e31815ce571]
 - 27 **Gordon K**, Conway J, Evans J, Petty J, Fortunato JE, Mishra G. "EUS and EUS Guided Interventions Alter Clinical Management in Children with Digestive Diseases". *J Pediatr Gastroenterol Nutr* 2015 Dec 28; Epub ahead of print [PMID: 26720768 DOI: 10.1097/MPG.0000000000001101]
 - 28 **Adams MA**, Hosmer AE, Wamsteker EJ, Anderson MA, Elta GH, Kubiliun NM, Kwon RS, Piraka CR, Scheiman JM, Waljee AK, Hussain HK, Elmunzer BJ. Predicting the likelihood of a persistent bile duct stone in patients with suspected choledocholithiasis: accuracy of existing guidelines and the impact of laboratory trends. *Gastrointest Endosc* 2015; **82**: 88-93 [PMID: 25792387 DOI: 10.1016/j.gie.2014.12.023]
 - 29 **Frossard JL**, Hadengue A, Amouyal G, Choury A, Marty O, Giostra E, Sivignon F, Sosa L, Amouyal P. Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration. *Gastrointest Endosc* 2000; **51**: 175-179 [PMID: 10650260 DOI: 10.1016/S0016-5107(00)70414-7]
 - 30 **Van Hoof VO**, Hoylaerts MF, Geryl H, Van Mullem M, Lepoutre LG, De Broe ME. Age and sex distribution of alkaline phosphatase isoenzymes by agarose electrophoresis. *Clin Chem* 1990; **36**: 875-878 [PMID: 2357825]
 - 31 **Bruneton JN**, Roux P, Fenart D, Caramella E, Occelli JP. Ultrasound evaluation of common bile duct size in normal adult patients and following cholecystectomy. A report of 750 cases. *Eur J Radiol* 1981; **1**: 171-172 [PMID: 7338243]
 - 32 **Bachar GN**, Cohen M, Belenky A, Atar E, Gideon S. Effect of aging on the adult extrahepatic bile duct: a sonographic study. *J Ultrasound Med* 2003; **22**: 879-882; quiz 883-885 [PMID: 14510259]
 - 33 **Cai H**, Kong WT, Chen CB, Shi GM, Huang C, Shen YH, Sun HC. Cholelithiasis and the risk of intrahepatic cholangiocarcinoma: a meta-analysis of observational studies. *BMC Cancer* 2015; **15**: 831 [PMID: 26526500 DOI: 10.1186/s12885-015-1870-0]

P- Reviewer: Chen CH, Lai KH, Sergi CM, Sun LM
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Lu YJ



Retrospective Study

Low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate, and clear liquid diet alone prior to small bowel capsule endoscopy

Erin Rayner-Hartley, Majid Alsahafi, Paula Cramer, Nazira Chatur, Fergal Donnellan

Erin Rayner-Hartley, Majid Alsahafi, Paula Cramer, Nazira Chatur, Fergal Donnellan, Division of Gastroenterology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia V6Z3H8, Canada

Majid Alsahafi, Department of Medicine, King Abdulaziz University, Jeddah 21342, Saudi Arabia

Author contributions: Chatur N and Donnellan F contributed to study concepts, design and interpretation; Donnellan F contributed to study analysis, editing the manuscript and final approval; Rayner-Hartley E and Cramer P contributed to data acquisition and analysis; Rayner-Hartley E and Alsahafi M contributed to interpretation of results and writing the manuscript.

Institutional review board statement: This was a retrospective study, and institution review board was not required.

Informed consent statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

Conflict-of-interest statement: No conflict of interest for all authors.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Fergal Donnellan, MD, Division of Gastroenterology, Vancouver General Hospital, University of British Columbia, 5153 - 2775 Laurel Street, Vancouver, British Columbia V6Z3H8, Canada. fergal.donnellan@vch.ca
Telephone: +1-604-8755244

Fax: +1-604-8755161

Received: November 5, 2015
Peer-review started: November 7, 2015
First decision: December 10, 2015
Revised: February 10, 2016
Accepted: February 23, 2016
Article in press: February 24, 2016
Published online: June 10, 2016

Abstract

AIM: To compare low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate and clear liquid diet alone as bowel preparation prior to small bowel capsule endoscopy (CE).

METHODS: We retrospectively collected all CE studies done from December 2011 to July 2013 at a single institution. CE studies were reviewed only if low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate or clear liquid diet alone used as the bowel preparation. The studies were then reviewed by the CE readers who were blinded to the preparation type. Cleanliness and bubble burden were graded independently within the proximal, middle and distal small bowel using a four-point scale according to the percentage of small bowel mucosa free of debris/bubbles: grade 1 = over 90%, grade 2 = between 90%-75%, grade 3 = between 50%-75%, grade 4 = less than 50%. Data are expressed as mean \pm SEM. ANOVA and Fishers exact test were used where appropriate. *P* values < 0.05 were considered statistically significant.

RESULTS: A of total of 123 CE studies were reviewed. Twenty-six studies were excluded from analysis because of incomplete small bowel examination. In the remaining

studies, 48 patients took low volume polyethylene glycol with ascorbic acid, 31 took sodium picosulfate-magnesium citrate and 27 took a clear liquid diet alone after lunch on the day before CE, followed by overnight fasting in all groups. There was no significant difference in small bowel cleanliness (1.98 ± 0.09 vs 1.84 ± 0.08 vs 1.76 ± 0.08) or small bowel transit time (213 ± 13 vs 248 ± 14 vs 225 ± 19 min) for clear liquid diet alone, MoviPrep and Pico-Salax respectively. The bubble burden in the mid small bowel was significantly higher in the MoviPrep group (1.6 ± 0.1 vs 1.9 ± 0.1 vs 1.6 ± 0.1 , $P < 0.05$). However this did not result in a significant difference in diagnosis of pathology.

CONCLUSION: There was no significant difference in small bowel cleanliness or diagnostic yield of small bowel CE between the three preparations regimens used in this study.

Key words: Capsule endoscopy; Small bowel; Bowel preparation; Polyethylene glycol; Sodium picosulfate

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Adequate small bowel preparation is essential for diagnosing small bowel pathology on video capsule endoscopy, but the optimal small bowel preparation method remains unclear. Due the small volume and safety, low volume polyethylene glycol (PEG) based regimens become attractive. However no previous studies have compared low volume PEG with ascorbic acid to sodium picosulfate-magnesium citrate or clear liquid diet alone. In this retrospective study we performed a direct comparison between these three regimens. The bubble burden was significantly higher in the low PEG group but no differences in small bowel cleanliness or diagnostic yield were found between the three regimens.

Rayner-Hartley E, Alsahafi M, Cramer P, Chatur N, Donnellan F. Low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate, and clear liquid diet alone prior to small bowel capsule endoscopy. *World J Gastrointest Endosc* 2016; 8(11): 433-438 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i11/433.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i11.433>

INTRODUCTION

Capsule endoscopy (CE) has revolutionized the management of small bowel diseases including obscure GI bleeding, Crohn's disease, polyposis syndromes and advanced celiac disease^[1-4]. The diagnostic yield (DY) is affected by a number of factors including intraluminal material, bubbles, and both gastric and small bowel transit times^[5].

Adequate small bowel preparation is important to increase the DY. Multiple studies have been done comparing various bowel preparation regimens, including just an

overnight fast. Despite numerous studies, controversy exists regarding the optimal bowel preparation prior to CE^[6-22]. Previous studies have examined the use of laxatives, prokinetics as well as surfactant agents. The bowel preparation regimen may also have an impact on the gastric and small bowel transit times. Recent consensus guidelines recommend polyethylene glycol (PEG) based laxatives as first line agents^[23].

The primary aim of this study was to evaluate the DY, small bowel cleanliness, bubble burden and both gastric and small bowel transit times following three different preparation regimens. To our knowledge, no previous studies compared a low volume PEG based agent to a sodium picosulfate - magnesium citrate based agent and clear liquid diet alone.

MATERIALS AND METHODS

The charts for all patients referred for outpatient CE between December 2011 and July 2013 were reviewed. Patients were included only if they were given one of the following three bowel preparation regimens: Low volume PEG based agent (MoviPrep, Norgine), sodium picosulfate and magnesium citrate based agent (Pico-Salax, Ferring) and a clear liquid diet alone. In this study, the patients in the groups of MoviPrep and Pico-Salax were instructed to take the first sachet at 14h00 and the second at 17h00. All patients ingested the capsule at approximately 8 am of the study day. All CE examinations were performed using the Olympus Endocapsule.

Two experienced reviewers who were blinded to preparation method (FD and NC) reviewed all CE studies for diagnostic evaluation, and both gastric and small bowel transit time. Clinical disagreement was solved by joint review and discussion. One CE reader who was blinded to preparation (ERH) reviewed all CE studies for mucosal visibility grading related to cleanliness and bubble burden. Once the CE studies have been reviewed, patients were assigned into one of the three different groups based on the bowel preparation regimen given according to chart review.

Only CE studies with complete small bowel examinations, determined by identification of the cecum were included for analysis. The primary outcome measures included the DY, intraluminal small bowel cleanliness and bubble burden. Small bowel cleanliness and bubble burden were graded independently within the proximal, mid and distal small bowel using a four-point scale according to the percentage of small bowel mucosa free of debris/bubbles: Grade 1 = over 90%, grade 2 = between 90%-75%, grade 3 = between 50%-75%, grade 4 = less than 50% (Figure 1). This grading system was developed by the authors based on the commonly used grading criteria as there is no validated scoring system available. The anatomic divisions were determined by dividing the small bowel into three segments based on the small bowel transit time.

According to CE protocol in our center, patients are

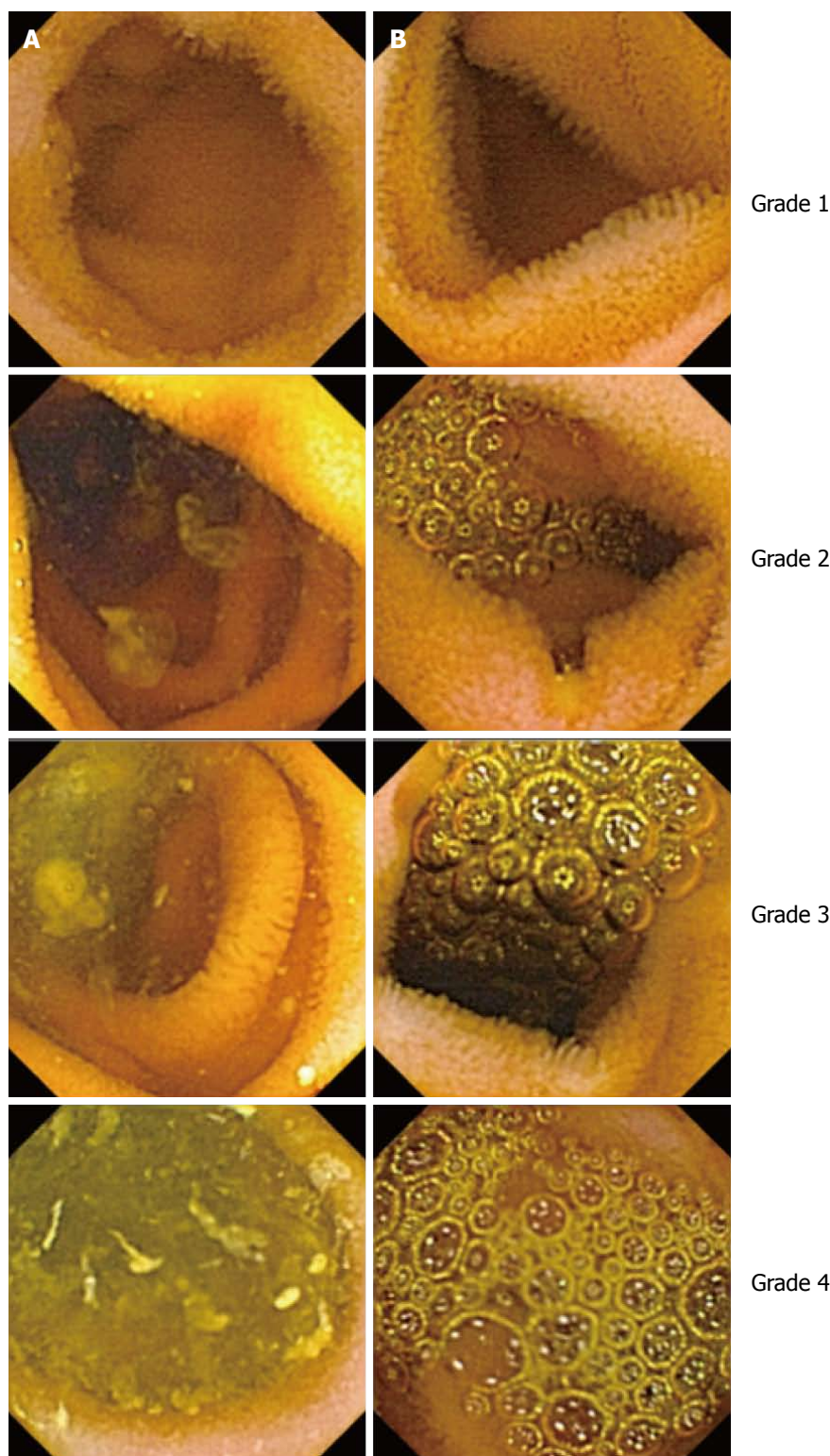


Figure 1 Grading scales of (A) cleanliness and (B) bubble burden. The bowel preparation was graded independently in the proximal, mid and distal third of the small bowel using a 4-grade scale according to the percentage of small bowel mucosa free of debris/bubbles: Grade 1 = over 90%, grade 2 = between 90%-75%, grade 3 = between 50%-75%, grade 4 = less than 50%.

instructed to follow a clear liquid diet after lunch the day prior to CE, followed by an overnight fast as of 21h00. They are permitted to resume a clear fluid diet 2 h after recording begin and a light meal 4 h later. Patients return 8 h after ingestion of the capsule to disconnect the recorder. An abdominal X-ray is obtained at one week following ingestion to determine if the capsule is retained if it did not reach the cecum or the patient did

not report its passage.

Statistical analysis

Data are expressed as mean \pm SEM. ANOVA and Fishers exact test were used where appropriate. *P* value < 0.05 were considered statistically significant. Statistical analysis was performed by Fergal Donnellan (University of British Columbia).

Table 1 Patient characteristics *n* (%)

Variable	No prep <i>n</i> = 38	MoviPrep <i>n</i> = 48	Pico-Salax <i>n</i> = 37
Male	11 (28.9)	22 (45.8)	18 (48.6)
Mean age (yr)	52.7	54.1	53.2
Indication			
Obscure bleeding	17 (44.7)	27 (56.3)	19 (51.4)
Abnormal imaging	3 (7.9)	4 (8.3)	5 (15.3)
Suspected IBD	11 (28.9)	11 (22.9)	10 (27)
Other	7 (18.4)	6 (12.5)	3 (8.1)
Completion rate	27 (71)	39 (81.3)	31 (83.8)

IBD: Inflammatory bowel disease.

Table 2 Results of small bowel cleanliness, bubble burden and transit time according to the bowel preparation regimen

Result	No prep <i>n</i> = 27	MoviPrep <i>n</i> = 39	Pico-Salax <i>n</i> = 31	<i>P</i> value
Cleanliness				
Proximal	1.4 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	0.1
Mid	1.8 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	0.7
Distal	2.1 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	0.6
Bubble burden				
Proximal	1.5 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	0.1
Mid	1.6 ± 0.1	1.9 ± 0.1	1.6 ± 0.1	< 0.05
Distal	1.6 ± 0.1	1.8 ± 0.2	1.5 ± 0.1	0.09
Gastric transit time (min)	26 ± 5	25 ± 6	47 ± 9	< 0.05
Small bowel transit time (min)	213 ± 13	248 ± 14	225 ± 19	0.3

RESULTS

One hundred and twenty-three patients were included, 48 patients took MoviPrep, 37 took Pico-Salax and 38 took a clear liquid diet alone. Table 1 depicts the patients' characteristics. There was no statistically significant difference between the three groups in regard to gender, age or complete small bowel examination. Ninety-seven (78.9%) patients had a complete small bowel examination and thus included in the final analysis. This included 39 (81%) patients in the MoviPrep group, 31 (84%) patients in the Pico-Salax group and 27 (71%) patients in the clear liquid group (Figure 2).

Table 2 depicts the results for small bowel cleanliness, bubble burden and both gastric and small bowel transit times. There was a significant increase in the bubble burden in the mid small bowel in the MoviPrep group ($P < 0.05$). Otherwise there was no difference between the three groups in terms of cleanliness or bubble burden. Similarly there was no difference in the small bowel transit time. The gastric transit time, however, was significantly longer in the Pico-Salax group only ($P < 0.05$).

Table 3 depicts the results for DY and abnormal findings. Overall there was no difference in detection of pathology between the three groups ($P = 0.6$). However, there was a trend towards increased detection of vascular lesions in the MoviPrep group and ulceration

Table 3 Diagnostic Yield according to the bowel preparation *n* (%)

Finding	No prep <i>n</i> = 27	MoviPrep <i>n</i> = 39	Pico-Salax <i>n</i> = 31
Abnormal study	13 (48.1)	19 (48.7)	13 (41.9)
Gastric	2 (7.4)	1 (2.6)	0 (0.0)
Small bowel			
Vascular	1 (3.7)	10 (25.6)	5 (16.1)
Ulcer/erosion	7 (25.9)	3 (7.7)	3 (9.7)
Polyp/mass	0 (0.0)	1 (2.6)	3 (9.7)
Blood	0 (0.0)	1 (2.6)	1 (3.2)
Abnormal mucosa	2 (7.4)	3 (7.7)	1 (3.2)
other	1 (3.7)	0 (0.0)	0 (0.0)

in the clear liquid diet group, however these findings were not statistically significant ($P = 0.06$ and 0.07 respectively).

DISCUSSION

Since its introduction in 2000, CE is now recognized as a widely applicable, non-invasive tool with a high DY^[24]. Unlike conventional endoscopy, which has the advantage of washing and suctioning to improve mucosal visibility, CE relies on the state of the small bowel at time of exam. No universally accepted bowel preparation regimen exists amongst clinicians^[6-22].

The most studied agents in small bowel CE preparation are PEG, sodium phosphate and sodium picosulphate. Recent meta-analyses found that the DY and small bowel visualization quality were superior with PEG or sodium phosphate in comparison to clear fluid diet^[5,6]. None of these studies included sodium picosulphate. Lower volume PEG (2L) has been shown as effective as 4L, which is preferable for patient tolerance^[7,8]. Magnesium citrate is another agent that is less well studied. One retrospective analysis showed significant improvement in clarification of intestinal juices with magnesium citrate as compared to simethicone^[10]. Subsequent studies however, have not reported significant differences in cleansing efficacy^[9-11].

In our study, we did not find a significant difference in cleanliness, bubble burden or transit time in the three groups studied. Only the bubble burden in the mid small bowel in the MoviPrep group and the gastric transit time in the Pico-Salax group were significantly different. When considering that no difference in pathology detection was noted between the groups, our results concur with previously published studies that CE DY may be preserved with the simplicity of a clear liquid diet. The small bowel is primarily a site of nutrient absorption and not stool formation. Thus, unlike colonoscopy preparation, it is logical that a preparation method without purgative agents could be adequate. We did note a non-significant trend towards increased detection of vascular lesions only in the MoviPrep group and ulceration in the clear liquid diet alone group. It is difficult to conclude that this is due to the regimen, but more likely due to small sample size.

Recent consensus guidelines along with European

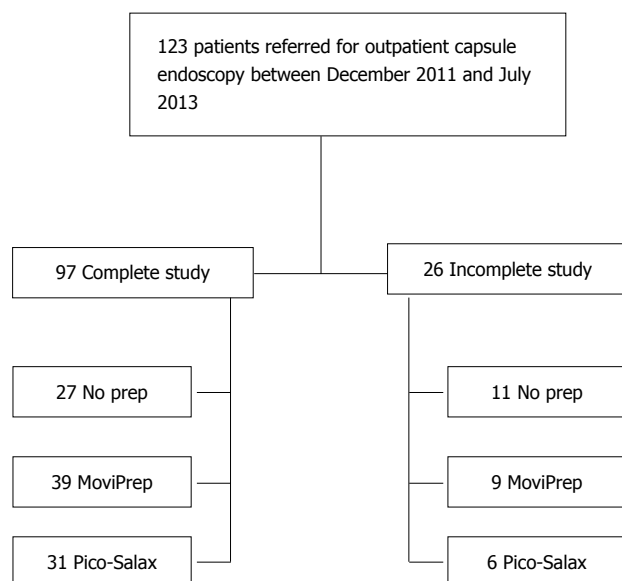


Figure 2 Study diagram.

Society of Gastrointestinal Endoscopy recommendations support the use of PEG based purgative agents prior to CE^[23,25,26]. Our findings suggest that a clear liquid diet the day prior to CE followed by an overnight fast is as effective for detection of pathology on CE. We included preparation agents that have not been previously directly compared.

Our study has several limitations. This was a retrospective study with a relatively small sample size. However we reviewed all the CE examinations blindly for the purpose of this study. The compliance with bowel preparation used could not be verified given the retrospective design. The anatomical sections of the small bowel were arbitrarily determined by dividing the total small bowel transit time into three periods, while the CE speed might be variable.

In conclusion, our study demonstrates no clinically significant difference in small bowel cleanliness or DY between three preparations regimens used in this study. Only the bubble burden in the mid small bowel in the MoviPrep group and the gastric transit time in the Pico-Salax group were significantly different. Our study suggests that it is reasonable to consider eliminating the use of bowel preparation prior to outpatient CE.

COMMENTS

Background

Capsule endoscopy (CE) has revolutionized the management of small bowel diseases including obscure GI bleeding, Crohn's disease, polyposis syndromes and advanced celiac disease. Adequate small bowel preparation is required to increase the diagnostic yield (DY). The DY is affected by a number of factors including intraluminal material, bubbles, and both gastric and small bowel transit times. Multiple studies have been done comparing various bowel preparation regimens, including just an overnight fast. Previous studies have also examined the use of laxatives, prokinetics as well as surfactant agents. Despite numerous studies, controversy exists regarding the optimal bowel preparation prior to CE.

Research frontiers

To the authors' knowledge, no previous studies compared a low volume polyethylene glycol (PEG) based agent to a sodium picosulfate and magnesium citrate based agent and clear liquid diet alone.

Innovations and breakthroughs

In this study, the authors compared low volume PEG with ascorbic acid (MoviPrep), sodium picosulfate-magnesium citrate (Pico-Salax) and clear liquid diet alone as bowel preparation prior to small bowel CE. Only the bubble burden in the mid small bowel in the MoviPrep group and the gastric transit time in the Pico-Salax group were significantly different. However the authors did not find a significant difference in the small bowel cleanliness or the DY.

Applications

When considering that no difference in the DY was noted between the three groups, the results concur with previously published studies that CE DY may be preserved with the simplicity of a clear liquid diet alone.

Terminology

Small bowel CE: A pill sized video camera ingested by the patient which allows examination of small bowel.

Peer-review

This is a retrospective study which compared low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate and clear liquid diet alone as bowel preparation prior to small bowel CE.

REFERENCES

- 1 **Fisher L**, Lee Krinsky M, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, Cash BD, Decker GA, Fanelli RD, Friis C, Fukami N, Harrison ME, Ikenberry SO, Jain R, Jue T, Khan K, Maple JT, Strohmeyer L, Sharaf R, Dominitz JA. The role of endoscopy in the management of obscure GI bleeding. *Gastrointest Endosc* 2010; **72**: 471-479 [PMID: 20801285 DOI: 10.1016/j.gie.2010.04.032]
- 2 **Dionisio PM**, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010; **105**: 1240-1248; quiz 1249 [PMID: 20029412 DOI: 10.1038/ajg.2009.713]
- 3 **Mata A**, Llach J, Castells A, Rovira JM, Pellisé M, Ginès A, Fernández-Esparrach G, Andreu M, Bordas JM, Piqué JM. A prospective trial comparing wireless capsule endoscopy and barium contrast series for small-bowel surveillance in hereditary GI polyposis syndromes. *Gastrointest Endosc* 2005; **61**: 721-725 [PMID: 15855978 DOI: 10.1016/S0016-5107(05)00289-0]
- 4 **Culliford A**, Daly J, Diamond B, Rubin M, Green PH. The value of wireless capsule endoscopy in patients with complicated celiac disease. *Gastrointest Endosc* 2005; **62**: 55-61 [PMID: 15990820 DOI: 10.1016/S0016-5107(05)01566-X]
- 5 **Rokkas T**, Papaxoinis K, Triantafyllou K, Pistiolas D, Ladas SD. Does purgative preparation influence the diagnostic yield of small bowel video capsule endoscopy? A meta-analysis. *Am J Gastroenterol* 2009; **104**: 219-227 [PMID: 19098872 DOI: 10.1038/ajg.2008.63]
- 6 **Belsey J**, Crosta C, Epstein O, Fischbach W, Layer P, Parente F, Halphen M. Meta-analysis: efficacy of small bowel preparation for small bowel video capsule endoscopy. *Curr Med Res Opin* 2012; **28**: 1883-1890 [PMID: 23136911 DOI: 10.1185/03007995.2012.747953]
- 7 **Park SC**, Keum B, Seo YS, Kim YS, Jeon YT, Chun HJ, Um SH, Kim CD, Ryu HS. Effect of bowel preparation with polyethylene glycol on quality of capsule endoscopy. *Dig Dis Sci* 2011; **56**: 1769-1775 [PMID: 21161380 DOI: 10.1007/s10620-010-1500-2]

- 8 **Hartmann D**, Keuchel M, Philipper M, Gralnek IM, Jakobs R, Hagenmüller F, Neuhaus H, Riemann JF. A pilot study evaluating a new low-volume colon cleansing procedure for capsule colonoscopy. *Endoscopy* 2012; **44**: 482-486 [PMID: 22275051 DOI: 10.1055/s-0031-1291611]
- 9 **Ninomiya K**, Yao K, Matsui T, Sato Y, Kishi M, Karashima Y, Ishihara H, Hirai F. Effectiveness of magnesium citrate as preparation for capsule endoscopy: a randomized, prospective, open-label, inter-group trial. *Digestion* 2012; **86**: 27-33 [PMID: 22710397 DOI: 10.1159/000337937]
- 10 **Esaki M**, Matsumoto T, Kudo T, Yanaru-Fujisawa R, Nakamura S, Iida M. Bowel preparations for capsule endoscopy: a comparison between simethicone and magnesium citrate. *Gastrointest Endosc* 2009; **69**: 94-101 [PMID: 18710720 DOI: 10.1016/j.gie.2008.04.054]
- 11 **Postgate A**, Tekkis P, Patterson N, Fitzpatrick A, Bassett P, Fraser C. Are bowel purgatives and prokinetics useful for small-bowel capsule endoscopy? A prospective randomized controlled study. *Gastrointest Endosc* 2009; **69**: 1120-1128 [PMID: 19152909 DOI: 10.1016/j.gie.2008.06.044]
- 12 **Wei W**, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. Effect of mosapride on gastrointestinal transit time and diagnostic yield of capsule endoscopy. *J Gastroenterol Hepatol* 2007; **22**: 1605-1608 [PMID: 17683491 DOI: 10.1111/j.1440-1746.2007.05064.x]
- 13 **Ida Y**, Hosoe N, Imaeda H, Bessho R, Ichikawa R, Naganuma M, Kanai T, Hibi T, Ogata H. Effects of the oral administration of mosapride citrate on capsule endoscopy completion rate. *Gut Liver* 2012; **6**: 339-343 [PMID: 22844562 DOI: 10.5009/gnl.2012.6.3.339]
- 14 **Leung WK**, Chan FK, Fung SS, Wong MY, Sung JJ. Effect of oral erythromycin on gastric and small bowel transit time of capsule endoscopy. *World J Gastroenterol* 2005; **11**: 4865-4868 [PMID: 16097060 DOI: 10.3748/wjg.v11.i31.4865]
- 15 **Caddy GR**, Moran L, Chong AK, Miller AM, Taylor AC, Desmond PV. The effect of erythromycin on video capsule endoscopy intestinal-transit time. *Gastrointest Endosc* 2006; **63**: 262-266 [PMID: 16427932 DOI: 10.1016/j.gie.2005.07.043]
- 16 **Niv E**, Bongor I, Barkay O, Halpern Z, Mahajna E, Depsames R, Kopelman Y, Fireman Z. Effect of erythromycin on image quality and transit time of capsule endoscopy: a two-center study. *World J Gastroenterol* 2008; **14**: 2561-2565 [PMID: 18442206 DOI: 10.3748/wjg.14.2561]
- 17 **Selby W**. Complete small-bowel transit in patients undergoing capsule endoscopy: determining factors and improvement with metoclopramide. *Gastrointest Endosc* 2005; **61**: 80-85 [PMID: 15672061 DOI: 10.1016/S0016-5107(04)02462-9]
- 18 **Koulaouzidis A**, Giannakou A, Yung DE, Dabos KJ, Plevris JN. Do prokinetics influence the completion rate in small-bowel capsule endoscopy? A systematic review and meta-analysis. *Curr Med Res Opin* 2013; **29**: 1171-1185 [PMID: 23790243 DOI: 10.1185/03007995.2013.818532]
- 19 **Shiotani A**, Opekun AR, Graham DY. Visualization of the small intestine using capsule endoscopy in healthy subjects. *Dig Dis Sci* 2007; **52**: 1019-1025 [PMID: 17380402 DOI: 10.1007/s10620-006-9558-6]
- 20 **Wei W**, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. Purgative bowel cleansing combined with simethicone improves capsule endoscopy imaging. *Am J Gastroenterol* 2008; **103**: 77-82 [PMID: 18005366 DOI: 10.1111/j.1572-0241.2007.01633.x]
- 21 **Spada C**, Riccioni ME, Familiari P, Spera G, Pirozzi GA, Marchese M, Bizzotto A, Ingrosso M, Costamagna G. Polyethylene glycol plus simethicone in small-bowel preparation for capsule endoscopy. *Dig Liver Dis* 2010; **42**: 365-370 [PMID: 19736051 DOI: 10.1016/j.dld.2009.07.017]
- 22 **Wu L**, Cao Y, Liao C, Huang J, Gao F. Systematic review and meta-analysis of randomized controlled trials of Simethicone for gastrointestinal endoscopic visibility. *Scand J Gastroenterol* 2011; **46**: 227-235 [PMID: 20977386 DOI: 10.3109/00365521.2010.525714]
- 23 **Mathus-Vliegen E**, Pellisé M, Heresbach D, Fischbach W, Dixon T, Belsey J, Parente F, Rio-Tinto R, Brown A, Toth E, Crosta C, Layer P, Epstein O, Boustiere C. Consensus guidelines for the use of bowel preparation prior to colonic diagnostic procedures: colonoscopy and small bowel video capsule endoscopy. *Curr Med Res Opin* 2013; **29**: 931-945 [PMID: 23659560 DOI: 10.1185/03007995.2013.803055]
- 24 **Iddan G**, Meron G, Glukhovskiy A, Swain P. Wireless capsule endoscopy. *Nature* 2000; **405**: 417 [PMID: 10839527]
- 25 **Song HJ**, Moon JS, Do JH, Cha IH, Yang CH, Choi MG, Jeon YT, Kim HJ. Guidelines for Bowel Preparation before Video Capsule Endoscopy. *Clin Endosc* 2013; **46**: 147-154 [PMID: 23614124 DOI: 10.5946/ce.2013.46.2.147]
- 26 **Ladas SD**, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; **42**: 220-227 [PMID: 20195992 DOI: 10.1055/s-0029-1243968]

P- Reviewer: Chen JQ, Mentos O **S- Editor:** Qi Y

L- Editor: A **E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 June 25; 8(12): 439-457





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hirotoshi Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hirotoshi Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciaccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Rajiman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



MINIREVIEWS

- 439 Endoscopic management of sigmoid volvulus in children

Parolini F, Orizio P, Bulotta AL, Garcia Magne M, Boroni G, Cengia G, Torri F, Alberti D

- 444 Single port laparoscopic liver surgery: A minireview

Karabicak I, Karabulut K

ORIGINAL ARTICLE

Retrospective Study

- 451 Effectiveness of clip-and-snare method using pre-looping technique for gastric endoscopic submucosal dissection

Yoshida N, Doyama H, Ota R, Takeda Y, Nakanishi H, Tominaga K, Tsuji S, Takemura K

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 12 June 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Ming-Yao Su, MD, Attending Doctor, Department of Gastroenterology and Hepatology, Linkou Medical Center, Tao-Yuan 333, Taiwan

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Xiao-Kang Jiao*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Shui Qiu*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
June 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Endoscopic management of sigmoid volvulus in children

Filippo Parolini, Paolo Orizio, Anna Lavinia Bulotta, Miguel Garcia Magne, Giovanni Boroni, Gianpaolo Cengia, Fabio Torri, Daniele Alberti

Filippo Parolini, Paolo Orizio, Anna Lavinia Bulotta, Miguel Garcia Magne, Giovanni Boroni, Fabio Torri, Daniele Alberti, Department of Paediatric Surgery, "Spedali Civili" Children's Hospital, 25123 Brescia, Italy

Gianpaolo Cengia, Unit of Digestive Endoscopy and Gastroenterology, "ASST Garda-Manerbio" Hospital, 25085 Gavardo, Italy

Daniele Alberti, Department of Clinical and Experimental Sciences, University of Brescia, 25123 Brescia, Italy

Author contributions: All Authors contributed equally to preparation of the manuscript, reviewed and approved the final manuscript as submitted.

Conflict-of-interest statement: We hereby declare that the following information relevant to this article are true to the best of our knowledge: The above mentioned manuscript has not been published, accepted for publication or under editorial review for publication elsewhere and it won't be submitted to any other journal while under consideration for publication in your Journal; we have no financial relationship relevant to this article to disclose; there isn't any conflict of interest relevant to this article; all authors participated in the concept and design, analysis and interpretation of data, drafting and revising the manuscript, and they have approved the manuscript as submitted.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Filippo Parolini, MD, Department of Paediatric Surgery, "Spedali Civili" Children's Hospital, Piazzale Spedali Civili 1, 25123 Brescia, Italy. parfil@hotmail.it
Telephone: +39-03-03996201
Fax: +39-03-03996154

Received: March 10, 2016

Peer-review started: March 15, 2016

First decision: March 25, 2016

Revised: April 19, 2016

Accepted: May 17, 2016

Article in press: May 27, 2016

Published online: June 25, 2016

Abstract

Sigmoid volvulus (SV) is extremely uncommon in children and is usually associated with a long-standing history of constipation or pseudo-obstruction. An early diagnosis and management are crucial in order to prevent the appearance of hemorrhagic infarction of the twisted loop, avoiding further complications such as necrosis, perforation and sepsis. In patients with no evidence of peritonitis or ischemic bowel, treatment starts with resuscitation and detorsion of the SV, accomplished by means of sigmoidoscopy and concomitant rectal tube placement. The bowel is then prepared and surgery is undertaken electively during the same hospitalization. We report a detailed review of the literature focusing on technical details, risks and benefits of endoscopic management of SV in childhood.

Key words: Sigmoid volvulus; Contrast enema; Children; Endoscopy; Surgery

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Authors provide a detailed review of the literature focusing on technical details, risks and benefits of endoscopic management of sigmoid volvulus in children.

Parolini F, Orizio P, Bulotta AL, Garcia Magne M, Boroni G, Cengia G, Torri F, Alberti D. Endoscopic management of sigmoid volvulus in children. *World J Gastrointest Endosc* 2016; 8(12): 439-443 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i12/439.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i12.439>

INTRODUCTION

Sigmoid volvulus (SV) is extremely uncommon in children and is usually associated with a long-standing history of constipation or pseudo-obstruction^[1,2]. Patients with SV present redundant sigmoid colon with a narrow mesenteric attachment to posterior abdominal wall, allowing the close approximation of two limbs of sigmoid colon and making it prone to torsion around the mesenteric axis. Less frequently, predisposing factors are Hirschsprung's disease (HD) and roundworm infestation, especially in smaller children. Presentations can range from acute to recurrent abdominal pain, often relieved by passage of stool or flatus^[2,3]. An early diagnosis and management are crucial in order to prevent the appearance of hemorrhagic infarction of the twisted loop, avoiding further complications such as necrosis, perforation and sepsis^[1-4]. If no signs of bowel ischemia and perforation are present, endoscopic decompression and detorsion of the volvulus has been proposed as the first step of treatment, followed by elective surgery with sigmoid resection and primary anastomosis^[2,4]. We report a detailed review of the literature focusing on technical details, risks and benefits of endoscopic management of SV in children.

REVIEW

Multicenter studies on endoscopic management of SV in children are lacking. The initial PubMed search yielded 39 potentially relevant articles on the topic. Inclusion criteria were articles that reported original data on endoscopic management of SV in children younger than 18 years and they clearly reported the method of endoscopic treatment. Titles and abstracts of the identified publications were checked and reviewed against the predefined inclusion criteria, and afterward, the full text articles was reviewed^[5]. Finally, 6 eligible articles were enclosed in the review, encompassing a total of 81 cases (Table 1)^[1,2,6-9]. All but one studies were single institution case reports or case presentation (classes of evidence III and rating scales of evidence E)^[5]. Only one multicenter study was found, encompassing 13 cases^[1]. Another study provided a detailed retrospective review of 63 children with SV published in literature from 1940 to 1999^[8]. HD was associated in 13 out of 81 patients (16%). All patients of this series underwent endoscopic detorsion; the procedure was successful in 56 of cases (69%). Although this limited pediatric experience, evidence suggests that endoscopic management of SV should be considered the first step of treatment of these patients, followed by definitive elective surgery. Operative and technical details of endoscopic management thereby originated from a larger adult experience, as more than 1000 cases of endoscopic detorsion are reported^[3,4].

ENDOSCOPIC MANAGEMENT OF SV IN CHILDREN

Which patients should be endoscopically managed?

All selected studies agree that emergency surgery is obviously indicated when the patient has clinical or radiological evidence or suspicion of peritonitis or perforation, which may clinically manifest as melanotic stool during anamnesis or rectal examination, guarding or rebound tenderness during abdominal examination^[10]. In this subset of patients, the surgical procedure is chosen on the basis of the history, clinical presentation and intraoperative findings^[10-12]. On the contrary, when signs of bowel ischemia and perforation are ruled out and a pediatric endoscopy service with high expertise or endoscopic guard with experience in pediatric procedures are available, endoscopic decompression and detorsion should represent the initial step of treatment in order to relief symptoms and to prepare the patient to semi-elective surgical exploration^[1-6]. Surgery in emergency situations, when the general condition of the patient is suboptimal and the bowel is not prepared, is reported to carry higher complication rate^[13].

How should the patient be prepared?

All selected studies agree that patients should actively be resuscitated by means of nasogastric suction and correction of fluid-electrolyte imbalance. Nasogastric intubation is necessary in order to allow gastric decompression, relief of symptoms and bowel rest and identification of the stomach on X-ray^[1,10,11]. Broad spectrum antibiotic covering anaerobic bacteria should be administered immediately after admission. In patients with no evidence of peritonitis or ischemic bowel, water-soluble contrast enema is advisable before the endoscopy, in order to confirm the diagnosis and to rule out other causes of obstruction, such as intussusception^[8]. Successful temporary reduction of SV by contrast enema is reported in up to 77% of the cases; moreover, enema could also facilitate preparation of both patient and bowel for subsequent endoscopy and surgery^[8,9].

What is necessary to perform a safe procedure?

The procedure should be performed under general anesthesia in operating room^[1]. This fact is different compared with adults, in whom the procedure could be safely performed under sedation in endoscopic suite. Different types of pediatric flexible colonoscopes less than 12-mm are commercially available. They are equipped with 3.2-mm biopsy channel, which allows the use of operative devices as biopsy forceps, snares and needles. Unfortunately, these instruments are more suitable for children 2 years and older (weight over 12-15 kg), and, as colonoscopes specifically designed for infants and toddlers do not exist, pediatric upper

Table 1 Endoscopic management of sigmoid volvulus in childhood

Ref.	No. of patients	Demographic	Associated anomalies, <i>n</i> (%)	Endoscopic detorsion success rate, %	Recurrence rate, %	Surgery
Salas <i>et al</i> ^[8]	1	M, 13 yr	Irritable bowel syndrome	100	100%, 2 d later	Sigmoidectomy with colostomy and Harmann's pouch
Salas <i>et al</i> ^[8]	63	M:F = 3.5:1, mean age 7 yr	Hirschsprung's disease: 11 (58%) Imperforate anus in 2 (11%)	47	53%	Sigmoidectomy: 19 (38.7%); Sigmoidopexy: 11 (22.4%) Colostomy: 15 (30.6%)
Ton <i>et al</i> ^[7]	1	M, 16 yr	-	100	100%	Open sigmoid colectomy
Patel <i>et al</i> ^[2]	1	M, 14 yr	Chronic constipation	100	100%	Sigmoidectomy
Colinet <i>et al</i> ^[11]	13	M:F = 0.85:1, mean age 12.8 yr	Mental retardation : 2 (15.3) Myopathy: 2 (15.3) Chronic intestinal pseudo-obstruction: 2 (15.3)	100	50%, from 3 d to 3 mo later	Sigmoidectomy 12 (84.6%)
Clermidi <i>et al</i> ^[6]	1	F, 11 yr	Cornelia de langes	100	100%, 2 d later	Open sigmoidectomy
Parolini <i>et al</i> ^[9]	1	F, 10 yr	Functional constipation	100	100 (%)	Sigmoidectomy and sigmoidopexy

M: Male; F: Female.

GI video endoscopes can be used. It is assumed that is more difficult to study the sigmoid colon with these instruments, but their smaller diameter prevents excessive stretching of the intestinal wall, especially in newborns and infant. Nevertheless, in this series endoscopic management of SV was not attempted in children younger than 6-year-old. Rigid colonoscopes should not be used, as in all but one selected studies^[3] they are generally associated to higher risks of perforation and lower volvulus reduction successful rate^[12-14].

Endoscopic procedure

Sigmoidoscopy is best performed with patient in the Sims or left lateral decubitus position. Hips and knees are partially flexed and the right knee is positioned above the left one^[12-16]. The pediatric endoscopist should stand between the light source and the back of the patient. Digital rectal examination is advisable, in order to lubricate the anal canal, relax the rectal sphincter and give an initial assessment of the effectiveness of the bowel preparation. The lubricated tip of the scope should be gently introduced into the rectum by flexion of the right index finger, guiding it into the anus at a 90° angle. The less amount of air is insufflated, in order to avoid the stretching of bowel loops and to reduce the patient's discomfort after the procedure^[16]. The evaluation of the colorectal mucosa should be performed during the withdrawal of the instrument. Liquid in the rectum should be aspirated *via* the sigmoidoscope for a clearer view. The sigmoidoscope is then advanced into the rectum under direct vision. The rectum is gently insufflated to provide good visibility and to facilitate identification of rectosigmoid junction, which represents the area of most difficulty during the examination. To overcome this step the endoscope should be advanced beyond the valve of Houston, then the tip should be deflect upwards and, with gentle clockwise torquing, slowly advanced beyond the rectosigmoid junction. Spirally twisted or converging colon mucosa ("whirl sign") at the rectosigmoid junction

indicates the distal point of torsional obstruction^[10-12]. The endoscope should be gently advanced through the apex of the converging mucosa into the dilated sigmoid colon. Ischemic changes of the mucosa or gangrene should be noticed and represent an absolute indication to discontinue the endoscopy and to convert to surgery^[2-6]. On the contrary, the management of children in whom endoscopic examination shows borderline ischemia is controversial^[10-12]. Once the dilated sigma is decompressed and the endoscope is in the descending colon, endoscopic detorsion of the decompressed volvulus is obtained performing by clockwise rotation and shortening of the endoscope by the right hand. Only occasionally, the pressure of the air causes detorsion with reduction of the volvulus. If detorsion does not occur, the spiraling rectal mucosa is followed upward to the apex, and a soft rectal tube is passed up through this under direct vision^[15,16]. The tip of the endoscope can also be used to apply a constant pressure at the apex of the twist, which can lead to detorsion and decompression^[2]. A successful deflation is accompanied by a large amount of release of gas and liquid stool from the anus^[1]. Eventually, rectal suction biopsies should be obtained, as HD has been reported in up to 17% of cases of SV in infancy^[8,17].

Is rectal tube placement necessary?

Evidence suggests that the placement of a rectal tube for 24-72 h helps to stabilize the patient further and prevents an early relapse of volvulus^[1]. After the placement of a guide wire (0.035 inch), a multiple side ports guiding catheter is advanced through the endoscopic channel into the descending or transverse colon. Several devices are available and used in the adult setting for treatment of acute non-toxic megacolon, pseudo-obstruction and colonic strictures, including the 14 Fr Colon Decompression Set (Cook Inc, Bloomington, Indiana, United States) and 7 Fr, 8.5 Fr and 10 Fr Marcon Colon Decompression Set

(Cook Inc). Endoscopic exchange was performed by gently pulling back the endoscope over the guidewire while advancing the guide wire. The drainage catheter was then advanced over the guide wire overcoming the point of the obstruction, and eventually the guidewire is removed through the drainage catheter^[1,16,17]. Placement of a larger red rubber catheter per rectum alongside the scope is suggested when colonic decompression kit is not available. When the tip of the catheter is visualized, biopsy forceps passed through the work channel of the scope are used to grasp the tip of the catheter and advanced it as far as necessary. The drainage catheter is taped over the perianal skin and should left in place for 1-3 d before surgery^[1].

The role of percutaneous endoscopic sigmoidopexy

Described in the first time by Choi *et al.*^[18] in 1998, percutaneous endoscopic sigmoidopexy (PES) has been proposed in order to prevent recurrence of volvulus for elder patients who otherwise had contraindication for elective surgery and general anesthesia. PES is performed using the percutaneous endoscopic gastrostomy technique. Nevertheless, as only one fixation point may be insufficient for preventing SV, Ito *et al.*^[19] reported PES with multiple fixation points in a 86-year-old patient with recurrent SV. The sigmoid colon was fixed at six points to the abdominal wall using non-absorbable sutures, with the fixation knots buried subcutaneously, obviating the need for suture removal. Pinedo *et al.*^[20] reported two patients in whom sigmoidopexy was performed percutaneously under sedation in the endoscopy suite. Fixation to abdominal wall was obtained using also T-fasteners in a triangular disposition in the colon; the T-fasteners were cut at the skin after 4 wk. According to evidence, the experience of PES in pediatric settings is extremely limited, and this procedure should be reserved only for the small subset of children with recurrent SV and high anesthesiological risks for open surgery.

Is surgery necessary?

After successful endoscopic reduction of the colon, the recurrence of SV was achieved in up two thirds of the cases. The largest data in adult population is provided by Atamanalp, who reported a 46-year experience with 952 patients with SV, in whom primary endoscopic derotation was successfully performed in 77% of patients, with the highest success rate in rigid sigmoidoscopy group (78.1%) compared with flexible sigmoidoscopy group (76.4%). A 4.5% of early recurrent rate was reported, and all the patients of this series eventually underwent elective or emergent surgical treatment^[3]. In the pediatric review of Salas and colleagues, proctosigmoidoscopy and endoscopic rectal tube placement was attempted in 53.5% of cases, with a success rate of 47%^[8]. Basing to the limited pediatric experience, we suggest that the initial endoscopic decompression and subsequent semi-

elective operation results in a satisfactory outcome in managing SV. Waiting for surgery, a 48-72 h interval seems adequate for bowel preparation and optimization of the patient's clinical status^[1,21]. Definitive semi-elective surgery is strongly recommended during the initial hospital admission for most of the patients^[1]. Clinical evidence of peritonitis or perforation, unsuccessful endoscopic detorsion, gangrenous or ischemic bowel endoscopically evident obviously necessitates emergency surgical intervention^[1,22].

What are the risks of the endoscopic procedure?

Inability to endoscopically endorse the SV is an indication for immediate surgical intervention. Shaft-induced perforations during endoscopy are due to a big loop formation. In these cases perforations are usually larger than expected and located on the antimesenteric wall. Tip perforations are smaller and typically occur when the "sliding by" technique is used inappropriately or a tip is trapped in wide diverticula or imbedded into mucosa when orientation is lost. Excessive air pressure perforation has been documented primarily in patients with strictures of the left colon, but are extremely uncommon in children^[17,18]. In the historical review in adult setting provided by Atamanalp, iatrogenic perforations during endoscopy were recorded in 14 patients (2%); mortality rate of endoscopy was 0.05%^[3]. Interestingly, no complications occurred during endoscopy were recorded in this review of pediatric series. To prevent excessive air insufflation water-immersion colonoscopy for SV was reported in adults^[10-13]. Nevertheless, according to evidence, the experience of water-immersion endoscopy in pediatric settings is extremely limited, especially in emergency setting.

CONCLUSION

Sigmoid volvulus is extremely uncommon in children and operative and technical details of endoscopic management is borrowed by the larger adult experience. If no signs of bowel ischemia and perforation are present, water contrast enema followed by endoscopic decompression and detorsion of the volvulus represents the initial step of treatment also in pediatric setting. Nevertheless, the procedure requires a high degree of pediatric endoscopy expertise and is associated to high rate of early recurrence even when successfully performed. Elective surgery with sigmoid resection, primary anastomosis and sigmoidopexy is mandatory also in children successfully managed by endoscopic decompression and detorsion.

REFERENCES

1. Colinet S, Rebeuh J, Gottrand F, Kalach N, Paquot I, Djeddi D, Le Henaff G, Rebouissoux L, Robert V, Michaud L. Presentation and endoscopic management of sigmoid volvulus in children. *Eur J Pediatr* 2015; **174**: 965-969 [PMID: 25623891 DOI: 10.1007/s00431-015-2489-5]

- 2 **Patel RV**, Njere I, Campbell A, Daniel R, Azaz A, Fleet M. Sigmoid volvulus in an adolescent girl: staged management with emergency colonoscopic reduction and decompression followed by elective sigmoid colectomy. *BMJ Case Rep* 2014; **2014**: pii: bcr2014206003 [PMID: 25143313 DOI: 10.1136/bcr-2014-206003]
- 3 **Atamanalp SS**. Treatment of sigmoid volvulus: a single-center experience of 952 patients over 46.5 years. *Tech Coloproctol* 2013; **17**: 561-569 [PMID: 23636444 DOI: 10.1007/s10151-013-1019-6]
- 4 **Osiro SB**, Cunningham D, Shoja MM, Tubbs RS, Gielecki J, Loukas M. The twisted colon: a review of sigmoid volvulus. *Am Surg* 2012; **78**: 271-279 [PMID: 22524761]
- 5 **Moher D**, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]
- 6 **Clermidi P**, Abadie V, Campeotto F, Irtan S. Sigmoid Volvulus: An Underestimated Cause of Intestinal Obstruction in Cornelia de Lange Syndrome. *J Pediatr* 2015; **167**: 941-941.e1 [PMID: 26233605 DOI: 10.1016/j.jpeds.2015.07.008]
- 7 **Ton MN**, Ruzal-Shapiro C, Stolar C, Kazlow PG. Recurrent sigmoid volvulus in a sixteen-year-old boy: case report and review of the literature. *J Pediatr Surg* 2004; **39**: 1434-1436 [PMID: 15359409 DOI: 10.1016/j.jpedsurg.2004.05.021]
- 8 **Salas S**, Angel CA, Salas N, Murillo C, Swischuk L. Sigmoid volvulus in children and adolescents. *J Am Coll Surg* 2000; **190**: 717-723 [PMID: 10873009 DOI: 10.1016/S1072-7515(00)00270-2]
- 9 **Parolini F**, Alberti D. Sigmoid volvulus in children. *Surgery* 2016 Mar 5; Epub ahead of print [PMID: 26953115 DOI: 10.1016/j.surg.2016.01.020]
- 10 **Atamanalp SS**, Atamanalp RS. The role of sigmoidoscopy in the diagnosis and treatment of sigmoid volvulus. *Pak J Med Sci* 2016; **32**: 244-248 [DOI: 10.12669/pjms.321.84100]
- 11 **Atamanalp SS**, Yildiran MI, Başoğlu M, Kantarci M, Yilmaz I. Sigmoid colon volvulus in children: review of 19 cases. *Pediatr Surg Int* 2004; **20**: 492-495 [PMID: 15241618 DOI: 10.1007/s00383-004-1222-7]
- 12 **Tang S**, Wu R. Endoscopic Decompression, Detorsion, and Reduction of Sigmoid Volvulus. *Video Journal and Encyclopedia of GI Endoscopy* 2014; **2**: 20-25 [DOI: 10.1016/j.vjgien.2013.10.003]
- 13 **Neilson IR**, Youssef S. Delayed presentation of Hirschsprung's disease: acute obstruction secondary to megacolon with transverse colonic volvulus. *J Pediatr Surg* 1990; **25**: 1177-1179 [PMID: 2273435 DOI: 10.1016/0022-3468(90)90758-2]
- 14 **Turan M**, Sen M, Karadayi K, Koyuncu A, Topcu O, Yildirim C, Duman M. Our sigmoid colon volvulus experience and benefits of colonoscope in detorsion process. *Rev Esp Enferm Dig* 2004; **96**: 32-35 [PMID: 14971995]
- 15 **Raveenthiran V**, Madiba TE, Atamanalp SS, De U. Volvulus of the sigmoid colon. *Colorectal Dis* 2010; **12**: e1-17 [PMID: 20236153 DOI: 10.1111/j.1463-1318.2010.02262.x]
- 16 **Gershman G**, Marvin A. Pediatric Colonoscopy. In: Practical Pediatric Gastrointestinal Endoscopy, Gershman G, Marvin A (eds). Malden: Blackwell Publishing Ltd Blackwell Publishing Inc., 2007: 272-341
- 17 **Zeng M**, Amodio J, Schwarz S, Garrow E, Xu J, Rabinowitz SS. Hirschsprung disease presenting as sigmoid volvulus: a case report and review of the literature. *J Pediatr Surg* 2013; **48**: 243-246 [PMID: 23331823 DOI: 10.1016/j.jpedsurg.2012.10.042]
- 18 **Choi D**, Carter R. Endoscopic sigmoidopexy: a safer way to treat sigmoid volvulus? *J R Coll Surg Edinb* 1998; **43**: 64 [PMID: 9560517]
- 19 **Ito E**, Ohdaira H, Suzuki N, Yoshida M, Suzuki Y. Percutaneous endoscopic sigmoidopexy for sigmoid volvulus: A case report. *Int J Surg Case Rep* 2015; **17**: 19-22 [PMID: 26519811 DOI: 10.1016/j.ijscr.2015.10.022]
- 20 **Pinedo G**, Kirberg A. Percutaneous endoscopic sigmoidopexy in sigmoid volvulus with T-fasteners: report of two cases. *Dis Colon Rectum* 2001; **44**: 1867-1869; discussion 1869-1870 [PMID: 11742176]
- 21 **Tsai MS**, Lin MT, Chang KJ, Wang SM, Lee PH. Optimal interval from decompression to semi-elective operation in sigmoid volvulus. *Hepatogastroenterology* 2006; **53**: 354-356 [PMID: 16795971]
- 22 **Ismail A**. Recurrent colonic volvulus in children. *J Pediatr Surg* 1997; **32**: 1739-1742 [PMID: 9434013 DOI: 10.1016/S0022-3468(97)90520]

P-Reviewer: Atamanalp SS, Sugimoto S

S-Editor: Kong JX **L-Editor:** A **E-Editor:** Jiao XK



Single port laparoscopic liver surgery: A minireview

Ilhan Karabicak, Kagan Karabulut

Ilhan Karabicak, Kagan Karabulut, Department of General Surgery, Medical Faculty, Ondokuz Mayıs University, 55000 Samsun, Turkey

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Ilhan Karabicak, MD, FEBS, Department of General Surgery, Medical Faculty, Ondokuz Mayıs University, 55000 Samsun, Turkey. ikarabicak@yahoo.com
Telephone: +90-533-2416895

Received: February 4, 2016

Peer-review started: February 14, 2016

First decision: March 23, 2016

Revised: April 20, 2016

Accepted: May 17, 2016

Article in press: May 27, 2016

Published online: June 25, 2016

incision with limited exposure. There are concerns over adverse oncological outcomes for single-port laparoscopic liver resections (SPL-LR) for hepatocellular carcinoma or metastatic colorectal cancer. In addition, getting familiar with using the operating instruments through a narrow incision with limited exposure is very challenging. In this article, we reviewed the published literature to describe history, indications, contraindications, ideal patients for new beginners, technical difficulty, advantages, disadvantages, oncological concern and the future of SPL-LR.

Key words: Single-port laparoscopic surgery; Single-port laparoscopic liver resection; Minimal invasive liver surgery; Laparoscopic liver resection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This manuscript highlights the indications, contraindications, technical difficulties, advantages and disadvantages of the single-incision laparoscopic (SIL) liver surgery. The authors wanted to share their experience of SIL liver surgery by this review and to create a reference review for new beginners.

Karabicak I, Karabulut K. Single port laparoscopic liver surgery: A minireview. *World J Gastrointest Endosc* 2016; 8(12): 444-450
Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i12/444.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i12.444>

Abstract

Nowadays, the trend is to perform surgeries with "scarless" incisions. In light of this, the single-port laparoscopic surgery (SPLS) technique is rapidly becoming widespread due to its lack of invasiveness and its cosmetic advantages, as the only entry point is usually hidden in the umbilicus. The interest in "scarless" liver resections did not grow as rapidly as the interest in other scarless surgeries. Hepatopancreatobiliary surgeons are reluctant to operate a malignant lesion through a narrow

INTRODUCTION

Laparoscopic liver resection is performed on benign and malignant liver tumors. Preliminary oncological results of liver resection have demonstrated that laparoscopic techniques are as effective as open procedures in a select group of patients^[1-4]. Laparoscopic liver surgery has been shown to be superior to open surgery in terms of intraoperative blood loss, pain control, duration of hospital stay, resumption of oral intake, and com-

Table 1 Baseline characteristics of small case series about single port laparoscopic liver resection

Ref.	Type of article	Year	Country	No. of patients by diagnosis			Type of Surgery				Child-Pugh classification of HCC patients
				Benign Lesion	HCC	Metastatic tumor	Right hepatectomy	Left hepatectomy	LLLS	Nonanatomic resection or segmentectomy	
Shetty <i>et al</i> ^[14]	Case series	2011	South Korea	-	23	-	1	1	4	17	No data
Pan <i>et al</i> ^[18]	Case series	2012	China	3	4	1	-	3	-	5	A (4)
Aikawa <i>et al</i> ^[21]	Case series	2012	Japan	2	5	1	-	-	-	8	A (3) B (1) C (1)
Hu <i>et al</i> ^[22]	Prospective, randomized, controlled study	2014	China	18	-	-	-	-	14	-	No data
Wu <i>et al</i> ^[24]	Case series	2014	China	13	2	2	-	1	8	8	No data
Aldrighetti <i>et al</i> ^[25]	Case-matched analysis	2012	Italy	5	6	2	-	-	13	-	No data
Karabıcak <i>et al</i> ^[27]	Case series	2016	Turkey	3	2	4	-	-	2	7	A (1) B (1)

HCC: Hepatocellular carcinoma; LLLS: Left lateral liver sectionectomy.

plication rates^[5-8].

Laparoscopic metastasectomy and left lateral sectionectomy are widely performed and accepted as the gold standard treatment for liver tumors in many hepatobiliary centers^[9]. Major hepatectomies, such as left and right hepatectomies or extended left and right hepatectomies, are performed laparoscopically by experienced hepatobiliary surgeons^[1,3,6,7,10].

Nowadays, the trend is to perform surgeries with "scarless" incisions. In light of this, the single-port laparoscopic surgery (SPLS) technique is rapidly becoming widespread due to its lack of invasiveness and its cosmetic advantages, as the only entry point is usually hidden in the umbilicus^[11-13].

As advances in laparoscopic liver resections have been slower than laparoscopic resections of other organs, the interest in "scarless" liver resections did not grow as rapidly as the interest in other scarless surgeries. Moreover, single-port laparoscopic liver resection (SPL-LR) has a significant learning curve, which can make surgeons reluctant to perform it^[14-18].

The most difficult part of this technique is getting familiar with using the operating instruments through a narrow incision with limited exposure^[12,14,18,19]. Surgeons with experience in both open and laparoscopic liver surgery are best suited to perform this challenging procedure^[14-18].

Those who intend to start performing SPL-LR have to be very selective in choosing first patients during the learning curve so as to not fail. A surgeon should combine his/her experience in both laparoscopic liver resection and SPLS for other organs such as gallbladder when performing the SPL-LR, especially during the initial stages of the learning curve^[14-19].

HISTORY

SPL-LR is a newly emerging technique, and it is still limited in practice. The development of special inst-

uments to facilitate this technique have made liver resection feasible and safe, but surgeons have been slow in applying this technique^[14-16].

The first report of SPL-LR, published by Aldrighetti *et al*^[19] in 2010, was a left lateral sectionectomy for a single colorectal metastasis. After the publication of this, many case reports and a few short series about SPL-LR and two case-matched analysis of traditional laparoscopic liver resection and SPL-LR were published^[14-18,20-27]. Table 1 shows baseline characteristics of small case series about SPL-LR. We published the first SPL pericystectomy for liver hydatid disease^[26].

INDICATIONS AND CONTRAINDICATIONS

Patient selection is of paramount importance for SPLS. The aim of SPLS is to reduce the operative trauma and to make the smallest possible incision (2.5 to 5 cm) that will allow the extraction of the resected specimen (Figure 1). Tumors that require a big incision to remove the resected specimen are against the SPLS mentality^[17,19,20,28]. It is mandatory to select the appropriate patient for this procedure, based on the size, malignancy potential and the location of the tumor^[15,29].

SPL-LR has been performed for many different benign and malignant lesions such as liver adenoma, focal nodular hyperplasia, hemangioma, hydatid cyst, giant simple cyst, intrahepatic biliary stones, cystadenoma, metastatic liver lesions and hepatocellular carcinoma (HCC)^[14,17,19,20,24,26,27,30].

The ideal lesions for SPL-LR are peripherally located superficial tumors^[17,21]. Wu *et al*^[24] recommend SPL-LR for patients with benign liver tumors that are less than 10 cm in diameter and located in segments II and III. Hu *et al*^[22] recommends localized benign left lateral liver disease as a suitable candidate for SPL-LR, because laparoscopic left lateral sectionectomy (LLLS) is technically less demanding. They also mention that



Figure 1 A 2-cm umbilical single-port incision.

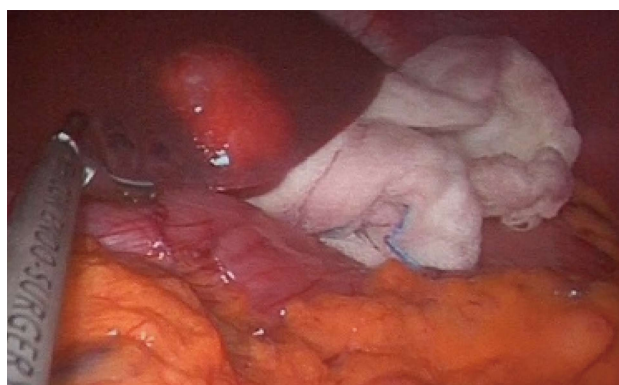


Figure 3 A peripherally located benign lesion.

the resection specimen of benign liver diseases can be fragmented and retrieved without requiring the addition or extension of a trocar incision (Figure 2).

In our experience with the hydatid cyst, the cyst can at times be large enough to totally replace the left lateral section. In cases where the cyst can be totally removed by left lateral sectionectomy, we prefer to use SPL-LR. Once the SPL left lateral sectionectomy performed, the cyst is placed into the retrieval bag and then, the cyst content can be aspirated through the incision while it is in the bag; this enables the collapsed cyst wall to be easily pulled out from the small incision without having to enlarge it.

Malignant tumors bigger than 5 cm are not suitable for SPLS, as the incision required to extract the specimen itself would defeat the purpose of such a procedure^[14-18]. Ideally, malignant liver lesions that are suitable for SPL-LR are less than 5 cm in diameter and located in the left lateral sector; alternatively, they are smaller than 2.5 cm in diameter and located at the surface in segments IV, V or VI^[24].

IDEAL PATIENTS FOR BEGINNERS

Beginner surgeons have to be very cautious while choosing the ideal patients for SPLS. Surgical candidates have to be carefully selected to optimize the benefits of this technique^[14-18,24]. One should never forget that,



Figure 2 Fragmentation of the specimen without extension of the single-port incision.

during the learning curve, it is difficult to obtain the angles necessary for parenchymal transection with instruments parallel to each other^[12,14,31]. That is why obese patients, patients who require big lesions or lesions located deep in the parenchyma, or cirrhotic patients are not good candidates to start with^[14,24,31].

Gkegkes *et al.*^[32] advise to start SPL-LR with the peripherally located lesions. The surgeon can then move on to anatomical resections and, finally, proceed to major hepatectomies before he/she can gain sufficient experience with SPL-LR. Wu *et al.*^[24] recommend starting with the lesion in the left lateral section or anterior and inferior liver segments (IV anterior, V and VI), since minimal mobilization of the liver is necessary in these locations.

Geller *et al.*^[31] recommend the ideal patient to be a thin, young female with a 3-4 cm hepatic adenoma, where cosmesis is of prime concern. Aikawa *et al.*^[21] and Aldrighetti *et al.*^[25] recommend that new surgeons start with the liver tumors located in the left lateral section, away from the hilum or anterior right hepatic segment.

We recommend that during the learning curve, beginners of this technique start with the peripherally located benign lesions to decrease the failure rate (Figure 3). The first few patients should not be cirrhotic patients, as the new surgeon can cause harm and jeopardize the patient's oncological safety.

We preferred to start performing SPL-LR on patients with peripherally located liver hydatid cysts since it is one of the most common benign liver tumors. Laparoscopic pericystectomy is the ideal surgical treatment for such a location^[26].

SPL-LS IN CIRRHOTIC PATIENTS

Laparoscopic liver surgery has already been shown to decrease intraoperative bleeding and postoperative general complications, such as ascites and wound infection, without worsening the oncological outcome in well-selected cirrhotic patients^[33-35].

The decrease in abdominal wall trauma in SPLS could be especially useful for cirrhotic patients. SPL-LR has been performed in well-selected cirrhotic patients with a medically and oncologically good outcome^[14,21,23].



Figure 4 Conflict between the surgeon and the camera holder extracorporeally.

A peripherally located small HCC is appropriate for SPL-LR, since the surgery can be performed without prolonging the operation time or increasing bleeding so as to avoid deterioration after the surgery^[14,16,23].

One has to be cautious with trans-umbilical incisions for the single port, as it can cause severe bleeding due to large umbilical veins. Gaujoux *et al.*^[17] recommends making incisions through the rectus abdominis muscle or in the supraumbilical position to avoid bleeding from large umbilical veins.

PORT TYPES

The first single-port device created for SPLS is the SILS port system (Covidien, Mansfield, MA), which has three access channel, and which is suitable for a 2.5 cm incision. Nowadays, there are many different types of port devices suitable for 2.5 to 5 cm incisions with three or four access channel, each having advantages over the others^[18,21,32]. The ideal port has to have flexible access parts to reduce the overlapping of the instruments^[14,32]. The size of the port has to be chosen according to the size of the liver to be resected. The port size should not be smaller than the malignant tumor since, eventually, the incision will need to be enlarged^[20,21].

TECHNICAL DIFFICULTIES

SPLS has some technical problems that are peculiar to operating through a single-port^[12,14,32]. The main problems of this technique are instrument crowding, the absence of triangulation, the parallel field of view, and a two/three instrument restriction depending on the port choice^[12-14,19,22,24,27,31,35].

Having all the instruments and the camera inserted parallel to each other within the single port causes restricted range of movement and conflict between the surgeon and the camera holder, both intracorporeally and extracorporeally^[12,16,26,32,36] (Figure 4). The absence of triangulation makes laparoscopic manipulation more complicated and troublesome^[22,25,31]. The "sword-fighting" is unavoidable, but this adversity can be decre-

ased by cross-handling the instruments, using single ports with a large outer cap or self-retaining sleeves, and using curved and articulating instruments and flexible scopes^[12,16,17,22,37,38].

Another apparent difficulty with SPL-LR is bleeding, which is the most common reason for conversion to traditional laparoscopy or open surgery^[32,36]. Experience and careful patient selection are the mainstays of preventing this complication^[14,22,25]. Prevention of major bleeding during parenchymal resection is an important step in SPL-LR, since the instruments are limited and the room is too narrow for manipulations^[13,22,31,38]. Weiss *et al.*^[39] showed reduced bleeding during single-incision laparoscopic minor liver resection with inline radiofrequency pre-coagulation (Habib 4X).

If acute massive bleeding occurs, it is very difficult to stop parenchymal bleeding by SPLS. Shetty *et al.*^[14] reported that suture ligation is too time-consuming to control bleeding during SPL-LR due to inadequate instrument angles and extremely uncomfortable needle-handling. Unless the bleeding cannot be treated, conversion to laparoscopy or laparotomy is required^[13,22,24,38].

Selection of the umbilicus for the single-port placement allows hiding the incision while achieving the resection. The transumbilical route is not appropriate for all patients, since the distances between the umbilicus and the liver vary from case to case. The entry of the port should be selected based on the patient's body type and the location of the lesion^[14,18,22] (Figure 5).

RESECTION TYPES

The development of new single ports, articulating special instruments and laparoscopic surgery experience facilitate this technique. In experienced hands, the SPL anatomical liver resection has become feasible and safe in carefully selected patients^[14-17,22,25].

Lesions limited to the left lateral sector of the liver are the most appropriate for this technique. SPL left lateral sectionectomy has been the main type of resection for such lesions^[22,25,37]. In this situation, the instruments are already aligned to the intended liver parenchyma transection plane, which helps to avoid "dueling swords" between the surgeon and the camera holder. Also, suspensory ligaments aid in surgical site exposure^[17,22,25,40].

SPLS has been performed for different types of resections such as living donor liver harvesting, right hepatectomy, extended left lobectomy, left hepatectomy, left lateral sectionectomy, proximal left hemihepatectomy-segmentectomy, pericystectomy, wedge resection, liver cyst deroofing, biliary exploration, and pericystectomy for hydatid cyst^[14,17,18,24,26,41-43].

ONCOLOGICAL CONCERNS

There are concerns over adverse oncological outcomes for SPL-LR for HCC or metastatic colorectal cancer. Few publications about SPL-LR for malignant lesions



Figure 5 The entry of the port should be selected based on the patient's body type and the location of the lesion.

are available; a majority of them are case reports, and a few of them are short case series. The role of SPL-LR for malignancy is reported for small HCCs and solitary liver metastasis^[15,17,21]. Shetty *et al.*^[14] showed that, in the hands of experienced hepatobiliary and laparoscopic surgeons, SPL-LR is oncologically as safe as conventional laparoscopy in a variety of well-selected cases.

Strict oncological principles should not be compromised simply to achieve a SPL-LR. Free resection margins have to be achieved with the "no touch" technique^[9,16,28,44]. Shetty *et al.*^[14] recommend making 5 cm incisions for SPL-LR in patients with malignant lesions, as this would make surgical handling relatively easy. By making a 5-cm incision, the necessity of the unfamiliar articulating instruments for the resection of the malignant tumor decreases. A 5-cm incision is usually large enough to deliver the specimen while maintaining its contours^[14].

ADVANTAGES

The advantages of SPL-LR usually include a hidden incision, minimization of abdominal trauma, less postoperative pain, quicker recovery, earlier resumption of normal activities, and shorter hospital stays compared to conventional surgeries^[14-16,24,30]. Small case-control series comparing the SPL limited liver resection and the LLS showed similarities in operating times, blood loss, length of stay and intra- and post-operative complications^[25,30].

SPL-LR may be especially appealing in cirrhotic patients with HCC as it reduces the risk of complications such as ascites and wound infections, which can deteriorate the patient's condition after a conventional liver resection^[14,23].

Tayar *et al.*^[15] mentioned that after laparoscopic wedge resections of a liver tumor, one of the trocar incisions is usually enlarged for the specimen removal. They emphasize that this is an advantage of SPLS since, at the end of the surgery, the single-port incision will be used to extract the specimen. Therefore, the surgery can be completed without the need for an additional three or four ports.

An alternative to SPL liver surgery is multiport laparoscopic liver resection. Whenever necessary, one can easily convert single-port to standard laparoscopy if one encounters difficulty during the liver parenchyma resection^[17,22,31].

DISADVANTAGES

SPL liver surgery has some very well-known disadvantages when compared with conventional laparoscopic surgery. The articulating specific surgical instruments may be necessary during deep parenchymal resection, which may not be easily available in all institutions, thus increasing the cost of the operation^[15,21,22,32].

Colorectal cancer solitary small liver metastasis is an indication for SPL-LR. Performing this technique in a patient with a history of previous surgery may not always be possible because of the severe intra-abdominal adhesions (Figure 6). The presence of severe adhesions can diminish the number of patients suitable for this technique, even if the tumor is small and peripherally located. For such patients, conventional laparoscopy is the preferred technique. After making the umbilical incision for the single port, we usually make blunt and sharp dissections under direct visualization to create enough space for the port and the instruments.

SPL liver surgery has a significant learning curve that initially increases the operation time, the conversion rate and complications^[14-18,21,22,25,31]. Aikawa *et al.*^[21] shortened the SPL-LR time by using multi-functional devices such as division, hemostasis, irrigation and suction.

The location and size of the malignant lesion is crucial. Malignant lesions bigger than 5 cm are considered to be a contraindication for this technique^[14,18,24,45]. Anatomic resection of tumors located deep in the liver or in the posterior right lobe are not suitable for this technique, either^[18,24,35].

Moreover, patient-related restrictions can diminish the application of SPL-LR. Longer single-port instruments may be necessary in obese or tall patients. Extremely obese patients may not be suitable for SPLS, because the depth of the subcutaneous fatty tissue may not allow the placement of the single port. Single-port site hernia has been reported to be higher in obese patients^[15].

More blood loss can occur in cirrhotic patients during SPL-LR than during laparoscopic liver resections or major hepatic resections, especially during the learning curve^[14,18,31]. In our experience, articulating tissue sealer shortens the operation time, decreases blood loss and reduces the size of unnecessarily removed liver tissue, particularly in cirrhotic patients.

CONCLUSION

SPL-LR is a new and emerging technique. Initially, surgeons were reluctant to perform this technique due to concerns about the oncological safety in malignant



Figure 6 A single-port laparoscopic liver resection incision a patient with a previous history of colon resection.

liver lesions^[16,22,24,36]. However, the development of special instruments and ports have facilitated this technique and made it a feasible, effective and safe alternative to conventional laparoscopy for the treatment of peripherally located benign or malignant liver lesions in cautiously selected patients^[14-18,22,24-26,45].

SPL-LR should be performed by surgeons with expertise in both liver and advanced laparoscopic surgery in centers where laparoscopic liver resection is routinely performed^[14, 22-26].

There are a limited number of studies comparing single-port and conventional laparoscopic liver resections, each with a very small sample size owing to strict patient-selection criteria due to safety concerns. Additional indications and contraindications of single-incision laparoscopic liver resections need to be stated in the light of large randomized studies^[22,25,32]. Larger, particularly randomised studies are especially necessary to determine whether SPL-LR is safe and feasible for massive hepatic resections and resections of bigger malignant tumors^[14-18,25,45].

Studies comparing the oncological outcome and complication rates between SPL-LR and conventional laparoscopy, and between SPL-LR and conventional liver surgery, will determine the future of this emerging technique.

REFERENCES

- 1 **Nguyen KT**, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg* 2009; **250**: 831-841 [PMID: 19801936 DOI: 10.1097/SLA.0b013e3181b0c4df]
- 2 **Castaing D**, Vibert E, Ricca L, Azoulay D, Adam R, Gayet B. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. *Ann Surg* 2009; **250**: 849-855 [PMID: 19801934 DOI: 10.1097/SLA.0b013e3181b0caf63]
- 3 **Tzani D**, Shivathirthan N, Laurent A, Abu Hilal M, Soubrane O, Kazaryan AM, Ettore GM, Van Dam RM, Lainas P, Tranchart H, Edwin B, Belli G, Campos RR, Pearce N, Gayet B, Dagher I. European experience of laparoscopic major hepatectomy. *J Hepatobiliary Pancreat Sci* 2013; **20**: 120-124 [PMID: 23053354 DOI: 10.1007/s00534-012-0554-2]
- 4 **Cugat E**, Pérez-Romero N, Rotellar F, Suárez MA, Gastaca M, Artigas V, Olsina JJ, Noguera J, Martínez S, Moreno-Sanz C, Figueras J, Herrera J, Díaz H, Caballé J, Pereira F. Laparoscopic liver surgery: 8 years of multicenter Spanish register. *J Hepatobiliary Pancreat Sci* 2010; **17**: 262-268 [PMID: 19763386 DOI: 10.1007/s00534-009-0170-y]
- 5 **Azagra JS**, Goergen M, Gilbert E, Jacobs D. Laparoscopic anatomical (hepatic) left lateral segmentectomy-technical aspects. *Surg Endosc* 1996; **10**: 758-761 [PMID: 8662435 DOI: 10.1007/BF00193052]
- 6 **Lai EC**, Tang CN, Ha JP, Li MK. Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. *Arch Surg* 2009; **144**: 143-147; discussion 148 [PMID: 19221325 DOI: 10.1001/archsurg.2008.536]
- 7 **Dagher I**, Belli G, Fantini C, Laurent A, Tayar C, Lainas P, Tranchart H, Franco D, Cherqui D. Laparoscopic hepatectomy for hepatocellular carcinoma: a European experience. *J Am Coll Surg* 2010; **211**: 16-23 [PMID: 20610244 DOI: 10.1016/j.jamcollsurg.2010.03.012]
- 8 **Pearce NW**, Di Fabio F, Teng MJ, Syed S, Primrose JN, Abu Hilal M. Laparoscopic right hepatectomy: a challenging, but feasible, safe and efficient procedure. *Am J Surg* 2011; **202**: e52-e58 [PMID: 21861979 DOI: 10.1016/j.amjsurg.2010.08.032]
- 9 **Azagra JS**, Goergen M, Brondello S, Calmes MO, Philippe P, Schmitz B. Laparoscopic liver sectionectomy 2 and 3 (LLS 2 and 3): towards the "gold standard". *J Hepatobiliary Pancreat Surg* 2009; **16**: 422-426 [PMID: 19466378 DOI: 10.1007/s00534-009-0117-3]
- 10 **O'Rourke N**, Fielding G. Laparoscopic right hepatectomy: surgical technique. *J Gastrointest Surg* 2004; **8**: 213-216 [PMID: 15036198 DOI: 10.1016/j.gassur.2003.11.008]
- 11 **Hong TH**, You YK, Lee KH. Transumbilical single-port laparoscopic cholecystectomy: scarless cholecystectomy. *Surg Endosc* 2009; **23**: 1393-1397 [PMID: 19118436 DOI: 10.1007/s00464-008-0252-y]
- 12 **Rao PP**, Rao PP, Bhagwat S. Single-incision laparoscopic surgery - current status and controversies. *J Minim Access Surg* 2011; **7**: 6-16 [PMID: 21197236]
- 13 **Karabıcak I**, Karabulut K. Is single-port laparoscopy feasible after liver transplant? *Pediatr Transplant* 2016; Epub ahead of print [PMID: 27161386 DOI: 10.1111/petr.12719]
- 14 **Shetty GS**, You YK, Choi HJ, Na GH, Hong TH, Kim DG. Extending the limitations of liver surgery: outcomes of initial human experience in a high-volume center performing single-port laparoscopic liver resection for hepatocellular carcinoma. *Surg Endosc* 2012; **26**: 1602-1608 [PMID: 22179464 DOI: 10.1007/s00464-011-2077-3]
- 15 **Tayar C**, Subar D, Salloum C, Malek A, Laurent A, Azoulay D. Single incision laparoscopic hepatectomy: Advances in laparoscopic liver surgery. *J Minim Access Surg* 2014; **10**: 14-17 [PMID: 24501503 DOI: 10.4103/0972-9941.124454]
- 16 **Chang SK**, Mayasari M, Ganpathi IS, Wen VL, Madhavan K. Single port laparoscopic liver resection for hepatocellular carcinoma: a preliminary report. *Int J Hepatol* 2011; **2011**: 579203 [PMID: 21994864 DOI: 10.4061/2011/579203]
- 17 **Gaujoux S**, Kingham TP, Jarnagin WR, D'Angelica MI, Allen PJ, Fong Y. Single-incision laparoscopic liver resection. *Surg Endosc* 2011; **25**: 1489-1494 [PMID: 20976489 DOI: 10.1007/s00464-010-1419-x]
- 18 **Pan M**, Jiang Z, Cheng Y, Xu X, Zhang Z, Zhou C, He G, Xu T, Liu H, Gao Y. Single-incision laparoscopic hepatectomy for benign and malignant hepatopathy: initial experience in 8 Chinese patients. *Surg Innov* 2012; **19**: 446-451 [PMID: 22474017 DOI: 10.1177/1553350612438412]
- 19 **Aldrighetti L**, Guzzetti E, Ferla G. Laparoscopic hepatic left lateral sectionectomy using the LaparoEndoscopic Single Site approach: evolution of minimally invasive liver surgery. *J Hepatobiliary Pancreat Sci* 2011; **18**: 103-105 [PMID: 20552231 DOI: 10.1007/s00534-010-0280-6]
- 20 **Kobayashi S**, Nagano H, Marubashi S, Wada H, Eguchi H, Takeda Y, Tanemura M, Sekimoto M, Doki Y, Mori M. A single-incision laparoscopic hepatectomy for hepatocellular carcinoma: initial experience in a Japanese patient. *Minim Invasive Ther Allied Technol* 2010; **19**: 367-371 [PMID: 20945973 DOI: 10.3109/13645706.2010.

- 518731]
- 21 **Aikawa M**, Miyazawa M, Okamoto K, Toshimitsu Y, Okada K, Ueno Y, Yamaguchi S, Koyama I. Single-port laparoscopic hepatectomy: technique, safety, and feasibility in a clinical case series. *Surg Endosc* 2012; **26**: 1696-1701 [PMID: 22179479 DOI: 10.1007/s00464-011-2095-1]
- 22 **Hu M**, Zhao G, Wang F, Xu D, Liu R. Single-port and multi-port laparoscopic left lateral liver sectionectomy for treating benign liver diseases: a prospective, randomized, controlled study. *World J Surg* 2014; **38**: 2668-2673 [PMID: 24867469]
- 23 **Belli G**, Fantini C, D'Agostino A, Cioffi L, Russo G, Belli A, Limongelli P. Laparoendoscopic single site liver resection for recurrent hepatocellular carcinoma in cirrhosis: first technical note. *Surg Laparosc Endosc Percutan Tech* 2011; **21**: e166-e168 [PMID: 21857451 DOI: 10.1097/SLE.0b013e3182207d3a]
- 24 **Wu S**, Yu XP, Tian Y, Siwo EA, Li Y, Yu H, Yao D, Lv C. Transumbilical single-incision laparoscopic resection of focal hepatic lesions. *JSLs* 2014; **18**: pii: e2014.00397 [PMID: 25392646 DOI: 10.4293/JSLs.2014.00397]
- 25 **Aldrighetti L**, Ratti F, Catena M, Pulitanò C, Ferla F, Cipriani F, Ferla G. Laparoendoscopic single site (LESS) surgery for left-lateral hepatic sectionectomy as an alternative to traditional laparoscopy: case-matched analysis from a single center. *Surg Endosc* 2012; **26**: 2016-2022 [PMID: 22278101 DOI: 10.1007/s00464-012-2147-1]
- 26 **Karabıcak I**, Yuruker S, Seren DT, Kesicioglu T, Cinar H, Ozen N. Single incision laparoscopic surgery for hepatic hydatid disease. Report of a case. *Ann Ital Chir* 2013; **84**: 451-453 [PMID: 23241840]
- 27 **Karabıcak I**, Karabulut K, Yuruker S, Kesicioglu T, Ozen N. Single-Port laparoscopic liver resection: Largest Turkish Experience. *Indian J Surg*; Published online: January 11, 2016: 1-5 [DOI: 10.1007/s12262-015-1435-0]
- 28 **Patel AG**, Belgaumkar AP, James J, Singh UP, Carswell KA, Murgatroyd B. Video. Single-incision laparoscopic left lateral segmentectomy of colorectal liver metastasis. *Surg Endosc* 2011; **25**: 649-650 [PMID: 20652322 DOI: 10.1007/s00464-010-1237-1]
- 29 **Wang E**, Kow AW, Chan CY, Liao KH, Ho CK. Starting a laparoscopic hepatectomy programme. *Singapore Med J* 2009; **50**: 354-359 [PMID: 19421677]
- 30 **Sasaki K**, Watanabe G, Matsuda M, Hashimoto M, Harano T. Original method of transumbilical single-incision laparoscopic deroofing for liver cyst. *J Hepatobiliary Pancreat Sci* 2010; **17**: 733-734 [PMID: 20703853 DOI: 10.1007/s00534-010-0279-z]
- 31 **Geller DA**. Laparoscopic or SILS liver resection for hepatic left lateral sectionectomy? *World J Surg* 2014; **38**: 2674-2675 [PMID: 24817474 DOI: 10.1007/s00268-014-2625-9]
- 32 **Gkegkes ID**, Iavazzo C. Single incision laparoscopic hepatectomy: A systematic review. *J Minim Access Surg* 2014; **10**: 107-112 [PMID: 25013325 DOI: 10.4103/0972-9941.134872]
- 33 **Dagher I**, Lainas P, Carloni A, Caillard C, Champault A, Smadja C, Franco D. Laparoscopic liver resection for hepatocellular carcinoma. *Surg Endosc* 2008; **22**: 372-378 [PMID: 17704878 DOI: 10.1007/s00464-007-9487-2]
- 34 **Belli G**, Fantini C, D'Agostino A, Cioffi L, Langella S, Russolillo N, Belli A. Laparoscopic versus open liver resection for hepatocellular carcinoma in patients with histologically proven cirrhosis: short- and middle-term results. *Surg Endosc* 2007; **21**: 2004-2011 [PMID: 17705086 DOI: 10.1007/s00464-007-9503-6]
- 35 **Cherqui D**, Laurent A, Tayar C, Chang S, Van Nhieu JT, Loriau J, Karoui M, Duvoux C, Dhumeaux D, Fagniez PL. Laparoscopic liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: midterm results and perspectives. *Ann Surg* 2006; **243**: 499-506 [PMID: 16552201 DOI: 10.1097/01.sla.0000206017.29651.99]
- 36 **Montero PN**, Acker CE, Heniford BT, Stefanidis D. Single incision laparoscopic surgery (SILS) is associated with poorer performance and increased surgeon workload compared with standard laparoscopy. *Am Surg* 2011; **77**: 73-77 [PMID: 21396310]
- 37 **Machado MA**, Surjan RC, Makdissi FF. Intrahepatic glissonian approach for single-port laparoscopic liver resection. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 534-537 [PMID: 24927363 DOI: 10.1089/lap.2013.0539]
- 38 **Toyama Y**, Yoshida S, Okui N, Kitamura H, Yanagisawa S, Yanaga K. Transumbilical single-incision laparoscopic hepatectomy using pre-coagulation and clipless technique in a patient with combined hepatocellular-cholangiocarcinoma: a case report. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: e194-e199 [PMID: 24105295 DOI: 10.1097/SLE.0b013e31828b8602]
- 39 **Weiss M**, Mittermair C, Brunner E, Schirmerhofer J, Obrist C, Pimpl K, Hell T, Weiss H. Inline radiofrequency pre-coagulation simplifies single-incision laparoscopic minor liver resection. *J Hepatobiliary Pancreat Sci* 2015; **22**: 831-836 [PMID: 26510122 DOI: 10.1002/jhbp.295]
- 40 **Aldrighetti L**, Pulitanò C, Arru M, Catena M, Guzzetti E, Casati M, Ferla G. Ultrasonic-mediated laparoscopic liver transection. *Am J Surg* 2008; **195**: 270-272 [PMID: 18154765 DOI: 10.1016/j.amjsurg.2007.02.022]
- 41 **Imamura H**, Kawashita Y, Koga N, Sanada Y, Azuma T, Matsuo S, Eguchi S. A large hepatic cyst with obstructive jaundice successfully treated with single-incision laparoscopic deroofing. *Case Rep Gastroenterol* 2013; **7**: 503-510 [PMID: 24474900 DOI: 10.1159/000357304]
- 42 **Yeo D**, Mackay S, Martin D. Single-incision laparoscopic cholecystectomy with routine intraoperative cholangiography and common bile duct exploration via the umbilical port. *Surg Endosc* 2012; **26**: 1122-1127 [PMID: 22170316 DOI: 10.1007/s00464-011-2009-2]
- 43 **Choi HJ**, You YK, Na GH, Hong TH, Shetty GS, Kim DG. Single-port laparoscopy-assisted donor right hepatectomy in living donor liver transplantation: sensible approach or unnecessary hindrance? *Transplant Proc* 2012; **44**: 347-352 [PMID: 22410013 DOI: 10.1016/j.transproceed.2012.01.018]
- 44 **Gigot JF**, Glineur D, Santiago Azagra J, Goergen M, Ceuterick M, Morino M, Etienne J, Marescaux J, Mutter D, van Krunkelsven L, Descottes B, Valleix D, Lachachi F, Bertrand C, Mansvelt B, Hubens G, Saey JP, Schockmel R. Laparoscopic liver resection for malignant liver tumors: preliminary results of a multicenter European study. *Ann Surg* 2002; **236**: 90-97 [PMID: 12131090 DOI: 10.1097/00000658-200207000-00014]
- 45 **Tan EK**, Lee VT, Chang SK, Ganpathi IS, Madhavan K, Lomanto D. Laparoendoscopic single-site minor hepatectomy for liver tumors. *Surg Endosc* 2012; **26**: 2086-2091 [PMID: 22234591 DOI: 10.1007/s00464-011-2128-9]

P- Reviewer: Biebl MO, Sinha R

S- Editor: Kong JX L- Editor: A E- Editor: Jiao XK



Retrospective Study

Effectiveness of clip-and-snare method using pre-looping technique for gastric endoscopic submucosal dissection

Naohiro Yoshida, Hisashi Doyama, Ryosuke Ota, Yasuhito Takeda, Hiroyoshi Nakanishi, Kei Tominaga, Shigetsugu Tsuji, Kenichi Takemura

Naohiro Yoshida, Hisashi Doyama, Ryosuke Ota, Yasuhito Takeda, Hiroyoshi Nakanishi, Kei Tominaga, Shigetsugu Tsuji, Kenichi Takemura, Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Ishikawa 920-8530, Japan

Author contributions: Yoshida N designed and performed the research and wrote the paper; Doyama H designed the research and supervised the report; Ota R, Takeda Y, Nakanishi H, Tominaga K, Tsuji S and Takemura K supervised the report.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of Ishikawa Prefectural Central Hospital No. 544.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study were published on the home page of Ishikawa Prefectural Central Hospital.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Naohiro Yoshida, MD, Department of Gastroenterology, Ishikawa Prefectural Central Hospital, 2-1 Kuratsuki-Higashi, Kanazawa city, Ishikawa 920-8530, Japan. ynaohiro@ipch.jp

Telephone: +81-76-2378211

Fax: +81-76-2382377

Received: February 9, 2016

Peer-review started: February 9, 2016

First decision: March 14, 2016

Revised: April 6, 2016

Accepted: May 7, 2016

Article in press: May 9, 2016

Published online: June 25, 2016

Abstract

AIM: To evaluate efficacy and safety of clip-and-snare method using pre-looping technique (CSM-PLT) for gastric endoscopic submucosal dissection (ESD).

METHODS: In the CSM-PLT method, a clip attached to the lesion side was strangulated with a snare, followed by application of an appropriate tension to the lesion independent of an endoscope. Twenty consecutive lesions were resected by ESD using CSM-PLT (CSM-PLT group) and compared with a control group, including 20 lesions that were resected by conventional ESD. The control group was matched based on the size and location of the lesion, presence of pathologic fibrosis, and experience of endoscopists. Total procedure time of ESD, proportion of *en bloc* resection, and complications were analyzed.

RESULTS: The total procedure time for the CSM-PLT group was significantly shorter than that for the control group (38.5 min *vs* 59.5 min, $P = 0.023$); all lesions were resected *en bloc* by ESD. There was no significant difference in complications between the two groups. Moreover, there was no complication in the CSM-PLT group. In one large lesion (size: 74 mm) that underwent

extensive CSM-PLT during ESD, we used an additional CSM-PLT on another edge of the lesion after achieving submucosal resection to the maximum extent possible during initial CSM-PLT. In two lesions, the snare came off the lesion together with the clip after a sudden pull; nevertheless, ESD was successful in all lesions.

CONCLUSION: CSM-PLT was an effective and safe method for gastric ESD.

Key words: Endoscopic submucosal dissection; Clip-and-snare method; Pre-looping technique; Endoscope; Dissection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This was a retrospective matched-pair analysis to evaluate the efficacy and safety of clip-and-snare method using pre-looping technique (CSM-PLT) for gastric endoscopic submucosal dissection (ESD). CSM-PLT is one of the traction methods that was developed to perform gastric ESD more effectively. Compared with conventional ESD, ESD using CSM-PLT had significantly shorter total procedure time (38.5 min *vs* 59.5 min, $P = 0.023$). With regard to proportion of *en bloc* resection and complications, there was no significant difference between the groups. Hence, CSM-PLT is a promising method for gastric ESD.

Yoshida N, Doyama H, Ota R, Takeda Y, Nakanishi H, Tominaga K, Tsuji S, Takemura K. Effectiveness of clip-and-snare method using pre-looping technique for gastric endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016; 8(12): 451-457 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i12/451.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i12.451>

INTRODUCTION

Endoscopic submucosal dissection (ESD) was developed in the late 1990s for the purpose of *en bloc* and less invasive resection of early gastric cancer^[1]. In the earliest years, some problems including difficulty of the procedure and high risk of complications were encountered. Over the years, ESD has evolved to become an easier and safer procedure due to establishment of strategies, improvement of devices and injection solution^[2], and use of CO₂ insufflation pump^[3].

Although ESD is performed for early gastric cancer, which satisfies the indication criteria of Japanese guideline^[4], difficulty in technicalities of the procedure are still occasionally encountered. The difficulty of gastric ESD depends on the size and location of a tumor, presence of ulceration, or the endoscopist's skills. Therefore, an innovative technique is necessary to constantly make ESD a safer and more effective procedure, regardless of the characteristic of the lesions or skills of the operator.

Traction method has been described as a technique for an effective ESD; with this technique, an appropriate tension is applied to the lesion to visualize the submucosal layer and effectively perform submucosal dissection. Recently, several traction methods have been reported for use in gastric ESD such as internal traction^[5], medical ring^[6], clip-with-line (including "dental floss clip traction")^[7-10], use of double-channel endoscope^[11], external grasping forceps^[12], magnetic anchor^[13,14], and the double-scope method^[15]. Each method has its advantages and disadvantages^[16]; therefore, the most ideal method has not yet been established.

Recently, as new traction method, the clip-and-snare method (CSM), has been reported. CSM is a concept that includes "clip and snare lifting"^[17] and "yo-yo technique"^[18]. In this technique, the clip attached to the side of the lesion is strangulated with a snare, followed by application of an appropriate tension to the lesion independent of an endoscope. CSM does not only facilitate control of the degree of strength but also of the direction of traction by pulling and pushing the snare. The major difference between "clip and snare lifting"^[17] and "yo-yo technique"^[18] is the course through which the snare passes. The snare passes through the oral cavity in the "clip and snare lifting"^[17], whereas it passes through the nostril in the "yo-yo technique"^[18]. Conventional CSM^[17,18] entails the use of forceps to derive the snare to the clip; this technique is not easy, particularly for lesions in the upper third of the stomach. We improved this method with a new and easy technique for snare derivation, which we reported as pre-looping technique (PLT)^[19] to simplify the CSM technique during gastric ESD on all sites.

The aim of this study was to evaluate the efficacy and safety of CSM using PLT (CSM-PLT) for gastric ESD.

MATERIALS AND METHODS

General

This retrospective study was conducted at the Ishikawa Prefectural Central Hospital, a tertiary referral center in Japan. In accordance with the Declaration of Helsinki, the protocol was approved by the Institutional Review Board of the said institution. Patients were not required to provide informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For complete disclosure, the details of the study were published on the home page of Ishikawa Prefectural Central Hospital.

In this manuscript, we reported a retrospective matched-pair comparison of ESD using CSM-PLT with conventional ESD.

Lesion selection

From January 2014 to March 2014, 20 consecutive gastric lesions resected by ESD using CSM-PLT were included in the CSM-PLT group. From 1033 gastric lesions resected by conventional ESD between January

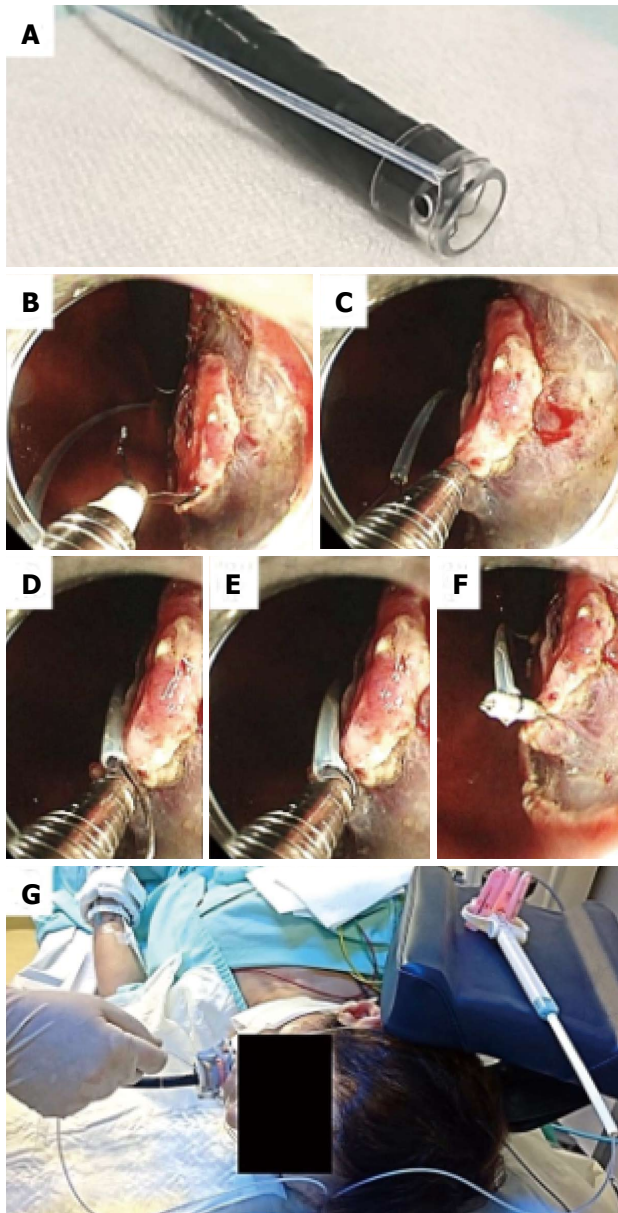


Figure 1 Clip-and-snare method using pre-looping technique. A: The transparent cap is tightened with a snare from the outside of the endoscope (pre-looping technique) after completion of a circumferential incision; B: A tumor is seen on the lesser curvature of the upper third of the stomach. The endoscope is bent to a maximum. A hemoclip with a reusable clip deployment device is inserted through the endoscope channel and is used to grasp the edge of the tumor while avoiding its detachment from its deployment device; C, D: The pre-looped snare is loosened from the transparent cap and moved along the device toward the hemoclip; E, F: The hemoclip is tightened with the snare and released from the clip deployment device; G: The endoscopist can apply appropriate tension to the lesion using the snare independent of the endoscope. The slider of the snare is fixed with clothespins.

2009 and December 2013, we set a control group that included 20 lesions, which matched those of the CSM-PLT group in terms of tumor size, location, pathologic fibrosis, and endoscopist's experience with ESD. The location and presence of pathologic fibrosis were completely matched. Regarding the location of the lesion, the stomach was divided into the following three longitudinal sections: Upper, middle, and lower; the cross-sectional

circumference of the stomach was divided into four equal parts according to the Japanese classification of gastric cancer: Lesser curvature, greater curvature, anterior wall, and posterior wall^[20]. Depending on the experience of endoscopists on ESD, further matching was performed. ESD experience was classified into "3 years or under", "more than 3 years and less than 7 years", and "7 years or over". To minimize differences in specimen size, definitive matching was performed. Lesions that extended to the esophagus or duodenum were excluded.

Endoscopists

The endoscopists who performed ESD in this study had enough knowledge and skills related to conventional gastric ESD. To ensure the quality of gastric ESD, all of the participated endoscopists were required to have a level of knowledge and skills commensurate with those of a specialist accredited by the Japan Gastroenterological Endoscopy Society. In actuality, they had an experience of 4 years or more in gastroscopy. Endoscopists with less than 7 years of experience performed ESD procedures under the supervision of experts with more than 7 years of experience. For the CSM-PLT group, we retrospectively collected consecutive data immediately after the establishment of CSM-PLT. Therefore, all endoscopists who participated in the study had little experience on the established CSM-PLT.

ESD using CSM-PLT

A single-channel endoscope (GIF-Q260J; Olympus Co., Tokyo, Japan) with a disposable transparent cap (D-201-11804, Olympus Co.) on the endoscopic tip was used. A mixture of saline solution, 0.4% sodium hyaluronate, and indigo carmine was injected into the submucosal layer surrounding the lesion, and a circumferential incision was made using an insulation-tipped scalpel (IT knife2, Olympus Co) on ENDO CUT Q mode (effect 2) of the electrosurgical generator (VIO300D, ERBE Co, Tübingen, Germany). The endoscope was withdrawn and the transparent cap was tightened with a snare (SD-221U-25, Olympus Co.) from the outside of the endoscope (Figure 1A); this technique was named PLT^[19]. Then, the endoscope and snare were reinserted into the lesion before inserting a hemoclip (HX-610-090, Olympus Co.) with a reusable clip deployment device (EZ CLIP, Olympus Co.) through the endoscope channel. The hemoclip was used to grasp the edge of the tumor while taking utmost care to avoid complete detachment from its deployment device (Figure 1B). The pre-looped snare was loosened from the transparent cap and moved along the device toward the hemoclip (Figure 1C and D). The hemoclip was tightened with the snare and released from the clip deployment device (Figure 1E and F). After this, the endoscopist was able to apply an appropriate tension to the lesion using the snare independent of the endoscope and could incise the submucosal layer effectively (Figure

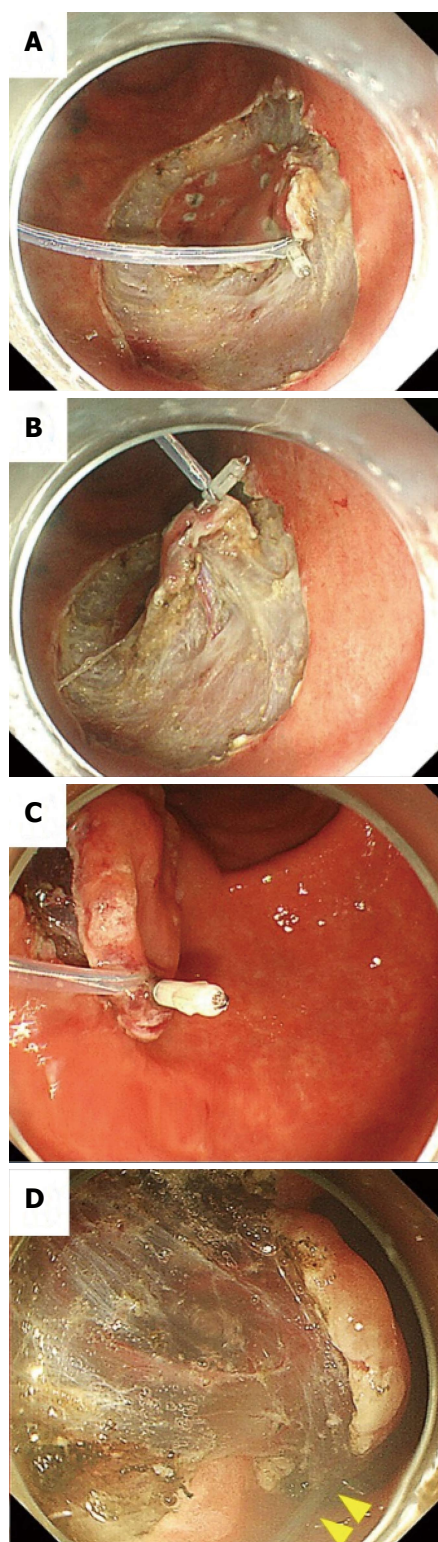


Figure 2 Pushing and pulling by the clip-and-snare method. A: Clip-and-snare method using pre-looping technique (CSM-PLT) for a tumor located on the greater curvature of the middle third of the stomach; B: The endoscopist is able to obtain good visibility of the submucosal layer by pulling the snare; C: CSM-PLT was performed for another tumor located on the anterior wall of the middle third of the stomach; D: The endoscopist is able to obtain good visibility of the submucosal layer by pushing the snare (yellow arrowheads).

1G). The submucosal layer was dissected using an IT knife 2 on SWIFT COAG mode (effect 4, 60W) of

VIO300D. Because the snare had moderate rigidity, the endoscopist could not only pull but also push the lesion through the snare (Figure 2). Fixing the slider of the snare with clothespins reduced the number of assistants needed for the procedure (Figure 1G). The use of an overtube was not necessarily required. All ESD procedures were performed under unconscious sedation without intubation. We used midazolam, pentazocine, and propofol for appropriate sedation during ESD.

Data evaluation

The primary endpoint of this study was comparison of total procedure time of gastric ESD. As secondary endpoints, the proportion of *en bloc* resection and complications were evaluated.

All videos of ESD procedure have been stored in an electronic archive. From these recorded videos, we measured the total time of the procedure from precutting up to tumor removal. *En bloc* resection was defined as a one-piece resection of the entire lesion that was endoscopically recognized. Complications included intractable bleeding during ESD, perforation during ESD, delayed perforation, delayed bleeding, and anesthesia-related complications. Intractable bleeding during ESD was defined as operative hemorrhage that required more than 1 min for hemostasis. Delayed perforation was defined as perforation occurring after the day of ESD. Delayed bleeding was defined as bleeding from an ulceration of ESD, which manifested as hematemesis or melena after the day of ESD. Anesthesia-related complications were defined as circulatory disturbance (systolic blood pressure ≤ 90 mmHg or heart rate ≤ 50 beats/min) or respiratory depression (oxygen saturation $\leq 90\%$ in spite of appropriate oxygen support) that were associated with anesthesia and occurred during the procedure.

Statistical analysis

All descriptive comparisons between the CSM-PLT lesions and their matched controls were made by Wilcoxon signed-rank test for continuous variables and by McNemar test or Bowker test for categorical variables. All *P* values calculated in this study were two-sided and were not adjusted for multiple testing. *P* values of < 0.05 were considered to be statistically significant. All analyses were performed using the statistical software JMP 11 (SAS Institute Inc., Cary, NC, United States). The statistical methods of this study were reviewed by Dr. Kunihiro Tsuji from the Department of Clinical Chemotherapy, Ishikawa Prefectural Central Hospital, Ishikawa, Japan.

RESULTS

According to match pairing, the demographics of both groups were completely similar in location, ulceration, specimen size, and experience of operators (Table 1). Additionally, macroscopic type, histologic type, and

Table 1 Comparison of lesion characteristics in patients who underwent gastric endoscopic submucosal dissection *n* (%)

	CSM-PLT group (<i>n</i> = 20)	Control group (<i>n</i> = 20)	<i>P</i> value
Location			1.000
Upper third	7 (35)	7 (35)	
Middle third	7 (35)	7 (35)	
Lower third	6 (30)	6 (30)	
Macroscopic type			0.475
0-II a	8 (40)	7 (35)	
0-II b	2 (10)	0 (0)	
0-II c	10 (50)	13 (65)	
Specimen size in mm, median (range)	35.5 (25-74)	34 (23-75)	0.999
Ulceration	1 (5)	1 (5)	1.000
Histologic type			0.783
Adenoma	4 (20)	2 (10)	
Tub1	14 (70)	15 (75)	
Tub2	2 (10)	2 (10)	
Por	0 (0)	1 (5)	
Tumor depth			0.655
Mucosal	17 (85)	18 (90)	
Submucosal	3 (15)	2 (10)	
Experience of ESD, yr			1.000
≤ 3	6 (30)	6 (30)	
4-6	10 (50)	10 (50)	
≥ 7	4 (20)	4 (20)	

Tub1: Well-differentiated adenocarcinoma; Tub2: Moderately differentiated adenocarcinoma; Por: Poorly differentiated adenocarcinoma; CSM-PLT: Clip-and-snare method using pre-looping technique; ESD: Endoscopic submucosal dissection.

Table 2 Comparison of clinical outcomes between the two techniques of gastric endoscopic submucosal dissection

	CSM-PLT group (<i>n</i> = 20)	Control group (<i>n</i> = 20)	<i>P</i> value
Total procedure time in minutes, median (range)	38.5 (8-145)	59.5 (19-132)	0.023
En bloc resection, number of lesion (%)	20 (100)	20 (100)	-
Complications			
Intractable bleeding during ESD, number of times, median (range)	0 (0-4)	1 (0-5)	0.086
Perforation during ESD, number of lesion (%)	0 (0)	0 (0)	-
Delayed perforation, number of lesion (%)	0 (0)	0 (0)	-
Delayed bleeding, number of lesion (%)	0 (0)	2 (10)	0.157
Anesthesia-related complications, number of lesions (%)	0 (0)	0 (0)	-

CSM-PLT: Clip-and-snare method using pre-looping technique; ESD: Endoscopic submucosal dissection.

tumor depth were comparable in both groups.

The total procedure time for the CSM-PLT group was significantly shorter than that for the control group (38.5 min vs 59.5 min, *P* = 0.023). All lesions were resected *en bloc* by ESD. There was no significant difference between the two groups with regard to the complications. In particular, there was no complication in the CSM-PLT group (Table 2).

In one large lesion (size: 74 mm) that underwent CSM-PLT during ESD, we used an additional CSM-PLT on another edge of the lesion after achieving the maximum possible submucosal resection during initial CSM-PLT. In two lesions, the snare came off the lesion together with the clip after a sudden pull; CSM-PLT was performed again for one lesion, whereas the other lesion did not undergo additional CSM-PLT because submucosal resection was almost completed with initial CSM-PLT.

DISCUSSION

The results of this retrospective study have demonstrated that CSM-PLT was able to shorten the total procedure time for gastric ESD without a decline in the proportion of *en bloc* resection and no increase in complications. A Shortening of the procedure time is clinically significant because it facilitates reduction in dose, duration of exposure, and risks of sedative use during ESD. Furthermore, a shortened procedure time can reduce the working hours of medical staff, including physicians and nurses. Consequently, a reduction in the cost associated with ESD can be expected, as Suzuki *et al*^[10] showed in their article.

We considered two reasons for the shortening of ESD procedure time by CSM-PLT. First, when we lifted the mucosal layer by applying an appropriate tension

to a lesion edge, we were able to obtain good visibility of the submucosal layer. Good visualization facilitated the identification of blood vessels and of the dissection line on the submucosal layer. Easy visualization of vascular structures resulted in easier hemostasis and pre-coagulation of vessels at a risk of bleeding. Identification of the dissection line greatly contributed to incision speed and safety. In this regard, it is necessary to understand that compared with conventional ESD, in ESD using CSM-PLT, the muscular layer may be elevated by traction. Accordingly, to avoid perforation during ESD using CSM-PLT, resection after recognizing a proper dissection line is more important. Second, the taut submucosal layer with traction allowed endoscopists to incise it with less power such as that for cutting a taut paper with a knife. These advantages are thought to be common among the other traction methods.

CSM-PLT is more advantageous than other traction methods. First, it not only facilitates the control of the degree of strength but also of the direction of traction. With the use of CSM-PLT, we could coordinate a two-way direction by pulling and pushing the snare, although the double-scope method would be more controllable^[15]. In contrast, internal traction^[5] and medical ring^[6] cannot coordinate both traction strength and direction. Clip-with-line^[7-10] can only pull but not push a lesion. Because traction adjustment is the most important factor in the traction method, this point was a major advantage of CSM-PLT. Second, PLT^[19], which is a new method for the delivery of a snare, made it easy to perform CSM for lesions on all sites of the stomach. Because the delivery of a device for traction is difficult for lesions located on the upper third of the stomach, performing conventional CSM or other traction methods, such as external forceps method^[12], is usually a challenge for such lesions. In one report involving one conventional CSM for intragastric proximal lesions, the procedure was successful in only one lesion on the corpus^[18]. PLT facilitated grasping of the clip by the snare, particularly in cases wherein the clip was attached to the anal side of the tumor on the upper third of the stomach (Figure 1). In this report, we performed CSM-PLT and accomplished ESD for seven upper third lesions. Furthermore, PLT enabled the use of CSM even in ESD without an overtube; this would be an advantage for institutions where an overtube is not usually used. Third, because snare and hemoclip are common devices in almost all institutions where ESD is performed, CSM-PLT may be easily reproducible.

However, there are some disadvantages of CSM-PLT. Interference between the endoscope and snare may occur to some extent, despite the use of a thin snare with a maximum external diameter of 1.8 mm. A snare may detach from the lesion together with the clip when the endoscope is manipulated roughly. In fact, this situation occurred in two cases in this study. To avoid this, it is necessary for endoscopists to move the endoscope with care. It would also help if an assistant secures the snare tube on the mouthpiece of the patient during considerable manipulation of the endoscope by

the operator. In addition, the incurred costs of the clip and snare are also a limitation of the method.

As Imaeda *et al.*^[16] described in their review, each of the several traction methods reported has both advantages and disadvantages. It is generally considered that traction method is useful for ESD, but it is unknown which technique is the best at present. As the advantages and disadvantages differ among the techniques, sufficient understanding of each method is needed for choosing the optimal procedure for an endoscopist and an institution. We are certain that CSM-PLT can become one of the promising alternative traction methods for gastric ESD.

There were several limitations of our study. First, it was conducted as a retrospective, single-institution study. Second, the sample size was small and subgroup analysis was not feasible. There were few lesions, such as large lesions or lesions with ulceration, which were typically difficult to treat by conventional ESD. In this study, we could not examine the efficacy and safety of CSM-PLT on these refractory lesions. At present, we are increasing the number of cases and we plan to clarify the characteristics of lesions for which CSM-PLT would be more effective. Third, because the control group in this study included lesions that were resected by conventional ESD, we cannot be certain whether CSM was more useful than the other traction methods. Further prospective, multi-institutional studies are warranted to confirm the efficacy and safety of CSM-PLT.

In conclusion, the CSM-PLT was an effective and safe technique for gastric ESD. CSM-PLT is a promising method, and we believe that it can contribute to further development of ESD.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is one of the standard treatments for early gastric cancer. However, ESD is complicated and difficult. Therefore, a technique that will facilitate ESD is desired.

Research frontiers

Several traction methods, which apply appropriate tension to the lesion in order to visualize the submucosal layer, have been described as techniques for an effective ESD.

Innovations and breakthroughs

Clip-and-snare method using pre-looping technique (CSM-PLT) is a type of traction method. CSM-PLT enables control of the degree and two-way direction of traction with the use of commonly available devices, such as hemoclip and snare.

Applications

CSM-PLT is considered to be effective when endoscopists who are able to perform conventional ESD apply it for lesions which conventional ESD have been intended for.

Terminologies

CSM (clip-and-snare method): A generic term for a traction method that facilitates control of traction to the lesion with the use of a snare, which

strangulates a clip attached to the lesion. CSM-PLT: CSM using pre-looping technique, which is a new technique for snare delivery, facilitates easy performance of CSM for lesions on all sites of the stomach.

Peer-review

This is a very interesting and very well done case-control study which tries to evaluate a new additional method for shortening the time spent during ESD and for making it easier and safer.

REFERENCES

- 1 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]
- 2 **Yamamoto H**, Yahagi N, Oyama T, Gotoda T, Doi T, Hirasaki S, Shimoda T, Sugano K, Tajiri H, Takekoshi T, Saito D. Usefulness and safety of 0.4% sodium hyaluronate solution as a submucosal fluid “cushion” in endoscopic resection for gastric neoplasms: a prospective multicenter trial. *Gastrointest Endosc* 2008; **67**: 830-839 [PMID: 18155216 DOI: 10.1186/1471-230X-9-1]
- 3 **Maeda Y**, Hirasawa D, Fujita N, Obana T, Sugawara T, Ohira T, Harada Y, Yamagata T, Suzuki K, Koike Y, Kusaka J, Tanaka M, Noda Y. A prospective, randomized, double-blind, controlled trial on the efficacy of carbon dioxide insufflation in gastric endoscopic submucosal dissection. *Endoscopy* 2013; **45**: 335-341 [PMID: 23468193 DOI: 10.1055/s-0032-1326199]
- 4 **Ono H**, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, Iishi H, Oka M, Ajioka Y, Ichinose M, Matsui T. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016; **28**: 3-15 [PMID: 26234303 DOI: 10.1111/den.12518]
- 5 **Chen PJ**, Chu HC, Chang WK, Hsieh TY, Chao YC. Endoscopic submucosal dissection with internal traction for early gastric cancer (with video). *Gastrointest Endosc* 2008; **67**: 128-132 [PMID: 18054010 DOI: 10.1016/j.gie.2007.07.021]
- 6 **Matsumoto K**, Nagahara A, Sakamoto N, Suyama M, Konuma H, Morimoto T, Sagawa E, Ueyama H, Takahashi T, Beppu K, Shibuya T, Osada T, Yoshizawa T, Ogihara T, Watanabe S. A new traction device for facilitating endoscopic submucosal dissection (ESD) for early gastric cancer: the “medical ring”. *Endoscopy* 2011; **43** Suppl 2 UCTN: E67-E68 [PMID: 21341187 DOI: 10.1055/s-0030-1255923]
- 7 **Oyama T**, Shimaya S, Tomori A, Hotta K, Miyata Y, Yamada S. Endoscopic mucosal resection using a hooking knife (hooking EMR). *Stomach Intest* 2002; **37**: 1155-1161
- 8 **Jeon WJ**, You IY, Chae HB, Park SM, Youn SJ. A new technique for gastric endoscopic submucosal dissection: peroral traction-assisted endoscopic submucosal dissection. *Gastrointest Endosc* 2009; **69**: 29-33 [PMID: 19111686 DOI: 10.1016/j.gie.2008.03.1126]
- 9 **Yoshida M**, Takizawa K, Ono H, Igarashi K, Sugimoto S, Kawata N, Tanaka M, Kakushima N, Ito S, Imai K, Hotta K, Matsubayashi H. Efficacy of endoscopic submucosal dissection with dental floss clip traction for gastric epithelial neoplasia: a pilot study (with video). *Surg Endosc* 2015; Epub ahead of print [PMID: 26487208 DOI: 10.1007/s00464-015-4580-4]
- 10 **Suzuki S**, Gotoda T, Kobayashi Y, Kono S, Iwatsuka K, Yagi-Kuwata N, Kusano C, Fukuzawa M, Moriyasu F. Usefulness of a traction method using dental floss and a hemoclip for gastric endoscopic submucosal dissection: a propensity score matching analysis (with videos). *Gastrointest Endosc* 2016; **83**: 337-346 [PMID: 26320698 DOI: 10.1016/j.gie.2015.07.014]
- 11 **Yonezawa J**, Kaise M, Sumiyama K, Goda K, Arakawa H, Tajiri H. A novel double-channel therapeutic endoscope (“R-scope”) facilitates endoscopic submucosal dissection of superficial gastric neoplasms. *Endoscopy* 2006; **38**: 1011-1015 [DOI: 10.1055/s-2006-944779]
- 12 **Imaeda H**, Iwao Y, Ogata H, Ichikawa H, Mori M, Hosoe N, Masaoka T, Nakashita M, Suzuki H, Inoue N, Aiura K, Nagata H, Kumai K, Hibi T. A new technique for endoscopic submucosal dissection for early gastric cancer using an external grasping forceps. *Endoscopy* 2006; **38**: 1007-1010 [PMID: 16673308 DOI: 10.1055/s-2006-925264]
- 13 **Kobayashi T**, Gotoda T, Tamakawa K, Ueda H, Kakizoe T. Magnetic anchor for more effective endoscopic mucosal resection. *Jpn J Clin Oncol* 2004; **34**: 118-123 [PMID: 15078906 DOI: 10.1093/jco/hyh025]
- 14 **Gotoda T**, Oda I, Tamakawa K, Ueda H, Kobayashi T, Kakizoe T. Prospective clinical trial of magnetic-anchor-guided endoscopic submucosal dissection for large early gastric cancer (with videos). *Gastrointest Endosc* 2009; **69**: 10-15 [PMID: 18599053 DOI: 10.1016/j.gie.2008.03.1127]
- 15 **Ahn JY**, Choi KD, Choi JY, Kim MY, Lee JH, Choi KS, Kim DH, Song HJ, Lee GH, Jung HY, Kim JH. Transnasal endoscope-assisted endoscopic submucosal dissection for gastric adenoma and early gastric cancer in the pyloric area: a case series. *Endoscopy* 2011; **43**: 233-235 [PMID: 21165828 DOI: 10.1055/s-0030-1256037]
- 16 **Imaeda H**, Hosoe N, Kashiwagi K, Ohmori T, Yahagi N, Kanai T, Ogata H. Advanced endoscopic submucosal dissection with traction. *World J Gastrointest Endosc* 2014; **6**: 286-295 [PMID: 25031787 DOI: 10.4253/wjge.v6.i7.286]
- 17 **Yasuda M**, Naito Y, Kokura S, Yoshida N, Yoshikawa T. Sa1687 Newly-Developed ESD (CSL-ESD) for Early Gastric Cancer Using Convenient and Low-Cost Lifting Method (Lifting Method Using Clips and Snares) for Lesions is Clinically Useful. *Gastrointest Endosc* 2012; **75**: AB244 [DOI: 10.1016/j.gie.2012.04.027]
- 18 **Baldaque-Silva F**, Vilas-Boas F, Velosa M, Macedo G. Endoscopic submucosal dissection of gastric lesions using the “yo-yo technique”. *Endoscopy* 2013; **45**: 218-221 [PMID: 23212725 DOI: 10.1055/s-0032-1325868]
- 19 **Yoshida N**, Doyama H, Ota R, Tsuji K. The clip-and-snare method with a pre-looping technique during gastric endoscopic submucosal dissection. *Endoscopy* 2014; **46** Suppl 1 UCTN: E611-E612 [PMID: 25502265 DOI: 10.1055/s-0034-1390752]
- 20 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

P- Reviewer: Amornyotin S, Rabago L

S- Editor: Qi Y **L- Editor:** A **E- Editor:** Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 July 10; 8(13): 458-476





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hirotoshi Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hirotoshi Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

ORIGINAL ARTICLE

Retrospective Study

- 458 Electrocautery vs non-electrocautery dilation catheters in endoscopic ultrasonography-guided pancreatic fluid collection drainage

Kitamura K, Yamamiya A, Ishii Y, Nomoto T, Honma T, Yoshida H

- 466 Efficacy and safety of endoscopic submucosal dissection under general anesthesia

Yamashita K, Shiwaoku H, Ohmiya T, Shimaoka H, Okada H, Nakashima R, Beppu R, Kato D, Sasaki T, Hoshino S, Nimura S, Yamaura K, Yamashita Y

CASE REPORT

- 472 Cut endotracheal tube for endoscopic removal of an ingested push-through pack

Tateno Y, Suzuki R

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 13 July 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Joo Young Cho, MD, Professor, Digestive Disease Center, Soonchunhyang University Hospital, Seoul 140-887, South Korea

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
July 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Retrospective Study

Electrocautery vs non-electrocautery dilation catheters in endoscopic ultrasonography-guided pancreatic fluid collection drainage

Katsuya Kitamura, Akira Yamamiya, Yu Ishii, Tomohiro Nomoto, Tadashi Honma, Hitoshi Yoshida

Katsuya Kitamura, Akira Yamamiya, Yu Ishii, Tomohiro Nomoto, Tadashi Honma, Hitoshi Yoshida, Division of Gastroenterology, Department of Medicine, Showa University School of Medicine, Tokyo 142-8666, Japan

Author contributions: Kitamura K designed this study and collected and analyzed the data; Kitamura K drafted the manuscript and gave final approval of the version to be published; Kitamura K, Yamamiya A, Ishii Y, Nomoto T, Honma T and Yoshida H participated in this study as endoscopic ultrasonography operators or assistants.

Institutional review board statement: This study was approved by the Medical Ethics Committee of Showa University.

Informed consent statement: Informed, written consent was obtained from each patient prior to the procedure.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Katsuya Kitamura, MD, PhD, Lecturer, Division of Gastroenterology, Department of Medicine, Showa University School of Medicine, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan. k.kitamura@med.showa-u.ac.jp
Telephone: +81-3-37848535
Fax: +81-3-37847553

Received: February 14, 2016
Peer-review started: February 16, 2016
First decision: March 25, 2016
Revised: May 13, 2016
Accepted: May 31, 2016
Article in press: June 2, 2016
Published online: July 10, 2016

Abstract

AIM: To investigate the safety and utility of an electrocautery dilation catheter for endoscopic ultrasonography (EUS)-guided pancreatic fluid collection drainage.

METHODS: A single-center, exploratory, retrospective study was conducted between August 2010 and August 2014. This study was approved by the Medical Ethics Committee of our institution. Informed, written consent was obtained from each patient prior to the procedure. The subjects included 28 consecutive patients who underwent EUS-guided transmural drainage (EUS-TD) for symptomatic pancreatic and peripancreatic fluid collections (PFCs) by fine needle aspiration using a 19-gauge needle. These patients were retrospectively divided into two groups based on the use of an electrocautery dilation catheter as a fistula dilation device; 15 patients were treated with an electrocautery dilation catheter (electrocautery group), and 13 patients were treated with a non-electrocautery dilation catheter (non-electrocautery group). We evaluated the technical and clinical successes and the adverse events associated with EUS-TD for the treatment of PFCs between the two groups.

RESULTS: There were no significant differences in age, sex, type, location and diameter of PFCs between the groups. Thirteen patients (87%) in the electrocautery

group and 10 patients (77%) in the non-electrocautery group presented with infected PFCs. The technical success rates of EUS-TD for the treatment of PFCs were 100% (15/15) and 100% (13/13) for the electrocautery and the non-electrocautery groups, respectively. The clinical success rates of EUS-TD for the treatment of PFCs were 67% (10/15) and 69% (9/13) for the electrocautery and the non-electrocautery groups, respectively ($P = 0.794$). The procedure time of EUS-TD for the treatment of PFCs in the electrocautery group was significantly shorter than that of the non-electrocautery group (mean \pm SD: 30 ± 12 min *vs* 52 ± 20 min, $P < 0.001$). Adverse events associated with EUS-TD for the treatment of PFCs occurred in 0 patients and 1 patient for the electrocautery and the non-electrocautery groups, respectively ($P = 0.942$).

CONCLUSION: EUS-TD using an electrocautery dilation catheter as a fistula dilation device for the treatment of symptomatic PFCs appears safe and contributes to a shorter procedure time.

Key words: Electrocautery dilation catheter; Endoscopic ultrasonography-guided transmural drainage; Fistula dilation device; Pancreatic and peripancreatic fluid collection; Procedure time

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic ultrasonography-guided transmural drainage using an electrocautery dilation catheter as a fistula dilation device for the treatment of symptomatic peripancreatic fluid collections appears to be safe and contributes to a shorter procedure time.

Kitamura K, Yamamiya A, Ishii Y, Nomoto T, Honma T, Yoshida H. Electrocautery *vs* non-electrocautery dilation catheters in endoscopic ultrasonography-guided pancreatic fluid collection drainage. *World J Gastrointest Endosc* 2016; 8(13): 458-465 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i13/458.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i13.458>

INTRODUCTION

Pancreatic and peripancreatic fluid collections (PFCs) are accumulations of liquid and/or necrotic tissue associated with acute pancreatitis, chronic pancreatitis, surgery, or abdominal trauma. The 1992 Atlanta Classification of acute pancreatitis was revised in 2012 to classify local complications caused by acute pancreatitis into the following 4 types: (1) acute peripancreatic fluid collection (APFC); within 4 wk of the onset of pancreatitis, without pancreatic and/or peripancreatic necrosis; (2) pancreatic pseudocyst (over 4 wk after the onset of pancreatitis without pancreatic and/or peripancreatic necrosis); (3) acute necrotic collection (ANC; within 4 wk of the onset of pancreatitis with pancreatic and/or peripancreatic

necrosis); and (4) walled-off necrosis (WON; over 4 wk after the onset of pancreatitis with pancreatic and/or peripancreatic necrosis)^[1].

Endoscopic transmural drainage is a minimally invasive procedure for PFC. Endoscopic drainage for PFCs is superior to percutaneous drainage or surgery in terms of the duration of hospital stay and cost^[2,3]. Recently, endoscopic ultrasonography-guided transmural drainage (EUS-TD) for the treatment of PFCs has been widely accepted^[4-6]. However, it has been reported that EUS-TD for PFCs causes adverse events, such as bleeding and perforation, at a rate of 0%-21%^[7,8], and the establishment of a safe procedure is necessary.

Electrocautery or non-electrocautery dilation catheters are currently used as fistula dilation devices for EUS-TD; however, few studies have investigated the safety and advantages of electrocautery dilation catheters for EUS-TD.

The aim of this study was to evaluate the safety and utility of an electrocautery dilation catheter as a fistula dilation device for EUS-TD in the treatment of PFCs.

MATERIALS AND METHODS

This study was conducted as an exploratory retrospective study at Showa University Hospital, was approved by the Medical Ethics Committee of our institution, and was registered at the UMIN Clinical Trials Registry (UMIN 000018352). Informed, written consent was obtained from each patient prior to the procedure.

Patients

Twenty-eight consecutive patients who underwent EUS-TD at our institution between August 2010 and August 2014 were retrospectively analyzed. All of these patients underwent EUS-TD using an electrocautery or a non-electrocautery dilation catheter as a fistula dilation device after undergoing PFC puncture with a 19-gauge fine needle aspiration needle.

We used a non-electrocautery dilation catheter from August 2010 to April 2012 for 13 patients. An electrocautery dilation catheter was used for 15 patients after May 2012, which is when the electrocautery dilation catheter became available as a treatment option at our institution. We conducted an exploratory retrospective study to compare the clinical outcomes between the electrocautery and the non-electrocautery groups. PFCs were classified into 4 types^[1] according to the revised 2012 Atlanta Classification. We diagnosed PFCs using computed tomography, magnetic resonance imaging and EUS. We performed EUS-TD in patients with signs of infection, abdominal pain and an increase of PFC size (*i.e.*, 6 cm or more). Signs of infection of PFCs were judged according to blood examination, blood culture examination and imaging results. We defined infected PFCs as those with bacteria present based on a culture examination of the PFC obtained by EUS-TD. Exclusion criteria of EUS-TD included coagulopathy, the interposition of blood vessels on the puncture tract for

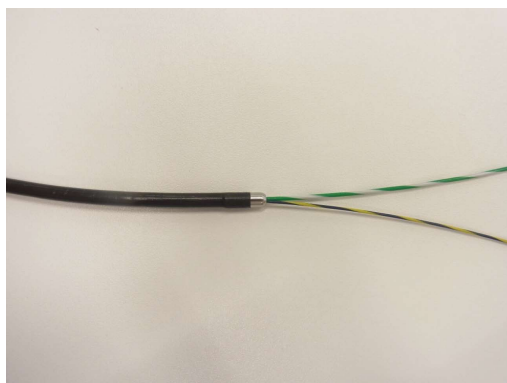


Figure 1 View of an electrocautery dilation catheter tip of an 8.5-Fr Cyst-Gastro-Set (Endo-Flex GmbH, Voerde, Germany).

the PFC, and the inability to obtain informed consent.

Devices

A convex array echoendoscope, GF-UCT 240-AL5 (Olympus Medical Systems Corp, Tokyo, Japan), was used for transmural drainage of the PFCs. A 19-gauge fine needle aspiration needle EchoTip® Ultra Endoscopic Ultrasound Needle (Cook Medical Inc., Bloomington Indiana, United States), Expect™ Endoscopic Ultrasound Aspiration Needle (Boston Scientific, Natick, MA, United States) or EZ shot 2 (Olympus Medical Systems) was used to puncture the PFC.

As a guide wire (GW) for insertion into the PFC, a 0.035-inch Hydra Jagwire™ (Boston Scientific) and/or a 0.025-inch VisiGlide™ or a 0.025-inch VisiGlide 2™ (Olympus Medical Systems) was used.

An electrocautery dilation catheter, 6-Fr and/or 8.5-Fr Cyst-Gastro-Set (Endo-Flex GmbH, Voerde, Germany), was used to dilate the puncture tract of the PFC. The electrocautery dilation catheter is a wire-guided dilation catheter with a distal electrocautery tip. An 8.5-Fr catheter allows for the insertion of two GWs of 0.035 and 0.025-inches (Figure 1).

An Erbotom ICC200 (ERBE Elektromedizin GmbH, Tübingen, Germany) was used for cautery with the Endocut; the effect 3 current was set at an output limit of 120 W, and the forced coagulation current was set at an output limit of 30 W.

For the use of non-electrocautery dilation catheters, an MTW cannula (MTW Endoscopy, Dusseldorf, Germany) and a 6-F-10-Fr Soehendra® Biliary Dilation Catheter (Cook Medical) and/or an 8 mm-diameter balloon Non-Slip Bile Duct Dilation Catheter (Sumitomo Bakelite Co. Ltd., Tokyo, Japan) were used.

As a drainage catheter and stent, a 6-Fr pigtail nasobiliary catheter (Create Medic Co. LTD., Tokyo, Japan) and/or a 7-Fr 4 cm Zimmon® Biliary Stent Set (Cook Medical) or a Double Pigtail Stent delivery system Through Pass (Gadelius Medical K.K., Tokyo, Japan) were used.

Procedure

A convex array echoendoscope was used in all cases

of EUS-TD for the treatment of PFCs. All patients underwent endoscopic procedures under deep sedation with benzodiazepines and/or pentazocine as analgesics. Carbon dioxide inflation was used after May 2011. Antibiotics were initiated on the procedure day and were continued until improvement of the infection.

PFCs were accessed from the stomach or duodenum using a 19-gauge fine needle aspiration needle with EUS guidance. When the needle punctured the PFC, a 0.035-inch GW was inserted through the needle and advanced into the PFC under fluoroscopic guidance.

The puncture tract was dilated over the length of the GW using a 6-Fr and/or an 8.5-Fr electrocautery dilation catheter. After an 8.5-Fr electrocautery dilation catheter was inserted into the PFC over the 0.035-inch GW, another 0.025-inch GW was inserted into the PFC through the catheter lumen under fluoroscopic guidance. After the 0.035-inch and 0.025-inch GWs were inserted into the PFC, a 7-Fr 4 cm double pigtail stent (as an internal drain) and a 6-Fr drainage catheter (as an external drain) were inserted as far as possible.

According to the method for using a non-electrocautery dilation catheter, the puncture tract was dilated using an endoscopic retrograde cholangiopancreatography cannula and biliary dilation catheter with a balloon dilatation catheter over the GW. After another GW was inserted into the PFC through the fistulous tract, a 7-Fr 4 cm double pigtail stent and a 6-Fr drainage catheter were inserted as far as possible.

The external drainage catheter was placed during the first 1 to 2 wk, and the infected PFC was washed with saline. The stent of the internal drain was maintained for 3 to 6 mo and was removed after the resolution of the PFC.

Outcome measurements

The primary endpoints were the technical and clinical successes of using an electrocautery dilation catheter as a fistula dilation device for EUS-TD in the treatment of PFCs.

Technical success was defined as good fistulous dilation and successful internal and/or external drain placement within the PFC.

Clinical success was defined as the resolution of the PFC and/or the improvement of the infected PFCs by the use of only the EUS-TD without the need for additional drainage or necrosectomy.

The secondary endpoints were the procedure time and the safety of EUS-TD for the treatment of PFCs using an electrocautery dilation catheter.

The procedure time was defined as the time from echoendoscopic insertion until the internal and/or external drain placement.

The safety of EUS-TD for the treatment of PFCs was evaluated according to the development of procedure-related adverse events, such as bleeding, perforation, stent migration, and free air in the abdomen.

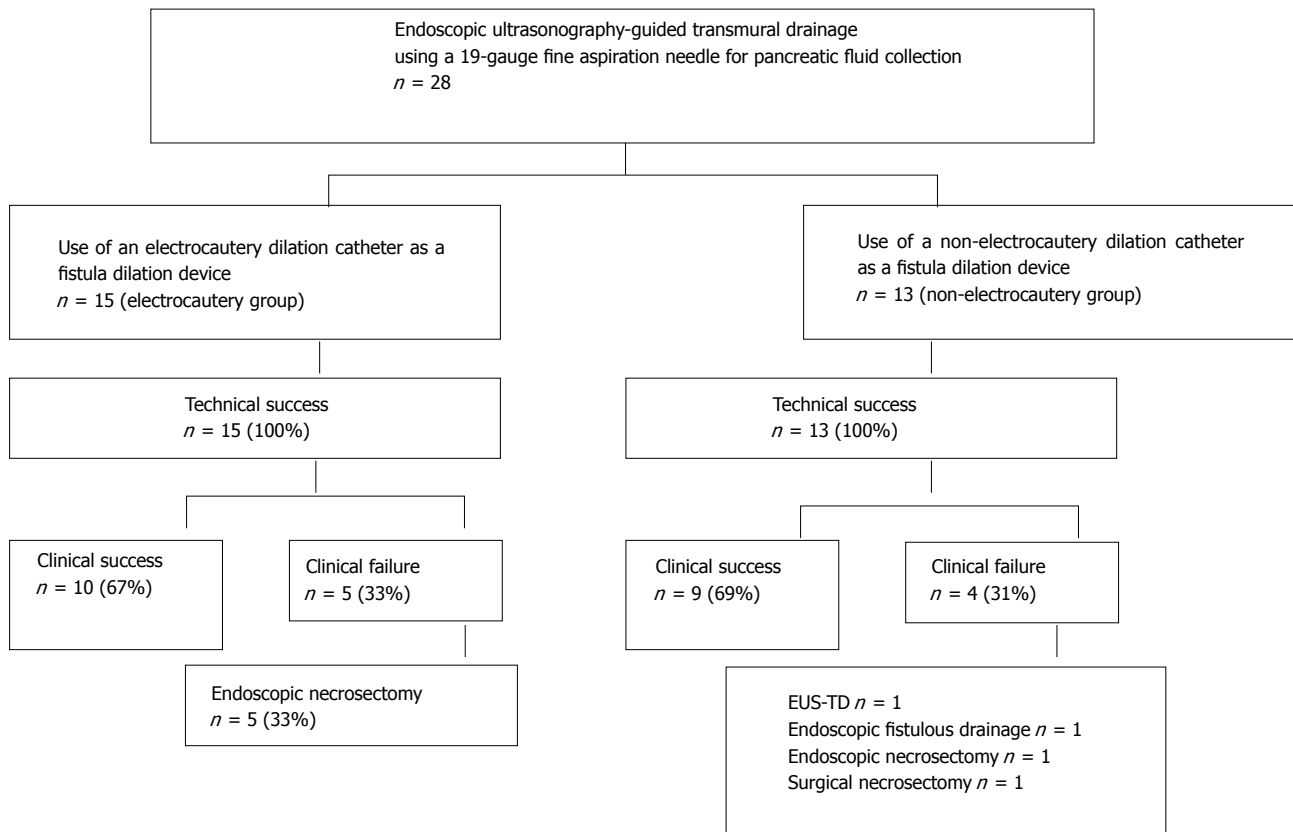


Figure 2 Flow diagram of patient selection and procedural outcomes in this study.

Statistical analysis

Continuous variables are expressed as the mean \pm SD. Statistical analyses were performed using StatMate III software (ATMS Co. Ltd., Tokyo, Japan). Data were analyzed using the Mann-Whitney *U* test and the χ^2 test. Differences of $P < 0.05$ were considered significant.

RESULTS

A total of 28 consecutive patients who underwent EUS-TD for the treatment of symptomatic PFCs by fine needle aspiration using a 19-gauge needle were investigated in this study. After we obtained permission to use an electrocautery dilation catheter at our institution in May 2012, we used the dilation catheter for these patients. Fifteen patients were treated with an electrocautery dilation catheter for the fistulous dilation of PFCs (electrocautery group), and 13 patients were treated with a non-electrocautery dilation catheter (non-electrocautery group) (Figure 2). The mean follow-up period of all patients was 1001 ± 463 d.

Patient characteristics

Patient characteristics are presented in Table 1. There were no statistically significant differences in age, sex, type of PFC based on the revised Atlanta Classification, location and diameter of PFCs between the groups. Thirteen patients (87%) in the electrocautery group and 10 patients (77%) in the non-electrocautery group

presented with infected PFCs (Table 1).

Technical and clinical success

The technical success rates of EUS-TD for the treatment of PFCs were 100% and 100% for the electrocautery and non-electrocautery groups, respectively. Transgastric puncture was carried out in 14 patients (93%) in the electrocautery group and in 13 patients (100%) in the non-electrocautery group ($P = 0.942$). Internal and external drain placements for PFCs were performed on 14 patients (93%) in the electrocautery group and on 11 patients (85%) in the non-electrocautery group ($P = 0.896$).

The clinical success rates of EUS-TD for the treatment of PFCs without the need for additional transmural drainage or necrosectomy were 67% (10/15) and 69% (9/13) for the electrocautery and non-electrocautery groups, respectively ($P = 0.794$).

In the non-electrocautery group, 1 patient required additional EUS-TD for the treatment of a pancreatic pseudocyst that showed exacerbation of infection due to the dislocation of the external drain, and 1 patient required additional endoscopic internal drainage through the fistula for WON that showed exacerbation of infection after external drain withdrawal.

In the electrocautery group, 5 patients required endoscopic necrosectomy for infections associated with WON and ANC due to the lack of efficacy of EUS-TD. In the non-electrocautery group, 1 patient required

Table 1 Baseline characteristics of the patients in the electrocautery and non-electrocautery groups

	Electrocautery group (n = 15)	Non-electrocautery group (n = 13)	P value
Age: mean \pm SD, yr	60 \pm 14	64 \pm 14	0.489 ¹
Sex: male/female, n	12/3	11/2	0.860 ²
Type of PFC, n (%)			0.615 ²
WON	4 (27)	6 (46)	
Pancreatic pseudocyst	6 (40)	4 (31)	
ANC	4 (27)	3 (23)	
APFC	1 (6)	0	
Location of PFC, n (%)			0.976 ²
Head	3 (20)	3 (23)	
Body-tail	11 (73)	9 (69)	
Head-body-tail	1 (7)	1 (8)	
Diameter of PFC, mean \pm SD, cm	7.2 \pm 3.1	9.9 \pm 3.7	0.061 ¹
Infected PFC, n (%)	13 (87)	10 (77)	0.860 ²

¹Mann-Whitney *U* test; ² χ^2 test. PFC: Pancreatic and peripancreatic fluid collection; WON: Walled-off necrosis; ANC: Acute necrotic collection; APFC: Acute peripancreatic fluid collection.

endoscopic necrosectomy, and 1 patient underwent surgical necrosectomy for uncontrolled infected WON (Figure 2 and Table 2).

EUS-TD procedure time

The procedure time for EUS-TD in the electrocautery group was significantly shorter than that of the non-electrocautery group (30 \pm 12 min vs 52 \pm 20 min, $P < 0.001$) (Table 2).

Adverse events

No adverse events occurred during the EUS-TD procedure in the electrocautery group. One patient in the non-electrocautery group presented with free air in the abdomen during the procedure but was relieved conservatively. There were no procedure-related deaths in either of the groups (Table 2).

DISCUSSION

Endoscopic drainage has recently replaced percutaneous or surgical drainage as the initial approach for the treatment of PFCs. Percutaneous drainage of PFCs allows for improved drainage by using a drainage tube with a larger diameter. A single-center, retrospective study reported that endoscopic drainage has a similar clinical success rate, fewer required re-interventions, a shorter hospital stay, and a decreased number of follow-up abdominal imaging studies for symptomatic pancreatic pseudocysts compared with percutaneous drainage^[2]. In a randomized trial for pancreatic pseudocyst drainage comparing endoscopic and surgical cystogastrostomy, endoscopic drainage was associated with shorter hospital stays, better physical and mental health of the patients, and lower costs^[3].

Recently, EUS-TD has been widely accepted as a

minimally invasive procedure that allows the safe puncture of PFCs using a visualized approach. In a prospective randomized trial comparing EUS-TD and conventional endoscopic drainage for pancreatic pseudocysts, the technical success associated with EUS-TD was significantly greater than that of conventional endoscopic drainage, from which the authors concluded that EUS should be considered the first-line treatment modality for pancreatic pseudocysts^[7].

A non-electrocautery dilation catheter has been used conventionally as a device for fistulous dilation for PFCs. However, sufficient dilation of the fistula site can be difficult using only a non-electrocautery dilation catheter. As a result, it may prove impossible to insert a drain catheter or a plastic stent into the cavities of PFCs using this method.

As an alternative to the non-electrocautery method, Azar *et al*^[9] reported that 21 of 23 patients with PFCs underwent technically successful wire-guided pancreatic pseudocyst drainage using a modified needle knife. Additionally, Ahlawat *et al*^[10] reported that 9 of 11 total PFC patients successfully underwent EUS-guided pseudocyst drainage using a single-step approach involving a cystotome to electrically enlarge the fistula site. However, misdirected PFC punctures may occur when using only a cystotome, as it is difficult to visualize the tip of an electrocautery catheter with EUS guidance. Our data show that the expansion of the puncture tract using dilator catheters after having punctured a PFC using a 19-gauge fine needle aspiration needle with EUS guidance is a safe and effective alternative procedure. An additional advantage of using a wire-guided electrocautery dilation catheter for EUS-TD in the treatment of PFCs is that we can penetrate the puncture tract without excessive resistance, which increases the efficiency of the procedure.

Prior to our study, few studies have compared the clinical effects of electrocautery and non-electrocautery dilation catheters as fistula dilation devices for EUS-guided transmural PFC drainage. Therefore, we retrospectively investigated the clinical outcomes and adverse events associated with the use of electrocautery and non-electrocautery dilation catheters for EUS-TD in the treatment of PFCs.

The technical success rate of EUS-TD for the treatment of symptomatic PFCs was 100% for the electrocautery and non-electrocautery groups. Moreover, the procedure time for EUS-TD in the electrocautery group was significantly shorter than that of the non-electrocautery group (30 \pm 12 min vs 52 \pm 20 min, $P < 0.001$). Median procedure times of EUS-TD using plastic stents for PFCs have been reported as 29.5 min (interquartile range: 23.5–42 min)^[11] and 42.6 \pm 14.2 min^[12].

We used a 6-Fr and/or an 8.5-Fr wire-guided electrocautery dilation catheter under fluoroscopic guidance to dilate the puncture tract of PFCs. An 8.5-Fr electrocautery dilation catheter offers the advantage of accommodating the insertion of a 0.035-inch and a 0.025-inch GW, and

Table 2 Procedural outcomes of the patients in the electrocautery and non-electrocautery groups

	Electrocautery group (<i>n</i> = 15)	Non-electrocautery group (<i>n</i> = 13)	<i>P</i> value
Technical success, <i>n</i> (%)	15 (100)	13 (100)	
Puncture tract, <i>n</i> (%)			0.942 ¹
Transgastric	14 (93)	13 (100)	
Transduodenal	1 (7)	0	
Drainage method, <i>n</i> (%)			0.896 ¹
Internal and external drainage	14 (93)	11 (85)	
External drainage	1 (7)	2 (15)	
Clinical success, <i>n</i> (%)	10 (67)	9 (69)	0.794 ¹
Procedure time, mean ± SD, min	30 ± 12	52 ± 20	< 0.001 ²
Adverse events, <i>n</i>			0.942 ¹
Free air	0	1	
Procedure-related death	0	0	
Additional procedure, <i>n</i>			0.794 ¹
EUS-TD	0	1	
Endoscopic fistulous drainage	0	1	
Endoscopic necrosectomy	5	1	
Surgical necrosectomy	0	1	

¹ χ^2 test; ²Mann-Whitney *U* test. EUS-TD: Endoscopic ultrasonography-guided transmural drainage.

the placement of internal and external drain catheters is possible at the same time.

The procedure time of EUS-TD for PFCs using an electrocautery dilation catheter was shorter than that of a non-electrocautery dilation catheter in part because we could easily create a large fistulous tract without changing devices, which allowed for the quick insertion of a drain catheter and a plastic stent into the PFC by simultaneously inserting two GWs through the catheter into the cavity.

Seewald *et al.*^[13] also reported that eight out of eight patients were successfully treated without complications using a one-step, simultaneous double-wire technique for the treatment of pancreatic pseudocysts and abscess drainage; the mean procedural time was 32.5 min (range 25–45 min).

The main adverse events for EUS-TD are bleeding and perforation. In this study, the use of an electrocautery dilation catheter resulted in no adverse events.

We hypothesized that using a wire-guided electrocautery dilation catheter under EUS and fluoroscopic guidance would allow us to safely expand the puncture tract.

The clinical success rates of EUS-TD for the treatment of PFCs without the need for additional treatments were 67% (10/15) in the electrocautery group and 69% (9/13) in the non-electrocautery groups, and there was no significant difference between the groups (*P* = 0.794).

The clinical success rate of EUS-guided or conventional transmural drainage for PFCs is related to the PFC type. In terms of clinical success rates of EUS-guided or conventional endoscopic transmural PFC drainage, the success rates for pancreatic pseudocysts are between 86% and 100%^[7,14–18], whereas the success rate for WON with necrosis is between 25% and 72%^[15,19–21]. A possible reason for the discrepancies in these results is that the

drainage effects of EUS-TD treatment of WON is poor due to the inclusion of necrotic material, which increases the risk of catheter and plastic stent occlusion. Because a plastic stent can be easily occluded by necrotic material, a novel, fully covered and self-expandable metal stent has become available to create a large fistulous site and reduce stent occlusion^[22,23]. More recently, Rinninella *et al.*^[24] reported that EUS-TD for the treatment of PFCs using a lumen-apposing metal stent on an electrocautery-enhanced delivery system is a safe, effective, and minimally invasive treatment.

In our study, clinical failure of EUS-TD for the treatment of PFCs occurred in 6 patients with WON, 2 patients with ANC, and 1 patient with a pancreatic pseudocyst. The clinical success rate of EUS-TD was 91% (10/11) for patients with pancreatic pseudocysts and APFC and 53% (9/17) for patients with WON and ANC. Approximately 50% of patients who experienced poor outcomes from EUS-TD treatment for WON and ANC, which include necrotic material, required additional treatment in our study.

Recently, endoscopic transmural necrosectomy has been accepted as a step-up approach in patients with infected necrotizing pancreatitis, in whom EUS-TD treatment is insufficient^[25]. In this report, the authors declared that an endoscopic step-up approach reduces mortality, major complications, hospital stay and related costs compared with a surgical step-up approach in patients with infected necrotizing pancreatitis.

A limitation of this study is the single-center, small, and exploratory retrospective nature of the study. The difference in procedure time may be related to increased experience of the clinicians with the procedure. Multi-center, randomized, controlled trials are needed to confirm our findings.

In conclusion, EUS-TD using an electrocautery dilation

catheter as a fistula dilation device for the treatment of PFCs appears to be safe and contributes to shorter procedure times.

ACKNOWLEDGMENTS

We express our deepest appreciation to Professor Kenichi Matsui and Professor Eiji Uchida, Office for Promoting Medical Research Showa University, for the statistical review of descriptions of study design.

COMMENTS

Background

Endoscopic ultrasonography-guided transmural drainage (EUS-TD) has been widely accepted as a minimally invasive procedure for pancreatic and peripancreatic fluid collections (PFCs). However, EUS-TD for the treatment of PFCs may cause adverse events, such as bleeding and perforation; thus, the establishment of a safe procedure for EUS-TD is necessary. Few articles have investigated the clinical outcomes associated with the use of an electrocautery dilation catheter as a fistula dilation method for EUS-TD in the treatment of PFCs. The aim of this study was to evaluate the safety and efficacy of an electrocautery dilation catheter as a fistula dilation device for EUS-TD in the treatment of PFCs by fine needle aspiration using a 19-gauge needle.

Research frontiers

Electrocautery or non-electrocautery dilation catheters are used as fistula dilation devices for EUS-TD in the treatment of PFCs; however, prior to this study, few studies have investigated the safety and efficacy of an electrocautery dilation catheter in this procedure.

Innovations and breakthroughs

The authors retrospectively compared the clinical outcomes between electrocautery and non-electrocautery dilation catheters for EUS-TD in the treatment of symptomatic PFCs. The results show that EUS-TD using an electrocautery dilation catheter as a fistula dilation device appears to be safe and contributes to shorter procedure times.

Applications

The results of this exploratory retrospective study suggest that EUS-TD for the treatment of PFCs using an electrocautery dilation catheter as a fistula dilation device appears to be safe and contributes to shorter procedure times. However, multi-center, randomized, controlled trials are needed to confirm these findings.

Terminology

An electrocautery dilation catheter was used to dilate the puncture tract of PFCs. This device is a wire-guided dilation catheter with a distal electrocautery tip. An 8.5-Fr electrocautery dilation catheter allows the simultaneous insertion of 0.035-inch and 0.025-inch guide wires, and the placement of internal and external drain catheters is possible at the same time.

Peer-review

This manuscript is generally well written. The data are of interest, although it is a rather specialized topic.

REFERENCES

- 1 Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]
- 2 Akshintala VS, Saxena P, Zaheer A, Rana U, Hutfless SM, Lennon AM, Canto MI, Kalloo AN, Khashab MA, Singh VK. A comparative evaluation of outcomes of endoscopic versus percutaneous drainage for symptomatic pancreatic pseudocysts. *Gastrointest Endosc* 2014; **79**: 921-928; quiz 983.e2, 983.e5 [PMID: 24315454 DOI: 10.1016/j.gie.2013.10.032]
- 3 Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583-590.e1 [PMID: 23732774 DOI: 10.1053/j.gastro.2013.05.046]
- 4 Giovannini M, Bernardini D, Seitz JF. Cystogastrostomy entirely performed under endosonography guidance for pancreatic pseudocyst: results in six patients. *Gastrointest Endosc* 1998; **48**: 200-203 [PMID: 9717789 DOI: 10.1016/S0016-5107(98)70165-8]
- 5 Seifert H, Dietrich C, Schmitt T, Caspary W, Wehrmann T. Endoscopic ultrasound-guided one-step transmural drainage of cystic abdominal lesions with a large-channel echo endoscope. *Endoscopy* 2000; **32**: 255-259 [PMID: 10718392 DOI: 10.1055/s-2000-93]
- 6 Braden B, Dietrich CF. Endoscopic ultrasonography-guided endoscopic treatment of pancreatic pseudocysts and walled-off necrosis: new technical developments. *World J Gastroenterol* 2014; **20**: 16191-16196 [PMID: 25473173 DOI: 10.3748/wjg.v20.i43.16191]
- 7 Varadarajulu S, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111 [PMID: 18640677 DOI: 10.1016/j.gie.2008.04.028]
- 8 Binmoeller KF, Weilert F, Shah JN, Bhat YM, Kane S. Endosonography-guided transmural drainage of pancreatic pseudocysts using an exchange-free access device: initial clinical experience. *Surg Endosc* 2013; **27**: 1835-1839 [PMID: 23299130 DOI: 10.1007/s00464-012-2682-9]
- 9 Azar RR, Oh YS, Janec EM, Early DS, Jonnalagadda SS, Edmundowicz SA. Wire-guided pancreatic pseudocyst drainage by using a modified needle knife and therapeutic echoendoscope. *Gastrointest Endosc* 2006; **63**: 688-692 [PMID: 16564874 DOI: 10.1016/j.gie.2005.10.032]
- 10 Ahlawat SK, Charabaty-Pishvaian A, Jackson PG, Haddad NG. Single-step EUS-guided pancreatic pseudocyst drainage using a large channel linear array echoendoscope and cystotome: results in 11 patients. *JOP* 2006; **7**: 616-624 [PMID: 17095841 DOI: 10.1055/s-2006-947743]
- 11 Lee BU, Song TJ, Lee SS, Park do H, Seo DW, Lee SK, Kim MH. Newly designed, fully covered metal stents for endoscopic ultrasound (EUS)-guided transmural drainage of peripancreatic fluid collections: a prospective randomized study. *Endoscopy* 2014; **46**: 1078-1084 [PMID: 25412095 DOI: 10.1055/s-0034-1390871]
- 12 Mukai S, Itoi T, Baron TH, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Tanaka R, Umeda J, Tonzuka R, Honjo M, Gotoda T, Moriyasu F, Yasuda I. Endoscopic ultrasound-guided placement of plastic vs. biflanged metal stents for therapy of walled-off necrosis: a retrospective single-center series. *Endoscopy* 2015; **47**: 47-55 [PMID: 25264765 DOI: 10.1055/s-0034-1377966]
- 13 Seewald S, Thonke F, Ang TL, Omar S, Seitz U, Groth S, Zhong Y, Yekebas E, Izbicki J, Soehendra N. One-step, simultaneous double-wire technique facilitates pancreatic pseudocyst and abscess drainage (with videos). *Gastrointest Endosc* 2006; **64**: 805-808 [PMID: 17055880 DOI: 10.1016/j.gie.2006.07.049]
- 14 Kahaleh M, Shami VM, Conaway MR, Tokar J, Rockoff T, De La Rue SA, de Lange E, Bassignani M, Gay S, Adams RB, Yeaton P. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. *Endoscopy* 2006; **38**: 355-359 [PMID: 16680634 DOI: 10.1055/s-2006-925249]
- 15 Hookey LC, Debroux S, Delhay M, Arvanitakis M, Le Moine O, Devière J. Endoscopic drainage of pancreatic-fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes. *Gastrointest Endosc* 2006; **63**: 635-643 [PMID: 17055880 DOI: 10.1016/j.gie.2006.07.049]

- 16564865 DOI: 10.1016/j.gie.2005.06.028]
- 16 **Weckman L**, Kylänpää ML, Puolakkainen P, Halttunen J. Endoscopic treatment of pancreatic pseudocysts. *Surg Endosc* 2006; **20**: 603-607 [PMID: 16424988 DOI: 10.1007/s00464-005-0201-y]
- 17 **Lopes CV**, Pesenti C, Bories E, Caillol F, Giovannini M. Endoscopic ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts. *Arq Gastroenterol* 2008; **45**: 17-21 [PMID: 18425223 DOI: 10.1590/S0004-28032008000100004]
- 18 **Giovannini M**, Pesenti C, Rolland AL, Moutardier V, Delperio JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. *Endoscopy* 2001; **33**: 473-477 [PMID: 11437038 DOI: 10.1055/s-2001-14967]
- 19 **Baron TH**, Harewood GC, Morgan DE, Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc* 2002; **56**: 7-17 [PMID: 12085029 DOI: 10.1067/mge.2002.125106]
- 20 **Gardner TB**, Chahal P, Papachristou GI, Vege SS, Petersen BT, Gostout CJ, Topazian MD, Takahashi N, Sarr MG, Baron TH. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. *Gastrointest Endosc* 2009; **69**: 1085-1094 [PMID: 19243764 DOI: 10.1016/j.gie.2008.06.061]
- 21 **Varadarajulu S**, Bang JY, Phadnis MA, Christein JD, Wilcox CM. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of treatment success in 211 consecutive patients. *J Gastrointest Surg* 2011; **15**: 2080-2088 [PMID: 21786063 DOI: 10.1007/s11605-011-1621-8]
- 22 **Itoi T**, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). *Gastrointest Endosc* 2012; **75**: 870-876 [PMID: 22301347 DOI: 10.1016/j.gie.2011.10.020]
- 23 **Yamamoto N**, Isayama H, Kawakami H, Sasahira N, Hamada T, Ito Y, Takahara N, Uchino R, Miyabayashi K, Mizuno S, Kogure H, Sasaki T, Nakai Y, Kuwatani M, Hirano K, Tada M, Koike K. Preliminary report on a new, fully covered, metal stent designed for the treatment of pancreatic fluid collections. *Gastrointest Endosc* 2013; **77**: 809-814 [PMID: 23453183 DOI: 10.1016/j.gie.2013.01.009]
- 24 **Rinninella E**, Kunda R, Dollhopf M, Sanchez-Yague A, Will U, Tarantino I, Gornals Soler J, Ullrich S, Meining A, Esteban JM, Enz T, Vanbiervliet G, Vleggaar F, Attili F, Larghi A. EUS-guided drainage of pancreatic fluid collections using a novel lumen-apposing metal stent on an electrocautery-enhanced delivery system: a large retrospective study (with video). *Gastrointest Endosc* 2015; **82**: 1039-1046 [PMID: 26014960 DOI: 10.1016/j.gie.2015.04.006]
- 25 **van Brunschot S**, van Grinsven J, Voermans RP, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, Cappendijk VC, Consten EC, Dejong CH, Dijkgraaf MG, van Eijck CH, Erkelens GW, van Goor H, Hadithi M, Haveman JW, Hofker SH, Jansen JJ, Laméris JS, van Lienden KP, Manusama ER, Meijssen MA, Mulder CJ, Nieuwenhuis VB, Poley JW, de Ridder RJ, Rosman C, Schaapherder AF, Scheepers JJ, Schoon EJ, Seerden T, Spanier BW, Straathof JW, Timmer R, Venneman NG, Vleggaar FP, Witteman BJ, Gooszen HG, van Santvoort HC, Fockens P. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. *BMC Gastroenterol* 2013; **13**: 161 [PMID: 24274589 DOI: 10.1186/1471-230X-13-161]

P- Reviewer: Chow WK, Ding XW, Kayaalp C, Kleeff J
S- Editor: Kong JX **L- Editor:** A **E- Editor:** Lu YJ



Retrospective Study

Efficacy and safety of endoscopic submucosal dissection under general anesthesia

Kanefumi Yamashita, Hironari Shiwaku, Toshihiro Ohmiya, Hideki Shimaoka, Hiroki Okada, Ryo Nakashima, Richiko Beppu, Daisuke Kato, Takamitsu Sasaki, Seiichiro Hoshino, Satoshi Nimura, Ken Yamaura, Yuichi Yamashita

Kanefumi Yamashita, Hironari Shiwaku, Toshihiro Ohmiya, Hideki Shimaoka, Hiroki Okada, Ryo Nakashima, Richiko Beppu, Daisuke Kato, Takamitsu Sasaki, Seiichiro Hoshino, Yuichi Yamashita, Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Fukuoka 814-0180, Japan

Satoshi Nimura, Department of Pathology, Fukuoka University Faculty of Medicine, Fukuoka 814-0180, Japan

Ken Yamaura, Department of Anesthesiology, Fukuoka University Faculty of Medicine, Fukuoka 814-0180, Japan

Author contributions: Yamashita K and Shiwaku H equally contributed to this work; Yamashita K collected and analyzed the data and drafted the manuscript; Shiwaku H provided analytical oversight; Sasaki T designed and supervised the study; Nimura S, Yamaura K and Yamashita Y revised the manuscript for important intellectual content; Nimura S, Yamaura K and Yamashita Y offered the technical or material support; Ohmiya T, Shimaoka H, Okada H, Nakashima R, Beppu R, Kato D, Sasaki T and Hoshino S provided administrative support; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Fukuoka University Faculty of Medicine.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license,

which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Hironari Shiwaku, MD, Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Nanakuma 7-45-1, Jonan-ku, Fukuoka 814-0180, Japan. hiro.shiwaku@gmail.com
Telephone: +81-92-8011011
Fax: +81-92-8639759

Received: February 14, 2016

Peer-review started: February 15, 2016

First decision: March 23, 2016

Revised: April 21, 2016

Accepted: May 17, 2016

Article in press: May 27, 2016

Published online: July 10, 2016

Abstract

AIM: To evaluate the efficacy and safety of endoscopic submucosal dissection (ESD) under general anesthesia.

METHODS: From January 2011 to July 2014, 206 consecutive patients had undergone ESD under general anesthesia for neoplasms of the stomach, esophagus, and colorectum were enrolled in this retrospective study. The efficacy and safety of ESD under general anesthesia were assessed.

RESULTS: The *en bloc* resection rate of esophageal, gastric, and colorectal lesions was 100.0%, 98.3%, and 96.1%, respectively. The complication rate of perforation

and bleeding were 0.0% and 0.0% in esophageal ESD, 1.7% and 1.7% in gastric ESD, and 3.9% and 2.0% in colorectal ESD, respectively. No cases of aspiration pneumonia were observed. All complications were managed by conservative treatment, with no surgical intervention required.

CONCLUSION: With the cooperation of an anesthesiologist, ESD under general anesthesia appears to be a useful method, decreasing the risk of complications.

Key words: Complication; Endoscopic submucosal dissection; General anesthesia; Conscious sedation

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Studies regarding endoscopic submucosal dissection (ESD) under general anesthesia in Japan are scarce because ESD is generally performed under conscious sedation. ESD requires minimal patient movement for optimal visualization, which may be hampered because of insufficient sedation. Thus, this retrospective study aimed to evaluate the efficacy and safety of ESD under general anesthesia in 206 consecutive patients. The complication rate was lower in our study than in previous studies. Moreover, no cases of aspiration pneumonia were observed. ESD under general anesthesia appears to be a useful method for reducing the risk of complications.

Yamashita K, Shiwa H, Ohmiya T, Shimaoka H, Okada H, Nakashima R, Beppu R, Kato D, Sasaki T, Hoshino S, Nimura S, Yamaura K, Yamashita Y. Efficacy and safety of endoscopic submucosal dissection under general anesthesia. *World J Gastrointest Endosc* 2016; 8(13): 466-471 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i13/466.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i13.466>

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a well-established treatment for early-stage malignant lesions of the stomach, esophagus, and colorectum with no risk of lymphatic metastasis^[1-4]. ESD requires precise and complicated maneuvers. Minimal patient movement for maintaining good visualization is important for a successful procedure, and intraoperative management of the patient's general condition is very important for achieving safe ESD. In Japan, ESD is usually performed under conscious sedation in the endoscopy room. However, some issues are associated with this procedure, including patient movement because of insufficient effect of sedation and a risk of aspiration pneumonia. Any patient movement during the procedure can result in complications such as perforation and hemorrhage because of impaired visual control. Aspiration pneumonia can induce respiratory failure. Therefore, we perform ESD under general anesthesia with

mechanical ventilation. In this study, we retrospectively investigated the efficacy and safety of ESD under general anesthesia.

MATERIALS AND METHODS

Indications for endoscopic submucosal dissection under general anesthesia at our institution

ESD under general anesthesia is performed in cases in which the predicted procedure time is > 120 min, an insufficient effect of conscious sedation (such as that in heavy drinkers) was observed, or strict anesthetic management is required (such as that in high-risk cases affected by comorbidities).

Patients

We retrospectively enrolled consecutive 206 patients who had undergone ESD under general anesthesia for neoplasms of the stomach, esophagus, and colorectum in accordance with our indications, except for two patients who rejected the treatment for neoplasms because of their old age, at the Fukuoka University Faculty of Medicine, Department of Gastroenterological Surgery between January 2011 and July 2014. Information collected from medical records included clinical and operative data.

General anesthesia

ESD was performed under general anesthesia with endotracheal intubation by the anesthesiologist in the operation room. General anesthesia was induced with rocuronium and propofol and was maintained with propofol or sevoflurane, remifentanyl, and intermittent rocuronium administration during the procedure. After endotracheal intubation, patients were placed in the left lateral position in cases of esophageal or gastric lesions or in the supine position in cases of colorectal lesions.

Endoscopic equipment

Esophageal and gastric lesion: A gastroscope (GIF H260Z; Olympus, Tokyo, Japan) was used for marking the lesion. The lesion's circumference was marked using argon plasma coagulation (APC). ESD was conducted using a gastroscope (GIF Q260J; Olympus, Tokyo, Japan) with a distal attachment cap (DH-28GR; Fujifilm, Tokyo, Japan). Submucosal injections were performed using a 25-G needle (3 mm; Impact Flow, Top Corporation, Tokyo, Japan) for esophageal lesions, and a 25-G needle (4 mm; Impact Flow, Top Corporation) for gastric lesions. Incision and dissection were performed using two types of Flush Knife BT (2.0 and 2.5 mm, respectively, DK2618JB, Fujifilm Medical, Tokyo, Japan). An electrosurgical generator (VIO 300D; ERBE, Tübingen, Germany) was used for all ESD procedures. All visible vessels were coagulated with hemostatic forceps (Coagrasper; FD-410LR, Olympus).

Colorectal lesions: The endoscope used was a colonoscope (PCF-Q260AZI; Olympus, Tokyo, Japan) with a distal attachment cap (DH-29GR; Fujifilm, Tokyo, Japan) for

Table 1 Baseline clinical and operational characteristics of patients undergoing esophageal endoscopic submucosal dissection

Age, (yr) ¹	69.7 ± 10.0
Sex, <i>n</i> (%)	
Male	41 (89.1)
Female	5 (10.9)
Preoperative co-morbidities, <i>n</i> (%)	39 (84.8)
ASA score, <i>n</i> (%)	
I	8 (17.4)
II	37 (80.4)
III	1 (2.2)
Histologic type, <i>n</i> (%)	
Squamous cell carcinoma	53 (91.4)
Leiomyoma	2 (3.4)
Others	3 (5.2)
Mean diameter of resected specimen, (mm) ¹	32.9 ± 12.1
<i>en bloc</i> resection rate, <i>n</i> (%)	58 (100)
Duration of anesthesia, (min) ¹	233.6 ± 95.0
Duration of operation, (min) ¹	164.5 ± 95.1
Postoperative hospital stay (d) ¹	8.3 ± 2.3
Complication rate, <i>n</i> (%)	0 (0.0)
Intraoperative bleeding	0 (0.0)
Delayed bleeding	0 (0.0)
Intraoperative perforation	0 (0.0)

¹Mean ± SD. ASA: American Society of Anesthesiologists score.

marking of the lesion and ESD. The lesion's circumference was marked using APC. Submucosal injections were performed using a 25-G needle (3 mm, Impact Flow, Top Corporation, Japan). Incision and dissection were performed with a Flush Knife BT (1.5 mm, DK2618JB, Fujifilm Medical, Tokyo, Japan). An electrosurgical generator (VIO 300D; ERBE, Tübingen, Germany) was used for all ESD procedures. All visible vessels were coagulated with hemostatic forceps (Coagrasper; FD-411UR, Olympus).

All ESD procedures were performed with carbon dioxide insufflation.

Ethical considerations

The study was reviewed and approved by the Ethics Committee of the Fukuoka University Faculty of Medicine.

RESULTS

Esophageal ESD under general anesthesia

We performed esophageal ESD under general anesthesia for 58 esophageal neoplasms in 46 patients. The baseline clinical and operative characteristics of the patients are summarized in Table 1. The male:female ratio was 41:5 (89.1%/10.9%) and the mean age of the patients was 69.7 ± 10.0 years (range, 26-82 years). The number of patients who had preoperative comorbidities was 39 (84.8%). The diameter of the resected specimen was 32.9 ± 12.1 mm (range, 10-70 mm). The *en bloc* resection rate was 100.0%. The mean operating time was 164.5 ± 95.1 min (range, 40-468 min). The mean anesthesia time was 233.6 ± 95.0 min (range, 105-545 min). With regard to complications, no cases of perforation or bleeding were observed, and there was no

Table 2 Baseline clinical and operational characteristics of patients undergoing gastric endoscopic submucosal dissection

Age, (yr) ¹	70.4 ± 10.2
Sex, <i>n</i> (%)	
Male	79 (71.2)
Female	32 (28.8)
Preoperative co-morbidities, <i>n</i> (%)	91 (75.2)
ASA score, <i>n</i> (%)	
I	20 (18.0)
II	88 (79.3)
III	3 (2.7)
Histologic type, <i>n</i> (%)	
Differentiated type adenocarcinoma	102 (84.3)
Undifferentiated type adenocarcinoma	8 (6.6)
Others	10 (8.3)
Mean diameter of resected specimen (mm) ¹	39.5 ± 13.9
<i>en bloc</i> resection rate, <i>n</i> (%)	119 (98.3)
Duration of anesthesia, (min) ¹	254.5 ± 95.4
Duration of operation, (min) ¹	188.4 ± 91.7
Postoperative hospital stay (d) ¹	7.5 ± 2.0
Complication rate, <i>n</i> (%)	4 (3.3)
Intraoperative bleeding	1 (0.8)
Delayed bleeding	1 (0.8)
Intraoperative perforation	2 (1.7)

¹Mean ± SD. ASA: American Society of Anesthesiologists score.

perioperative mortality (Table 1).

Gastric ESD under general anesthesia

We performed gastric ESD under general anesthesia for 121 gastric neoplasms from 111 patients. The baseline clinical and operative characteristics of the patients are summarized in Table 2. The male:female ratio was 79:32 (71.2%/28.8%) and the patients' mean age was 70.4 ± 10.2 years (range, 44-89 years). The number of patients who had preoperative comorbidities was 91 (75.2%). The diameter of the resected specimen was 39.5 ± 13.9 mm (range, 10-80 mm). The *en bloc* resection rate was 98.3%. The mean operating time was 188.4 ± 91.7 min (range, 50-615 min), and the mean anesthesia time was 254.5 ± 95.4 min (range, 110-680 min). With regard to complications, intraoperative bleeding occurred in 1 (0.8%) patient, delayed bleeding occurred in 1 (0.8%) patient, and intraoperative perforation occurred in 2 (1.7%) patients (Table 2). In all cases of intraoperative perforation, we were able to close the hole using endoclips. All complications were managed using conservative treatment, with no surgical intervention required. No perioperative mortality was observed.

Colorectal ESD under general anesthesia

We performed colorectal ESD under general anesthesia for 51 colorectal neoplasms from 49 patients. Baseline clinical and operative characteristics of the patients are summarized in Table 3. The male:female ratio was 22:27 (44.9%/55.1%), and patient mean age was 66.7 ± 9.6 years (range, 42-87 years). The number of patients who had preoperative comorbidities was 32 (65.3%). The diameter of the resected specimen was 36.5 ± 11.3

Table 3 Baseline clinical and operational characteristics of patients undergoing colorectal endoscopic submucosal dissection

Age, (yr) ¹	66.7 ± 9.6
Sex, n (%)	
Male	22 (44.9)
Female	27 (55.1)
Preoperative comorbidities, n (%)	32 (65.3)
ASA score, n (%)	
I	14 (28.6)
II	34 (69.4)
III	1 (2.0)
Histologic type, n (%)	
Adenocarcinoma	18 (35.3)
Adenoma	29 (56.9)
Carcinoid	3 (5.9)
Mean diameter of the resected specimen (mm) ¹	36.5 ± 11.3
<i>en bloc</i> resection rate, n (%)	49 (96.1)
Duration of anesthesia, (min) ¹	262.1 ± 93.0
Duration of operation, (min) ¹	199.4 ± 82.2
Postoperative hospital stay (d) ¹	7.4 ± 1.7
Complication rate, n (%)	3 (5.9)
Intraoperative bleeding	0 (0.0)
Delayed bleeding	1 (2.0)
Intraoperative perforation	2 (3.9)

¹Mean ± SD. ASA: American Society of Anesthesiologists score.

mm (range, 10–85 mm). The *en bloc* resection rate was 96.1%. The mean operating time was 199.4 ± 82.2 min (range, 68–465 min), and the mean anesthesia time was 262.1 ± 93.0 min (range, 130–630 min). With regard to complications, delayed bleeding occurred in 1 (2.0%) patient, and intraoperative perforation occurred in 2 (3.9%) patients (Table 3). Furthermore, in all cases of intraoperative perforation, we were able close the hole using endoclips. All complications were successfully managed using conservative treatment, with no surgical intervention required. No perioperative fatalities were observed.

DISCUSSION

In Japan, ESD is usually performed under conscious sedation in the endoscopy room. Therefore, reports regarding ESD under general anesthesia in Japan are scarce^[5,6].

ESD requires precise and complicated maneuvers with minimal patient movement for maintaining optimal visualization. However, such precise and complicated maneuvers are sometimes difficult to perform because of patient movement because of an insufficient effect of sedation. Benzodiazepines, such as diazepam and midazolam, have been used as standard sedation in patients undergoing endoscopic therapy. However, the range of effective doses of such agents considerably differs among patients; therefore, it is difficult to achieve a stable level of sedation^[7]. Moreover, the dose is often increased to suppress body movement, resulting in oversedation and potentially causing hypoxemia and decreased levels of consciousness upon the patient's return to the hospital ward^[8]. Recently, the usefulness of propofol anesthesia for

therapeutic endoscopy was reported^[7,9]; however, the safe use of propofol is limited.

The advantages of ESD under general anesthesia include optimal visualization in the absence of patient movement; the operator can concentrate on ESD maneuvers without having to attend to anesthetic management because of the assistance of an anesthesiologist; if complications, such as intraoperative perforation and bleeding occur, we can manage this with optimal visualization; there is no risk of aspiration pneumonia during the ESD procedure; and the supervisor can teach beginners without having to care regarding the patient's consciousness.

The reported rate of perforation and bleeding of ESD is 5.0% and 2.1% in esophageal ESD^[10], 0.3%–5.0% and 3.4%–5.8% in gastric ESD^[11–14], and 1.4%–10.4% and 0.0%–12.0% in colorectal ESD^[15–18], respectively.

However, the complication rate of perforation and bleeding in ESD under general anesthesia in our institution was 0.0% and 0.0% in esophageal ESD, 1.7% and 1.7% in gastric ESD, and 3.9% and 2.0% in colorectal ESD, respectively. Although half of ESDs were performed by an endoscopy fellow under direct supervision of an experienced endoscopist, the complication rate was lower in our study than that in previous reports.

If intraoperative perforation and bleeding occur, any patient movement during the procedure may cause difficulty in controlling the endoscope because of poor visualization. In our study, intraoperative massive bleeding occurred in only one case of gastric ESD. Furthermore we can safely and quickly control bleeding by maintaining optimal visualization. Moreover, in all cases of intraoperative perforation, we were able to close the hole using endoclips. Conservative treatment was sufficient for all complications, and no surgical intervention was required to manage any bleeding or perforation.

Aspiration pneumonia by vomiting can induce respiratory failure. Aspiration pneumonia is reported to occur in 2.2%–6.6% of patients undergoing ESD^[19–21]. Endotracheal intubation reportedly prevents aspiration, and positive pressure ventilation decreases the risk of air-related adverse events^[4,22]. Here we experienced no cases of aspiration pneumonia performing ESD under general anesthesia.

In this study, 25.5% patients of all ESD procedure under general anesthesia required strict anesthetic management because of severe heart or lung disease (data not shown). However, no complications associated with general anesthesia were observed. Strict anesthetic management by an anesthesiologist may be important in patients with severe heart or lung disease.

Postoperative hospital stay in our study may be longer than that in other advanced nations. The average number of hospitalization days is more in Japan than in other advanced nations because of difference in the medical insurance system. Therefore, the length of hospitalization days in our study was not because of general anesthesia.

The limitation of ESD under general anesthesia is that it can be performed only in a limited number of institutions because it requires the cooperation of an anesthesiologist.

With the cooperation of an anesthesiologist, ESD under general anesthesia will be a useful method for reducing ESD-related complications. Also, ESD under general anesthesia may be a favorable option for ESD beginners.

COMMENTS

Background

Studies regarding endoscopic submucosal dissection (ESD) under general anesthesia in Japan are scarce because ESD is generally performed under conscious sedation. ESD requires minimal patient movement for optimal visualization, which may be hampered because of insufficient sedation.

Research frontiers

This study aimed to evaluate the efficacy and safety of ESD under general anesthesia.

Innovations and breakthroughs

The *en bloc* resection rate of esophageal, gastric, and colorectal lesions was 100.0%, 98.3%, and 96.1%, respectively. The complication rate of perforation and bleeding were 0.0% and 0.0% in esophageal ESD, 1.7% and 1.7% in gastric ESD, and 3.9% and 2.0% in colorectal ESD, respectively. No cases of aspiration pneumonia were observed. All complications were managed by conservative treatment, with no surgical intervention required.

Applications

With the cooperation of an anesthesiologist, ESD under general anesthesia will be a useful method for reducing ESD-related complications.

Peer-review

In the article ESD under general anesthesia, authors tried to evaluate the efficacy and safety of ESD under general anesthesia in the retrospective manner.

REFERENCES

- 1 **Isomoto H**, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut* 2009; **58**: 331-336 [PMID: 19001058 DOI: 10.1136/gut.2008.165381]
- 2 **Fernández-Esparrach G**, Calderón A, de la Peña J, Díaz Tasende JB, Esteban JM, Gimeno-García AZ, Herreros de Tejada A, Martínez-Ares D, Nicolás-Pérez D, Nogales O, Ono A, Orive-Calzada A, Parra-Blanco A, Rodríguez Muñoz S, Sánchez Hernández E, Sánchez-Yagüe A, Vázquez-Sequeiros E, Vila J, López Rosés L. Endoscopic submucosal dissection. *Endoscopy* 2014; **46**: 361-370 [PMID: 24671864 DOI: 10.1055/s-0034-1364921]
- 3 **Maple JT**, Abu Dayyeh BK, Chauhan SS, Hwang JH, Komanduri S, Manfredi M, Konda V, Murad FM, Siddiqui UD, Banerjee S. Endoscopic submucosal dissection. *Gastrointest Endosc* 2015; **81**: 1311-1325 [PMID: 25796422 DOI: 10.1016/j.gie.2014.12.010]
- 4 **Zhai YQ**, Li HK, Linghu EQ. Endoscopic submucosal tunnel dissection for large superficial esophageal squamous cell neoplasms. *World J Gastroenterol* 2016; **22**: 435-445 [PMID: 26755889 DOI: 10.3748/wjg.v22.i1.435]
- 5 **Suzuki T**, Minami H, Komatsu T, Masusda R, Kobayashi Y, Sakamoto A, Sato Y, Inoue H, Serada K. Prolonged carbon dioxide insufflation under general anesthesia for endoscopic submucosal dissection. *Endoscopy* 2010; **42**: 1021-1029 [PMID: 21120775 DOI: 10.1055/s-0030-1255969]
- 6 **Mori H**, Kobara H, Muramatsu A, Inoue H, Kobayashi M, Nomura T, Hagiike M, Izuishi K, Suzuki Y, Gong J, Masaki T. Comparison of postoperative complications after endoscopic submucosal dissection: differences of insufflations and anesthetics. *Diagn Ther Endosc* 2011; **2011**: 709237 [PMID: 21785562 DOI: 10.1155/2011/709237]
- 7 **Matsumoto K**, Nagahara A, Matsumoto K, Akazawa Y, Komori H, Nakagawa Y, Takeda T, Ueyama H, Shimada Y, Asaoka D, Hojo M, Watanabe S. Optimization of Deep Sedation with Spontaneous Respiration for Therapeutic Endoscopy Combining Propofol and Bispectral Index Monitoring. *Gastroenterol Res Pract* 2015; **2015**: 282149 [PMID: 26351450 DOI: 10.1155/2015/282149]
- 8 **Patel S**, Vargo JJ, Khandwala F, Lopez R, Trolli P, Dumot JA, Conwell DL, Zuccaro G. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol* 2005; **100**: 2689-2695 [PMID: 16393221 DOI: 10.1111/j.1572-0241.2005.00320.x]
- 9 **Imagawa A**, Hata H, Nakatsu M, Matsumi A, Ueta E, Suto K, Terasawa H, Sakae H, Takeuchi K, Fujihara M, Endo H, Yasuhara H, Ishihara S, Kanzaki H, Jinno H, Kamada H, Kaji E, Moriya A, Ando M. A target-controlled infusion system with bispectral index monitoring of propofol sedation during endoscopic submucosal dissection. *Endosc Int Open* 2015; **3**: E2-E6 [PMID: 26134767 DOI: 10.1055/s-0034-1377519]
- 10 **Kim JS**, Kim BW, Shin IS. Efficacy and safety of endoscopic submucosal dissection for superficial squamous esophageal neoplasia: a meta-analysis. *Dig Dis Sci* 2014; **59**: 1862-1869 [PMID: 24619279 DOI: 10.1007/s10620-014-3098-2]
- 11 **Furuhata T**, Kaise M, Hoteya S, Iizuka T, Yamada A, Nomura K, Kuribayashi Y, Kikuchi D, Matsui A, Ogawa O, Yamashita S, Mitani T. Postoperative bleeding after gastric endoscopic submucosal dissection in patients receiving antithrombotic therapy. *Gastric cancer* 2016 Jan 11; Epub ahead of print [PMID: 26754296 DOI: 10.1007/s10120-015-0588-7]
- 12 **Akahoshi K**, Motomura Y, Kubokawa M, Gibo J, Kinoshita N, Osada S, Tokumaru K, Hosokawa T, Tomoeda N, Otsuka Y, Matsuo M, Oya M, Koga H, Nakamura K. Endoscopic Submucosal Dissection for Early Gastric Cancer using the Clutch Cutter: a large single-center experience. *Endosc Int Open* 2015; **3**: E432-E438 [PMID: 26528497 DOI: 10.1055/s-0034-1392509]
- 13 **Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838]
- 14 **Gotoda T**. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11 [PMID: 17334711 DOI: 10.1007/s10120-006-0408-1]
- 15 **Tanaka S**, Oka S, Kaneko I, Hirata M, Mouri R, Kanao H, Yoshida S, Chayama K. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc* 2007; **66**: 100-107 [PMID: 17591481 DOI: 10.1016/j.gie.2007.02.032]
- 16 **Tamegai Y**, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E, Liu Y, Uemura N, Saito K. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418-422 [PMID: 17516348 DOI: 10.1055/s-2007-966427]
- 17 **Isomoto H**, Nishiyama H, Yamaguchi N, Fukuda E, Ishii H, Ikeda K, Ohnita K, Nakao K, Kohno S, Shikuwa S. Clinicopathological factors associated with clinical outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2009; **41**: 679-683 [PMID: 19670135 DOI: 10.1055/s-0029-1214979]
- 18 **Yoshida N**, Yagi N, Naito Y, Yoshikawa T. Safe procedure in endoscopic submucosal dissection for colorectal tumors focused on preventing complications. *World J Gastroenterol* 2010; **16**: 1688-1695 [PMID: 20379999]
- 19 **Park CH**, Kim H, Kang YA, Cho IR, Kim B, Heo SJ, Shin S, Lee H, Park JC, Shin SK, Lee YC, Lee SK. Risk factors and prognosis of pulmonary complications after endoscopic submucosal dissection for gastric neoplasia. *Dig Dis Sci* 2013; **58**: 540-546 [PMID: 22996790 DOI: 10.1007/s10620-012-2376-0]
- 20 **Watarai J**, Tomita T, Toyoshima F, Sakurai J, Kondo T, Asano H, Yamasaki T, Okugawa T, Tanaka J, Daimon T, Oshima T, Fukui H, Hori K, Matsumoto T, Miwa H. The incidence of "silent" free air and aspiration pneumonia detected by CT after gastric endoscopic submucosal dissection. *Gastrointest Endosc* 2012; **76**: 1116-1123

- [PMID: 23164512 DOI: 10.1016/j.gie.2012.07.043]
- 21 **Saito I**, Tsuji Y, Sakaguchi Y, Niimi K, Ono S, Kodashima S, Yamamichi N, Fujishiro M, Koike K. Complications related to gastric endoscopic submucosal dissection and their managements. *Clin Endosc* 2014; **47**: 398-403 [PMID: 25324997 DOI: 10.5946/ce.2014.47.5.398]
- 22 **Linghu E**, Feng X, Wang X, Meng J, Du H, Wang H. Endoscopic submucosal tunnel dissection for large esophageal neoplastic lesions. *Endoscopy* 2013; **45**: 60-62 [PMID: 23254407 DOI: 10.1055/s-0032-1325965]

P- Reviewer: Kvolik S, Mentos O **S- Editor:** Qi Y **L- Editor:** A
E- Editor: Lu YJ



Cut endotracheal tube for endoscopic removal of an ingested push-through pack

Yuki Tateno, Ryoji Suzuki

Yuki Tateno, Ryoji Suzuki, Miyake Central Clinic, Tokyo 100-1101, Japan

Author contributions: Tateno Y and Suzuki R treated the patient, recorded the data, and wrote the report; all authors approved the final version of the article for publication.

Institutional review board statement: This case report was reviewed and approved by the Institutional Review Board of Miyake Central Clinic.

Informed consent statement: The patient described in this case report provided written informed consent prior to this submission.

Conflict-of-interest statement: No funding was received for this case report.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Yuki Tateno, MD, Miyake Central Clinic, 937 Kamitsuki, Miyake, Tokyo 100-1101, Japan. ytateno13044@gmail.com
Telephone: +81-4994-20016
Fax: +81-4994-21005

Received: March 5, 2016
Peer-review started: March 7, 2016
First decision: April 6, 2016
Revised: April 14, 2016
Accepted: May 7, 2016
Article in press: May 9, 2016
Published online: July 10, 2016

Abstract

A 52-year-old female presented to our clinic after accidentally

ingesting a push-through pack (PTP). After determining that the PTP was present in the stomach, we successfully and safely removed it endoscopically by using a handmade endoscopic hood fashioned from a cut endotracheal tube. Foreign body ingestion is a common clinical problem, and most ingested foreign bodies pass spontaneously. However, the ingestion of sharp objects, such as PTPs, increases the risk of complications, and urgent endoscopy is recommended to remove such objects. Previous studies have reported the use of other devices, both commercial and handmade, for the safe endoscopic removal of foreign bodies. The novel design of our handmade hood for the removal of the PTP, which was fashioned from a cut endotracheal tube, was beneficial in terms of maintaining a wide visual field, patient safety and tolerance, and easy preparation compared to previously reported commercial and handmade devices. It may be a viable and safe device for the retrieval of PTPs and other sharp foreign bodies.

Key words: Foreign body ingestion; Endoscopic removal; Push-through pack; Sharp object; Handmade

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Here, we report the successful and safe endoscopic removal of a push-through pack (PTP) from the stomach using a handmade endoscopic hood fashioned from a cut endotracheal tube. This novel design was beneficial in terms of maintaining a wide visual field, patient safety and tolerance, and easy preparation, compared to previously reported commercial or handmade devices. It may be a viable and safe device for the retrieval of PTPs and other sharp foreign bodies.

Tateno Y, Suzuki R. Cut endotracheal tube for endoscopic removal of an ingested push-through pack. *World J Gastrointest Endosc* 2016; 8(13): 472-476 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i13/472.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i13.472>

INTRODUCTION

Foreign body ingestion is commonly encountered in clinical practice, and most ($\geq 80\%$) foreign bodies pass spontaneously without the need for intervention^[1]. However, the ingestion of sharp and pointed objects, such as animal/fish bones, needles, and push-through packs (PTPs), increases the risk of perforation or obstruction by as much as 35%^[1].

PTPs are commonly used in Japan^[2] and South Korea^[3] for the packaging of drugs. PTPs have three or four sharp edges that, when they are accidentally ingested, can perforate the small intestine^[4]. Therefore, PTPs that have passed into the stomach or proximal duodenum should be immediately retrieved endoscopically, provided this procedure can be performed safely^[1]. Flexible endoscopy is the ideal choice for both diagnostic and therapeutic purposes in the management of upper gastrointestinal foreign bodies, with a reported success rate of over 95% and minimal complications^[5]. The risk of mucosal injury during retrieval can be minimized during extraction by orienting the sharp points of the object with handmade and commercial accessory instruments^[1], such as an overtube^[3], a latex hood over the endoscope^[6], a latex glove^[7], or a condom^[8].

Here, we report the successful and safe endoscopic removal of a PTP from the stomach using a novel handmade endoscopic hood fashioned from a cut endotracheal tube.

CASE REPORT

A 52-year-old female with no medical history of dementia or psychological impairment presented to our clinic due to the accidental ingestion of a PTP 2 h previously. She complained of sharp intermittent pain in the substernal region. She was alert, with a temperature of 36.5 °C, blood pressure of 120/80 mmHg, regular pulse of 96 bpm, and respiration of 18 breaths/min; there were no signs of abdominal tenderness or peritoneal irritation. Abdominal computed tomography showed no signs of perforation or the presence of a PTP. These findings, coupled with the fact that she had swallowed the PTP only 2 h before presentation, led us to suspect that the PTP was lodged in her esophagus or stomach. Urgent endoscopy revealed the PTP in the stomach (Figure 1).

We did not possess an overtube or commercial device for the removal of foreign bodies because our clinic is located on a remote island in Japan and is not sufficiently equipped for such medical emergencies. Therefore, to remove the PTP, a handmade hood protector was fashioned from a cut endotracheal tube (Teleflex, Endosoft 8.5; Willy R sch GmbH, Kernen im Remstal, Germany) (Figures 2 and 3) with an internal diameter of 8.5 mm, an external diameter of 11.3 mm, and a cuff composed of polyvinyl chloride. The hood was fastened to the distal end of the endoscope (GIF-H260; Olympus Corporation, Tokyo, Japan), which was 9.8 mm in diameter, without the use of rubber bands or string. The

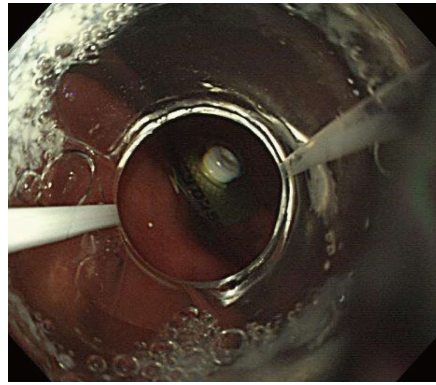


Figure 1 Endoscopic image of the push-through pack in the stomach.



Figure 2 An endotracheal tube was cut into three sections, and the middle section (white arrow) was used as an endoscopic hood. The red lines show the locations of the cuts made in the tube.



Figure 3 An endoscopic hood made from the cut endotracheal tube hood. The middle section of the cut endotracheal tube is shown in Figure 1.

cut cuff used to cloak the PTP edges was approximately 30 mm in diameter (Figure 4). The scope was inserted without the use of general anesthesia or sedation, and the PTP was captured using biopsy forceps, pulled into the cut cuff of the handmade hood, avoiding the inside of the tube (Figure 5), and extracted. All four edges of the PTP were cloaked with the cuff during retrieval (Figure 6). The size of the impacted PTP was 19 mm \times 16 mm (Figure 7). Following PTP removal, endoscopic evaluation of the esophagus showed no signs of mucosal damage, ulceration, bleeding, or perforation. The complete endoscopic procedure took only 20 min; the inspection time was thought to be acceptable without sedation. The patient was immediately discharged after endoscopy without any complications.

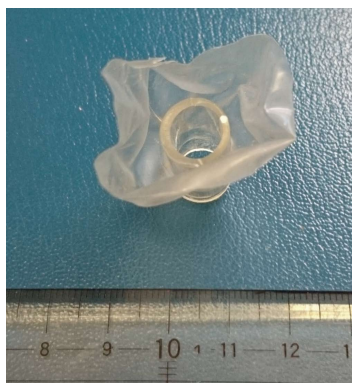


Figure 4 The cut cuff used to cloak the push-through pack was approximately 30 mm in diameter.



Figure 6 All four edges of the push-through pack were drawn into the cut cuff.

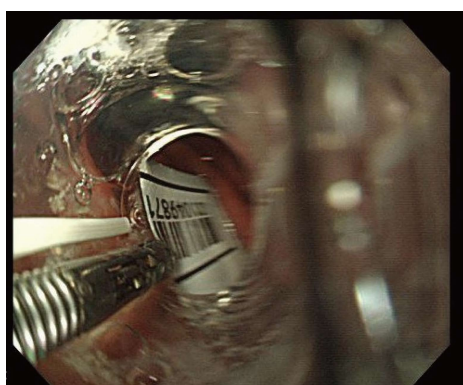


Figure 5 An endoscopic image. The push-through pack in the stomach was grasped with biopsy forceps and pulled into the cut cuff, not inside the tube.

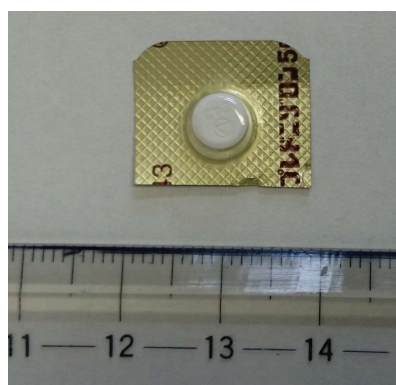


Figure 7 The size of the impacted push-through pack was 19 mm × 16 mm.

DISCUSSION

We successfully removed an ingested PTP from the stomach using a novel endoscopic hood fashioned from a cut endotracheal tube. A wide variety of handmade and commercial devices have been used for the endoscopic removal of foreign bodies^[1,3,6,7-11], including an overtube^[3], a latex protector hood fitted over an endoscope^[6], a latex glove^[7], and a condom^[8]. To the best of our knowledge, this is the first case report of the removal of an ingested foreign body using a handmade endoscopic hood cut from an endotracheal tube.

Our novel endoscopic hood was fashioned by cutting an endotracheal tube (CET hood), which consisted of a stalk-like tube and a petal-like cuff. This characteristic shape offers some advantages in the retrieval of PTPs. First, a CET hood can maintain a good visual field and wide working space. Previous reports showed that a transparent cap and overtube improve the visual field and working space^[3,12]. The CET hood contained a tube that resembled the stalk of a flower and offered advantages similar to those of a transparent cap attached to the end of the endoscope. Although we were concerned that the cuff would obscure the visual field, the tube had adequate length and sufficient hardness to resist hood collapse and maintain the visual field. Second, the

CET hood was able to cloak the PTP, which had a wider diameter than the endoscope. The endoscopic removal of a PTP with a wider diameter than the internal diameter of the overtube will occasionally fail because the unclashed edges can cause mucosal injury during retrieval^[3,8]. The internal diameter of the overtube used in this case was approximately 15 mm^[3]. Even if the diameter of the PTP exceeds 15 mm, as in our patient (19 mm), the flexibility of the tube may enable the operator to bend and pull the overtube^[3]. However, care should be taken not to cause mucosal injury by pinching the mucosa between the PTP and overtube. A bell-shaped simple latex protector hood^[6] or handmade hood constructed from a condom^[8] have been reported to be more suitable devices in cases that require a wide cover hood. The CET hood used in this case also contained a wide covering protector approximately 30 mm in diameter, which offered the same advantages as these devices. Third, the level of difficulty in the insertion and removal of an endoscope fitted with a CET hood was not different from that observed with typical endoscopic inspection. Lin^[8] reported the use of a condom protector hood for the successful removal of a PTP without complications, which exhibited good tolerance due to the thinness of the material. Endoscopic treatment using a CET hood minimizes patient discomfort during its insertion through

a narrow segment, such as the pharynx, because the cut cuff of a CET hood is sufficiently flexible to pass through the pharynx. In addition, a CET hood is suitable for emergency endoscopy due to the simple method of preparation and availability in an inadequately equipped medical institution.

Other articles have described the use of a handmade protector or hood for the endoscopic removal of foreign bodies^[1,3,6,7-11]. Handmade devices must be easily and swiftly prepared for use in emergency endoscopy^[1,11]. The preparation of a CET hood is relatively simple because it requires only the cutting and fitting of the apparatus to the endoscope. Of course, commercial devices are the simplest to use and prepare^[6]; however, not all medical institutions have these devices on hand. Although the ingestion of foreign bodies can occur anywhere, it is impractical for all medical institutions, especially those in developing countries or remote areas, to maintain a sufficient supply of commercial devices for the retrieval of foreign bodies. Therefore, under such circumstances, a CET hood can be easily fashioned from an endotracheal tube, which is readily available in most medical institutions.

However, the level of protection provided for the removal of sharp foreign bodies, such as needles or bones, should be determined in future studies. Further research should compare materials with varying cuff thicknesses (approximately 0.05 mm)^[13] compared to surgical gloves (approximately 0.29 mm)^[8] and a latex hood (2 mm), such as that manufactured by Kimberly/ Ballard Medical Products (Draper, UT, United States)^[8].

In conclusion, we report the successful and safe endoscopic removal of a PTP from a patient's stomach using a handmade endoscopic hood fashioned from a cut endotracheal tube. This novel handmade device offered some advantages compared to previously reported commercial and handmade devices and may be an alternative device for the retrieval of PTPs and other sharp foreign bodies.

COMMENTS

Case characteristics

A 52-year-old female presented after accidentally ingesting a push-through pack (PTP).

Clinical diagnosis

Accidental ingestion of PTP in the stomach.

Differential diagnosis

Accidental ingestion of PTP in the esophagus or small intestine.

Laboratory diagnosis

All laboratory tests were within normal limits.

Imaging diagnosis

Abdominal computed tomography showed no signs of perforation or the presence of a PTP, and urgent endoscopy revealed the PTP in the stomach.

Treatment

PTP was successfully and safely removed endoscopically using a handmade endoscopic hood fashioned from a cut endotracheal tube.

Related reports

Previous studies reported other devices, both commercial and handmade, for safe endoscopic removal of foreign bodies.

Term explanation

PTPs are commonly used in Japan and South Korea for packaging of drugs. PTPs have three or four sharp edges and, when accidentally ingested, can perforate the small intestine.

Experiences and lessons

The authors' novel handmade device conveyed some advantages, as compared to previously reported commercial and handmade devices, and can be an alternative device for retrieval of PTPs and other sharp foreign bodies.

Peer-review

The paper is an interesting case report.

REFERENCES

- 1 **Ikenberry SO**, Jue TL, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, Decker GA, Fanelli RD, Fisher LR, Fukami N, Harrison ME, Jain R, Khan KM, Krinsky ML, Maple JT, Sharaf R, Strohmeyer L, Dominitz JA. Management of ingested foreign bodies and food impactions. *Gastrointest Endosc* 2011; **73**: 1085-1091 [PMID: 21628009 DOI: 10.1016/j.gie.2010.11.010]
- 2 **Kumagai M**, Ikeda K, Oshima T, Nakatsuka S, Takasaka T. A press-through-pack in the larynx. *Tohoku J Exp Med* 1997; **183**: 293-295 [PMID: 9549829 DOI: 10.1620/tjem.183.293]
- 3 **Seo YS**, Park JJ, Kim JH, Kim JY, Yeon JE, Kim JS, Byun KS, Bak YT. Removal of press-through-packs impacted in the upper esophagus using an overtube. *World J Gastroenterol* 2006; **12**: 5909-5912 [PMID: 17007065]
- 4 **Hashizume T**, Tokumaru AM, Harada K. Small intestine perforation due to accidental press-through package ingestion in an elderly patient with Lewy body dementia and recurrent cardiopulmonary arrest. *BMJ Case Rep* 2015; **2015**: bcr2015212723 [PMID: 26678691 DOI: 10.1136/bcr-2015-212723]
- 5 **Yao CC**, Wu IT, Lu LS, Lin SC, Liang CM, Kuo YH, Yang SC, Wu CK, Wang HM, Kuo CH, Chiou SS, Wu KL, Chiu YC, Chuah SK, Tai WC. Endoscopic Management of Foreign Bodies in the Upper Gastrointestinal Tract of Adults. *Biomed Res Int* 2015; **2015**: 658602 [PMID: 26258140 DOI: 10.1155/2015/658602]
- 6 **Bertoni G**, Sassatelli R, Conigliaro R, Bedogni G. A simple latex protector hood for safe endoscopic removal of sharp-pointed gastroesophageal foreign bodies. *Gastrointest Endosc* 1996; **44**: 458-461 [PMID: 8905368 DOI: 10.1016/S0016-5107(96)70099-8]
- 7 **Kao LS**, Nguyen T, Dominitz J, Teicher HL, Kearney DJ. Modification of a latex glove for the safe endoscopic removal of a sharp gastric foreign body. *Gastrointest Endosc* 2000; **52**: 127-129 [PMID: 10882983 DOI: 10.1067/mge.2000.106689]
- 8 **Lin LF**. Condoms used to assist difficult endoscopic removal of impacted upper esophageal foreign bodies. *Advances in Digestive Medicine* 2016; **3**: 24-27 [DOI: 10.1016/j.aidm.2014.07.007]
- 9 **Ginsberg GG**. Management of ingested foreign objects and food bolus impactions. *Gastrointest Endosc* 1995; **41**: 33-38 [PMID: 7698622 DOI: 10.1016/S0016-5107(95)70273-3]
- 10 **Smith MT**, Wong RK. Foreign bodies. *Gastrointest Endosc Clin N Am* 2007; **17**: 361-382, vii [PMID: 17556153 DOI: 10.1016/j.giec.2007.03.002]
- 11 **Chiu KW**, Lu LS, Wu TC, Chiou SS. Novel low-cost endoscopic cap for esophageal foreign objects: a case report. *Medicine (Baltimore)* 2015; **94**: e796 [PMID: 25929932 DOI: 10.1097/

MD.0000000000000796]

- 12 **Hyun JJ**, Chun HJ, Keum B, Seo YS, Kim YS, Jeon YT, Lee HS, Um SH, Kim CD, Ryu HS. Alternative salvage technique for removing large sharp foreign body near upper esophageal sphincter. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: e48-e52

[PMID: 22318080 DOI: 10.1097/SLE.0b013e31824205a6]

- 13 **Lorente L**, Blot S, Rello J. New issues and controversies in the prevention of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2010; **182**: 870-876 [PMID: 20448095 DOI: 10.1164/rccm.201001-0081CI]

P- Reviewer: Akere A, Farhat S **S- Editor:** Ji FF **L- Editor:** A
E- Editor: Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 July 25; 8(14): 477-500





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



TOPIC HIGHLIGHT

- 477 Video capsule endoscopy in inflammatory bowel disease
Collins PD

SYSTEMATIC REVIEWS

- 489 Endoscopic full thickness resection for gastric tumors originating from muscularis propria
Jain D, Mahmood E, Desai A, Singhal S

CASE REPORT

- 496 Splenic artery aneurysm presenting as a submucosal gastric lesion: A case report
Tannoury J, Honein K, Abboud B

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 14 July 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Bojan Tepes, Professor, Diagnostic Center Rogaska, Prvomajska 29, Rogaska Slatina 3250, Slovenia

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jin-Xin Kong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerías Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lai Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
July 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at <http://www.wjgnet.com/bpg/gcrinfo/204>

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

2016 Gastrointestinal Endoscopy: Global view

Video capsule endoscopy in inflammatory bowel disease

Paul D Collins

Paul D Collins, Department of Gastroenterology and Hepatology, Royal Liverpool University Hospital, Liverpool L8 7NP, United Kingdom

Author contributions: Collins PD analysed the literature and wrote the manuscript.

Conflict-of-interest statement: The author has no conflict of interest to report.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Paul D Collins, MB, BCh, MD, FRCP, Consultant Gastroenterologist, Honorary Senior Lecturer, Department of Gastroenterology and Hepatology, Royal Liverpool University Hospital, Prescot Street, Liverpool L8 7NP, United Kingdom. paul.collins@rlbuht.nhs.uk
Telephone: +44-151-7063553
Fax: +44-151-7063582

Received: March 27, 2016

Peer-review started: March 29, 2016

First decision: April 19, 2016

Revised: May 10, 2016

Accepted: June 1, 2016

Article in press: June 16, 2016

Published online: July 25, 2016

Abstract

Video capsule endoscopy (VCE) has evolved to become an important tool for the non-invasive examination of the small bowel, which hitherto had been relatively inaccessible to direct visualisation. VCE has been

shown to play a role in monitoring the activity of small bowel Crohn's disease and can be used to assess the response to anti-inflammatory treatment in Crohn's disease. For those patients with Crohn's disease who have undergone an intestinal resection, VCE has been assessed as a tool to detect post-operative recurrence. VCE may also aid in the reclassification of patients with a diagnosis of Inflammatory Bowel Disease Unclassified to Crohn's disease. The evolution of colon capsule endoscopy (CCE) has expanded the application of this technology further. The use of CCE to assess the activity of ulcerative colitis has been described. This advance in capsule technology has also fuelled interest in its potential role as a minimally invasive tool to assess the whole of GI tract opening the possibility of its use for the panenteric assessment of Crohn's disease. VCE is a safe procedure. However, the risk of a retained capsule is higher in patients with suspected or confirmed Crohn's disease compared with patients having VCE examination for other indications. A retained video capsule is rare after successful passage of a patency capsule which may be utilised to pre-screen patients undergoing VCE. This paper describes the use of VCE in the assessment of inflammatory bowel disease.

Key words: Video capsule endoscopy; Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Patency capsule

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Video capsule endoscopy (VCE) has evolved to become an important tool for the non-invasive examination of the small bowel. Prior to the development of this technology, the small bowel had been relatively inaccessible to direct visualisation. In the setting of Crohn's disease, VCE has been shown to play a role in monitoring disease activity and response to treatment. The evolution of colon capsule endoscopy has expanded the application of this technology in inflammatory bowel disease (IBD). This paper describes

the use of VCE in the assessment of IBD.

Collins PD. Video capsule endoscopy in inflammatory bowel disease. *World J Gastrointest Endosc* 2016; 8(14): 477-488
Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i14/477.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i14.477>

INTRODUCTION

Since its development over a decade ago, small bowel video capsule endoscopy (VCE) has evolved to become an important tool for studying the small bowel. VCE directly visualises the mucosal surface of the small bowel that is relatively inaccessible to gastroscopy and ileocolonoscopy, and does so in a minimally invasive manner. Its position in the investigation of gastrointestinal conditions varies according to the condition and is complementary to other investigations of the small bowel.

Among patients undergoing VCE, the assessment of known Crohn's disease or the investigation of suspected Crohn's disease, is often cited as the second most common indication for VCE^[1]. The development of colon capsule endoscopy (CCE) has further expanded the potential applications of capsule technology to include the assessment of colonic inflammatory bowel disease (IBD).

In this article, the role of VCE in the diagnosis and assessment of IBD will be reviewed.

TECHNOLOGY

The first small bowel VCE system, M2A, later rebranded as PillCam SB, was developed by Given Imaging Limited (Yokneam, Israel) and was approved for use in 2001. Since then several other VCE systems, sharing a similar component set-up, have been developed (MiroCam, Intromedic, Seoul, South Korea; Endocapsule, Olympus Optical Co, Tokyo, Japan; OMOM capsule, Jinshan Science and Technology Group, Chongqing, China)^[2]. In each system, the capsule is ingested and images are transmitted from the capsule to a sensing system attached to a data recorder, upon which real-time images may be viewed if required. Data are later transferred from the recorder to a computer for subsequent review of the images. A further system, CapsoCam, differs from the other VCE devices. It obtains 360° images and information is stored within the capsule itself^[2]. The capsule is retrieved after it has been expelled and the information is downloaded wirelessly.

VCE FEATURES OF SMALL BOWEL CROHN'S DISEASE: MAKING THE DIAGNOSIS

The mucosal features of small bowel Crohn's disease

that may be seen at capsule endoscopy include erythema, aphthous ulceration, loss of villi, villous oedema, mucosal fissures and strictures^[3]. These findings are not specific to Crohn's disease, however, and may be seen in patients with other types of small bowel enteropathy.

There is, therefore, a potential risk for misinterpretation of inflammatory lesions seen at VCE. A non-selective approach to investigating patients may be associated with both a low yield from VCE examination and also may risk over-interpretation of small bowel findings^[4,5]. Histological confirmation may be thought of as the gold standard when diagnosing Crohn's disease. However, this may be difficult to achieve in patients in whom the mucosal changes are located in an area that is difficult to access endoscopically. The clinical context in which inflammatory lesions are seen within the small bowel is therefore an important factor for clinicians interpreting VCE findings.

Non-steroidal anti-inflammatory drug (NSAID)-associated enteropathy is, for example, the commonest mimic of Crohn's disease of the small bowel and, for this reason, patients undergoing VCE assessment are advised to avoid taking NSAIDs for 4 wk prior to the procedure^[2]. Despite this, surreptitious intake of NSAIDs has been reported in 13.6% of patients attending for VCE^[6].

Other enteropathies that share similar mucosal appearances to Crohn's disease of the small bowel include small bowel lymphoma, radiation enteropathy, intestinal tuberculosis, Behcet's disease and enteropathy related to human immunodeficiency virus-associated opportunistic infections^[7].

A further challenge to the interpretation of VCE findings is the recognition that lesions of the small bowel may be observed in healthy individuals. In a prospective randomised placebo-controlled study examining the incidence of NSAID-induced small bowel injury, 13.8% of healthy volunteers were found to have mucosal erosions at baseline^[8]. In addition, it was also observed that 7% of healthy volunteers with a negative initial VCE within the placebo group developed mucosal breaks after a 2-wk period. It would appear therefore that not only do small bowel lesions occur in a significant proportion of healthy subjects, but they may also appear and regress over time.

The International Conference on Capsule Endoscopy (ICCE) have formulated an algorithm to aid in the diagnosis of Crohn's disease^[9]. Patients are defined as having suspected Crohn's disease based on several clinical criteria. According to these criteria, a patient is considered to have suspected Crohn's disease if they have chronic diarrhoea, weight loss, abdominal pain or failure to thrive plus one other criterion in the form of extraintestinal symptoms raising a suspicion of Crohn's disease, evidence of elevated inflammatory biomarkers or abnormal imaging suggestive of Crohn's disease.

In a retrospective study of patients undergoing VCE for suspected Crohn's disease, those fulfilling ICCE criteria

Table 1 Scoring systems for the assessment of inflammatory burden in Crohn's disease: Capsule Endoscopy Crohn's Disease Activity Index

A: Inflammation	B: Extent	C: Strictureing	Score for each segment
0 = None	0 = None	0 = None	A × B + C
1 = Mild to moderate oedema/hyperaemia/denudation	1 = Focal	1 = Single (passed)	
	2 = Patchy	2 = Multiple (passed)	
2 = Severe oedema/hyperaemia/denudation	3 = Diffuse	3 = Obstructing	
3 = Small ulcer (5 mm)			
4 = Moderate ulcer (5-20 mm)			
5 = Large ulcer (20 mm)			

were more likely to be diagnosed with Crohn's disease during follow-up and had a higher burden of inflammation within the small bowel compared to those not fulfilling the ICCE criteria^[5]. Twenty-one point four percent (6 of 28 patients) and 60.7% (17 of 28 patients) received a diagnosis of Crohn's disease during follow-up in the group of patients not meeting ICCE criteria and in the group meeting the criteria, respectively ($P < 0.05$).

VCE APPEARANCES IN SMALL BOWEL CROHN'S DISEASE

Scoring systems assessing the inflammatory burden in Crohn's disease

Scoring systems quantifying the burden of small bowel inflammation have been developed in an attempt to refine and standardise the way in which findings at VCE are reported. The two commonest scoring systems used in the literature are the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) and the Lewis score. Both scores quantify the severity and extent of small bowel inflammation.

CECDAI (Table 1)

Three elements of VCE findings contribute to the CECDAI scoring system. The small bowel is divided into two equal segments and a score generated for each segment based on the parameters of inflammation, extent and stricturing. The CECDAI is the sum of the scores for the two segments. Niv *et al*^[10] have described the validation of this score in a prospective study.

Lewis score (Table 2)

The Lewis score is a semiquantitative validated scoring system used to assess the burden of small bowel inflammation and is the most commonly used scoring index^[11]. The small bowel transit time is divided into three equal parts. Each tertile is scored separately according to the formula: Tertile score = (Villous appearance × Extent × Descriptor) + (Ulcer number × Extent × Descriptor). The score for the most severely affected tertile is added to the stenosis score (Stenosis number × appearance × Traversed score). The final

score (Maximum Tertile Score + Stenosis Score) is the Lewis (Table 2)^[11]. A score of < 135 correlates with clinically insignificant inflammation, a score of 135-790 correlates with mild inflammation and scores of ≥ 790 correlate with moderate to severe inflammation.

The Lewis score is a measure of inflammatory activity and does not imply a diagnosis. However, the magnitude of the score may play a role in assessing the likelihood of Crohn's disease accounting for the lesions seen^[5,12]. A score of ≥ 135 was associated with a Crohn's diagnosis in 82.6% of patients undergoing VCE for suspected Crohn's disease. In contrast, only 12.1% of those with a Lewis score of ≤ 135 received a diagnosis of Crohn's ($P < 0.05$)^[5].

In a retrospective study assessing the diagnostic accuracy of the Lewis score in patients with suspected Crohn's disease, 58 patients met the ICCE criteria^[12]. Within this group, a Lewis score of ≥ 135 had a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of Crohn's disease of 89.5%, 78.9%, 73.9% and 91.8%, respectively.

VCE IN SUSPECTED CROHN'S DISEASE

The diagnosis of Crohn's disease is made on the basis of a clinical picture that encompasses biomarkers of inflammation, clinical symptoms and targeted investigations^[13].

Colonoscopy with ileal intubation is advised as the first line investigation for the diagnosis of Crohn's disease as it will enable the diagnosis of Crohn's disease to be made in the majority of patients. However, 30% of patients will have Crohn's disease restricted to the small bowel that will be beyond the reach of the ileocolonoscopy^[14]. It is in this group of patients that VCE may be useful in establishing a diagnosis of Crohn's disease^[2].

The role of VCE in investigating patients in whom Crohn's disease is suspected is complementary to other modes of examination. Cross-sectional small bowel imaging has the advantage of providing information about transmural disease and extra-intestinal features that may include fistulae, collections and significant stricturing disease^[3]. However, VCE is able to detect subtle mucosal lesions that may not be detected on small bowel radiological examinations.

In a meta-analysis assessing the yield of VCE vs other modalities for changes in keeping with Crohn's disease, VCE performed better than computed tomography enterography (CTE) and small bowel radiography^[15]. The incremental yield of VCE examination in patients with suspected or established Crohn's disease compared to CTE and small bowel radiography was 39% ($P < 0.00001$, 95%CI: 27%-50%), and 37% ($P < 0.00001$, 95%CI: 29%-45%), respectively. For magnetic resonance (MR) enterography, VCE for examination of patients with suspected or established Crohn's disease was not demonstrated to be superior to VCE, with a non-significant incremental yield for VCE of 7% ($P = 0.23$,

Table 2 Scoring systems for the assessment of inflammatory burden in Crohn's disease: Lewis score

Parameter		Weightings (Calculated for each tertile)	
Villous appearance	Appearance	Longitudinal extent	Descriptors
	0 = Normal	8 = Short segment	1 = Single
	1 = Oedematous	12 = Long segment	14 = Patchy
Ulcer	Number	20 = Whole tertile	17 = Diffuse
		Longitudinal extent	Descriptors
		5 = Short segment	9 = Less than 25% of circumference
		10 = Long segment	12 = 25% to 50% of circumference
		25 = Whole tertile	18 = Greater than 50% of circumference
Parameter		Weightings (Rated for the whole study)	
Stenosis	Number	Appearance	Passage of capsule past stricture
	0 = None	24 = Ulcerated	7 = Traversed
	14 = Single	2 = Non-ulcerated	10 = Not traversed
	20 = Multiple		

Short segment: $\leq 10\%$ of the tertile; Long segment: 11%-50% of a tertile; Whole tertile: $\geq 50\%$ of the tertile; Few: Two to seven lesions; Multiple: Eight or more ulcers, two or more stenoses.

95%CI: -4%-17%.) However, only four trials assessing VCE and MR enterography were available for inclusion in the meta-analysis and included only a small number of patients. This raises the possibility of a Type II error. VCE performed better than the endoscopic modalities of ileocolonoscopy and push enteroscopy with an incremental yield of 22% ($P = 0.009$, 95%CI: 5%-39%) and 57% ($P < 0.00001$, 95%CI: 43%-71%). Some caution must be drawn in interpreting these results, however, as the absence of a reference or gold standard for diagnosis may have resulted in a confirmation bias favouring VCE with false positive examinations potentially contributing to the incremental diagnostic yield.

Jensen *et al*^[16] addressed the issue of confirmation bias by comparing the diagnostic yield of VCE, MR enterography and CTE with ileocolonoscopy and/or surgery as the gold standard for assessing Crohn's. The authors reported a sensitivity and specificity for Crohn's disease affecting the terminal ileum of 100% and 91% for VCE, 81% and 86% for MR enterography and 76% and 85% by CTE, respectively. VCE was superior to both CT or MR small bowel studies for detecting lesions within the proximal small bowel ($P < 0.05$).

Leighton *et al*^[17] compared the diagnostic yield of VCE vs small bowel barium follow-through (SBFT) and ileocolonoscopy in a prospective trial of 80 patients with suspected Crohn's disease. SBFT performed less well than the other two modalities. The combination of VCE with ileocolonoscopy detected more inflammatory lesions than the combination of SBFT and ileocolonoscopy [(97.3% and 57.3% of all inflammatory lesions identified, respectively ($P < 0.01$)). Among the 25 patients with a final diagnosis of Crohn's disease, based on the physicians' global assessment of the findings of all three modalities, 11 were diagnosed with Crohn's disease on the basis of VCE findings alone, 5 by ileocolonoscopy findings alone but none by SBFT findings alone.

The place of VCE in a diagnostic algorithm for

Crohn's disease is not completely clear. If used as a third line investigation after ileocolonoscopy and small bowel imaging, it is not cost-effective^[18]. For those in whom Crohn's is suspected, VCE would miss stricturing or penetrating disease which has been reported in 25% of patients at diagnosis^[19]. However, as the above studies illustrate, radiological small bowel assessment is inferior to VCE for detecting proximal inflammatory lesions within the small bowel.

VCE IN PATIENTS WITH KNOWN CROHN'S DISEASE

In patients with an established diagnosis of Crohn's disease, VCE has some advantages over other modalities for assessing inflammatory activity. VCE has the potential to identify the presence of active disease that may not be evident from conventional biomarkers, or to identify mucosal lesions that are not visible on radiological imaging. Of patients with Crohn's colitis, 25.6% of patients will also have disease affecting the small bowel^[20]. VCE has a role in visualisation of the mucosa beyond the reach of the ileocolonoscopy, and is superior to MR and CTE for the detection of small bowel disease^[16,21]. This is of prognostic significance, as detection of proximal small bowel disease in patients with Crohn's disease has been associated with poorer clinical outcomes^[22,23].

As indicated above, VCE does however, have some limitations compared to cross-sectional imaging of the small bowel for the assessment of small bowel involvement with known Crohn's disease in that only the mucosal surface is visualised. Further, visualisation of the small bowel may be incomplete in up to 25% of patients^[24]. However, earlier versions of the video capsule had battery lives that were limited to only 6-8 h. Improvements in the battery life of the most recent iterations of the video capsule would be expected to enable an extended duration of the examination in patients

with the longest transit times. It would be expected that this would translate into a lower rate of incomplete examination.

Correlation of VCE findings with clinical symptoms and biomarkers of inflammation

Clinical symptoms can correlate poorly with the activity of IBD^[25]. C-reactive protein (CRP) and faecal calprotectin are inflammatory biomarkers that are frequently used to assess and monitor the activity of IBD. It is recognised that CRP's usefulness as a surrogate marker in IBD can be limited in some patients, however. It is normal in up to 49% of patients with active ulcerative colitis (UC) and in up to 30% of those with Crohn's disease, CRP is not elevated during relapses of disease^[26-28].

Several studies have investigated the degree to which findings at VCE correlate with inflammatory biomarkers. Niv *et al*^[29] assessed the correlation between laboratory and clinical markers of disease activity and findings at VCE in patients with active Crohn's disease. Forty-three studies were performed in 19 patients. No correlation was demonstrated between the Lewis score and CRP. A similarly poor correlation between the Lewis score and clinical symptoms as assessed by the Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ), was reported.

Faecal calprotectin has a stronger correlation with mucosal inflammation than CRP with a reported sensitivity and specificity for the detection of mucosal disease of 70%-100% and 44%-100%, respectively^[26]. Its reliability in the assessment of small bowel mucosal inflammation may be less good than for colonic disease^[28,30], although some centres have reported an equivalent efficacy for assessing small bowel and colonic inflammation^[31].

Koulaouzidis *et al*^[32] described the outcome of 70 patients in whom isolated small bowel Crohn's disease was suspected. All patients had undergone a negative ileocolonoscopy and gastroscopy. No patients with a faecal calprotectin value below 100 had active inflammation in keeping with Crohn's disease^[32]. In those with a calprotectin of > 200, the diagnostic yield was 65%. The same group reported a moderate correlation between faecal calprotectin and the Lewis score ($r = 0.448$, $P = 0.0014$)^[33]. When the analysis was restricted to patients with a faecal calprotectin of < 100 a strong correlation was reported ($r = 0.68$, $P = 0.0047$). There was no significant correlation between CECDAI and calprotectin ($r = 0.245$, $P = 0.089$).

In a multicentre cross-sectional study assessing 187 patients undergoing VCE, significant small bowel inflammation (defined as Lewis score of > 790) correlated poorly with elevation of faecal calprotectin, CRP or a combination of both markers ($r = 0.2$; $P = 0.14$)^[20]. On the basis of these data, the use of elevated biomarkers as a triage tool would have missed Crohn's in 40% of patients with moderate to severely inflamed

small bowel.

Kopylov *et al*^[34] assessed the inflammatory burden in the small bowel in patients with Crohn's disease in clinical remission, defined as those with a CDAI score of < 150. In line with previous observations that the absence of clinical symptoms does not reliably indicate a low inflammatory burden, 44 of 52 (84.6%) patients in clinical remission had significant mucosal inflammation of the small bowel (Lewis score > 135). Of the 21 patients in clinical remission who also had inflammatory biomarkers with a normal range (faecal calprotectin and CRP), 14 (67%) had significant mucosal inflammation of the small bowel (Lewis score > 135). The correlation between faecal calprotectin and the Lewis score was stronger than between CRP and mucosal inflammation ($r = 0.39$, $P = 0.003$ vs $r = 0.28$, $P = 0.036$, respectively). Both biomarkers had a high positive predictive value but low negative predictive value for the presence of moderate to severe inflammation (Lewis score ≥ 790) (96.2% and 24.1%, respectively, for faecal calprotectin; and 100% and 20.5%, respectively, for CRP).

The reported correlation between the Lewis score and biomarkers of inflammation is therefore variable, with the strongest correlation reported for calprotectin levels < 100^[33]. In calculating the Lewis score, only the inflammatory score from the tertile with the most severe inflammation contributes to the final score. This may, in part, explain the variable correlation reported between faecal calprotectin and the Lewis score. That is, mild inflammation in the other two tertiles could reasonably be expected to contribute to an elevation in faecal calprotectin, but would not contribute to an elevation in the overall endoscopic score of inflammation^[20]. For Crohn's patients in clinical remission, a stronger correlation between a cumulative Lewis score (using a summation of the individual tertile scores) and faecal calprotectin than the correlation between the conventional Lewis score and faecal calprotectin was demonstrated ($r = 0.483$, $P = 0.001$ and $r = 0.39$, $P = 0.003$, respectively)^[34]. The use of a cumulative score requires further investigation.

Mucosal healing and VCE

Mucosal healing, as demonstrated at colonoscopy, has become established as an important endpoint for treatment in Crohn's disease. It has been associated with improvements in quality of life and in clinically relevant outcomes including rates of hospitalisation, rates of surgery and sustained steroid-free remission^[35,36]. Although, there are fewer data on the prognostic significance of small bowel mucosal inflammation as assessed by VCE (see below), it is not unreasonable to infer that an improvement in VCE features of small bowel inflammation would also lead to better outcomes. Mucosal healing and the restoration of mucosal barrier function prevents the translocation of bacteria and the subsequent pathological inflammatory response^[37]. It has been observed that in those with Crohn's

affecting both the colon and small bowel, improvement in the mucosal appearances in one section of the gastrointestinal tract may not parallel improvement in other locations^[38].

Although a “gold standard” for small bowel mucosal healing in Crohn’s disease has not yet been established^[39], a Lewis score of < 135 is accepted as representing clinically insignificant inflammation^[11]. This has been correlated with a CECDAI score of less than 3.8^[33].

VCE findings as a predictor of disease outcome

Long *et al*^[40] reported on the outcomes of 86 patients with Crohn’s disease undergoing VCE. Severe findings, defined as multiple aphthous ulcers or stenosis, as compared to minimal or no inflammatory change, was associated with the addition of new medication (58.5% vs 22.2%, $P < 0.01$), and also with the likelihood of surgery (21.9% vs 4.4%, $P = 0.01$) in the 3 mo following the examination. Similarly, in study of 53 patients with Crohn’s restricted to the small bowel, moderate-to-severe inflammation (defined as a Lewis score of ≥ 790) was associated with an increased risk of corticosteroid therapy and hospitalisation during a mean follow-up period of 42 mo [RR = 5 ($P = 0.011$; 95%CI: 1.5-17.8) and 13.7 ($P = 0.028$; 95%CI: 1.3-141.9), respectively]^[41]. There was a trend towards surgery in patients with a Lewis score ≥ 790 that was not statistically significant. It appears, therefore, that the severity of inflammation as quantified by the Lewis score may predict a more aggressive course of the disease in patients with Crohn’s disease.

Disease location has also been identified as a predictor of disease outcome with proximal disease predicting clinical relapse in a retrospective review of 108 VCE examinations in patients with Crohn’s disease^[23].

Impact of VCE findings on clinical decisions

As the role of VCE in the assessment of Crohn’s disease has expanded, several studies have described the impact of the findings at VCE on clinicians’ clinical decisions.

In a retrospective study of small bowel capsule tests performed in 71 patients undergoing VCE for assessment of their Crohn’s disease, the findings at VCE led to a change in medical therapy in 38 of 71 patients within 3 mo of the investigation^[42]. Similarly, in a study that included 86 patients with Crohn’s disease, an alteration in therapy occurred in 62% of patients as a consequence of findings from VCE within the 3 mo after the procedure. In 40%, this took the form of a new anti-inflammatory medication, the most common of which was a corticosteroid^[40]. Cotter *et al*^[43] reported in a retrospective study of 50 patients that, in the 3-mo period after VCE examination, 44% of patients initiated new IBD medication. the proportion of patients on a thiopurine or biologic increased in their cohort from 4% to 30%.

In the largest of the studies describing the impact

of the findings at VCE on disease management data were collected on 187 patients undergoing VCE for assessment of known Crohn’s disease^[20]. Fifty-two point three percent of patients had their management altered as a consequence of the VCE findings. Initiation or dose-intensification of anti-inflammatory medications was undertaken in 82.5% of patients.

Impact of Crohn’s treatment on small bowel inflammation as assessed by VCE

A small number of studies have described the impact of Crohn’s treatments on small bowel appearances at VCE^[44-46].

In a prospective study of 40 patients treated for a flare of Crohn’s disease, VCE was performed at baseline and after at least four weeks of treatment, the choice of which was at the discretion of the treating physician^[46]. All patients showed a clinical response. However, of the endoscopic variables assessed, only the number of large ulcers showed a statistically significant improvement after treatment [8.3 ± 1.4 and 5 ± 0.8 (mean \pm SEM), before and after treatment, respectively (mean difference 3.3 ± 1.2 , 95%CI: 0.8-5.9, $P = 0.01$)]. No patients achieved mucosal healing within the 4-wk period of treatment period examined.

In another small prospective study, 43 patients with active Crohn’s were offered VCE assessment, following which they were offered additional treatment. In contrast to the short follow-up period in the previous study, 37 patients underwent a further VCE examination at week 12, and 28 patients underwent VCE at week 52^[44,45]. Eighty-four percent received Adalimumab and 16% azathioprine. At initial assessment, 33% had mild disease (CECDAI score < 3.5) and the remainder moderate to severe disease (CECDAI score ≥ 5.8). At 12 wk, 54% were in clinical remission. None had achieved complete mucosal healing, but the CECDAI had normalised in 27% of patients. Significant reductions in median faecal calprotectin and CRP values were observed. At 12 mo, 42% had complete mucosal healing.

Assessment of post-operative recurrence

Asymptomatic recurrence of Crohn’s disease after resection is a common occurrence. Seventy-three percent of patients undergoing ileal resection have endoscopic recurrence in the neoterminal ileum one year after surgery^[47]. Eighty percent of patients of these patients were symptom free. Some IBD experts advocate routine endoscopic assessment 6 mo post-operatively and offer a step-up in treatment to those with significant recurrence (Rutgeerts score ≥ 2)^[48].

Conflicting results have been reported in two prospective studies comparing the superiority of VCE or ileocolonoscopy for the detection of recurrent disease in patients who have previously had an ileocolonic resection. However, both studies reported that VCE detected lesions in the small bowel beyond the reach of

the ileocolonoscopy in up to two thirds of patients^[49,50].

ROLE OF VCE IN THE RECLASSIFICATION OF IBD

The term, Inflammatory Bowel Disease Unclassified (IBDU) is conventionally used to classify patients with an intact colon in whom colonic biopsies are not able to distinguish between UC and Crohn's disease. Following a diagnosis of IBDU approximately 30% of patients will be reclassified as Crohn's disease during follow-up^[51]. It is not possible to distinguish between UC and Crohn's disease on histological examination of the resection specimen in up to 15% of patients with colitis undergoing colectomy^[52]. These patients are conventionally classified as having indeterminate colitis.

These observations have implications for the monitoring and treatment of IBD in these patients. VCE aid in the reclassification of the diagnosis to Crohn's disease which is of particular relevance, for example, to patients in whom the formation of an ileoanal pouch is being considered as rates of pouch failure are higher in patients with Crohn's disease compared to UC or indeterminate colitis^[53].

Mow *et al*^[54] described the use of VCE in patients with an established diagnosis of IBD who had previously undergone radiological assessment of the small bowel. Twelve of 21 patients with UC or IBDU were reclassified as having probable Crohn's disease after VCE. In this study, Crohn's disease was defined as the presence of small bowel ulcers that were serpiginous, deep-fissuring, coalescing, linear or nodular. Patients with multiple small or indistinct ulcers could also be classified as having Crohn's disease. Similarly, Mehdizadeh *et al*^[55] 2008 reported that 19 of 120 patients with IBDU or UC were found to have VCE findings consistent with Crohn's disease (defined as three or more ulcers in the small bowel). In both these studies, the reclassification of patients as having Crohn's disease was based on the identification of inflammatory lesions within the small bowel. However, it should be noted that a negative VCE examination does not exclude a reclassification of IBDU to Crohn's disease. In a cohort of 30 patients with IBDU, a subsequent diagnosis of Crohn's disease (5 patients) and UC (one patient) was made at ileocolonoscopy after a negative VCE examination^[56].

In a paediatric population, higher rates of reclassification of IBDU and UC to Crohn's disease have been reported, with more than 50% having their diagnosis revised after VCE^[57,58].

CCE

The technology

In an extension of the technology that had been developed to examine the small bowel, a wireless capsule endoscopy system has been developed examination the colonic mucosa. CCE uses a capsule that differs slightly

from the small bowel capsule. The wider diameter of colon means that the tendency of the capsule to flip around its axis is greater. A second camera was added in order that both ends of the capsule could capture images simultaneously. Advances in battery technology have extended the battery life sufficiently for the capsule to capture images of the entire colon. The most recent version of the CCE, the PillCam COLON 2 (Given Imaging, Yokneam, Israel) has an angle of view of 172°^[59].

Standard bowel cleansing regimes used for conventional colonoscopy are insufficient for examination of the colon with CCE. The bowel cleansing regime for CCE includes 4 L polyethylene glycol. During the procedure, further boosters based on sodium phosphate are used in order to enhance the propulsion of the capsule through the small bowel and colon^[60].

CCE in Crohn's disease

CCE has been assessed as a tool for assessing colonic inflammation in active Crohn's disease. In a study prospectively following 40 patients with Crohn's disease, all patients underwent colonoscopy and CCE^[61]. There was substantial agreement between the Crohn's Disease Endoscopic Index of Severity (CDEIS) scores calculated using both modalities [intraclass correlation coefficient (ICC), 0.65; 95%CI: 0.43-0.80]. There was also a substantial inter-observer agreement for CDEIS scores (ICC, 0.67; 95%CI: 0.35-0.86). Agreement between the two modalities of examination was less good for Simplified Endoscopic Score for Crohn's Disease (SES-CD). However, CCE appeared to systematically underestimate of the severity of disease. The greatest agreement between colonoscopy and CCE was observed in the ileum (ICC, 0.73; 95%CI: 0.54-0.85) with a trend towards poorer agreement towards the distal colon. The sensitivity for the detection of ulcers within the colon was 86%. However, a low specificity for colonic ulceration of 40% indicates that CCE may not be an adequate tool to assess mucosal healing. In common with other studies of CCE, patients found CCE examination to be more tolerable than optical colonoscopy.

Although, CCE was developed as a tool to assess the colonic mucosa, images of the entire GI tract are captured. This has prompted interest in investigating a potential role for CCE's effectiveness in assessing both the large and small bowel^[62]. Its potential role as a single minimally invasive tool to assess the entire gastrointestinal (GI) tract in Crohn's is appealing. A small study assessing the efficacy of CCE for panenteric evaluation of Crohn's disease reported the outcomes for 12 patients with Crohn's disease in steroid-free remission^[63]. The entire GI tract could be visualised in 10 of the 12 patients. The use of CCE identified isolated SB disease in three patients.

CCE in UC

Several studies have addressed a potential role for CCE

as a minimally invasive investigation for the assessment of the activity of UC. In the largest of the studies, 100 patients with suspected or confirmed UC were assessed with CCE and colonoscopy^[64]. CCE was had a sensitivity and specificity for the detection of colonic inflammation of 89% and 75%, respectively. In a prospective study including 26 patients with UC, CCE compared to colonoscopy showed a moderate agreement for assessing extent of disease and a substantial agreement for the assessment of severity of disease ($\kappa = 0.522$, $P < 0.001$ and $\kappa = 0.751$, $P < 0.001$, respectively)^[65]. Hosoe *et al*^[66] reported a strong correlation between CCE and colonoscopic assessment of the severity of inflammation (average $\rho = 0.797$).

There are several limitations in the use of CCE to assess UC. UC may only involve the distal colon and an incomplete CCE examination would fail to identify inflammatory pathology in these patients. In common with VCE of the small bowel, the inability to obtain biopsy specimens is a further limitation. Its role in UC would therefore not encompass surveillance for dysplastic change or scenarios in which biopsies to exclude superadded CMV infection are required.

COMPLICATIONS OF VCE

Capsule retention

Capsule retention, defined as the failure of the video capsule to pass through the GI tract after 2 wk, is a significant concern for clinicians who perform capsule endoscopy. It is more common in patients undergoing VCE for suspected or definite Crohn's disease. In a systematic review which included 2538 VCE procedures performed in patients with definite or suspected Crohn's disease, a capsule retention rate of 2.6% was reported in this group, compared to an overall retention rate of 1.4% in 22840 VCE procedures as a whole^[24].

In patients with a retained capsule due to a Crohn's inflammatory stricture, a short course of steroids may enable the capsule to pass spontaneously. However, most patients with a retained capsule may require endoscopy or surgery to retrieve the capsule^[67]. Surgical retrieval has been reported to be necessary in 53%-100% of cases of capsule retention. In one small study of 12 patients with a retained capsule, of whom 8 had a Crohn's-associated stricture, double balloon enteroscopy avoided the need for surgery in 75% of cases^[68].

Strategies to reduce the risk of capsule retention in IBD

Among patients with Crohn's disease undergoing VCE assessment, those thought to be at highest risk of capsule retention include those with extensive small bowel disease, small bowel strictures, previous abdominal surgery and those with a prior history of small bowel obstruction. Conventional small bowel imaging (small bowel barium studies, CTE and MR enterography) or assessment with a patency capsule (PC) (see later) are useful adjuncts to identify small

bowel features that may contraindicate the use of VCE.

However, in one study examining the use of PC assessment of the small bowel (see below), the authors assessed the use of selective PC assessment^[69]. Those at higher risk of capsule retention were defined as those patients with obstructive symptoms, previous small bowel resection or bowel obstruction, or those deemed to require a PC by the referring clinician. Interestingly, a selective selection strategy vs a non-selective strategy did not correlate with the risk of retention of the video capsule.

Small bowel imaging and prediction of capsule retention

Among patients with an established diagnosis of Crohn's disease, CTE or MR enterography may identify stenotic lesions that would contraindicate VCE in 27%-40% of patients^[70]. However, capsule retention may still occur if small bowel imaging misses clinically significant stricturing disease. In a retrospective study of 50 patients with a confirmed diagnosis of Crohn's disease, for example, 6% of the patients had capsule retention despite normal cross-sectional small bowel imaging studies and no history of obstructive symptoms^[43].

PC

The Agile PC (Given Imaging Limited, Yokneam, Israel) was developed for use as a pre-screening tool to reduce the risk of capsule retention in patients undergoing VCE. The PC is the same size and shape as the video capsule. It consists of a core containing lactose and 10% barium, the latter component rendering the capsule radio-opaque. The core is contained within a cellophane wrapping with hollow wax plugs at each end of the capsule. Enteric fluid pass through the hollow wax plugs and the capsule disintegrates after 30 h^[71]. The PC contains a radiofrequency emitter that can be detected by a hand-held scanner. If, after 30 h, the PC is detected, then its position within the GI tract can be assessed radiologically.

Video capsule retention is a rare occurrence after a negative PC test with retention rates of between 0.6% and 2.1% reported after a satisfactory PC assessment^[20,69,72].

There are a number of possible explanations for the observation that the video capsule may become retained after a negative PC test. Rapid disintegration of a PC leading to false negative patency test and subsequent VCE retention has been reported^[73]. Assadsangabi *et al*^[72] utilized low-dose CT scanning to assess the position of the PC. In the single case of video capsule retention that occurred in this study, the PC was seen to have been retained in a dilated, faecalisated segment of ileum that had been misinterpreted as a segment of colon^[72].

A positive PC test is associated with a significant risk of video capsule retention. The retention rate in 18 patients with established Crohn's disease who underwent a VCE examination after a positive PC test was 11.1% ($P = 0.01$)^[69].

Adverse effects of PC include abdominal discomfort which has been reported to occur in 20% of patients with established Crohn's disease in one series^[69]. Surgical intervention for small bowel obstruction secondary to retention of a PC has been reported^[71,74,75]. It is thought that this may arise if the PC lodges in such a way that the enteric luminal contents are unable to access the lactose core of the PC.

A retrospective study of 42 patients undergoing PC and radiological assessment demonstrated a similar sensitivity and specificity for both tests for detecting significant small bowel stricturing [sensitivity for patency and radiological tests of 57% and 71%, respectively ($P = 1.00$) and specificity of 86% and 97%, respectively ($P = 0.22$)]^[76].

Current European guidelines advise use of a PC prior to VCE in patients with a confirmed diagnosis disease^[2].

Other complications of VCE

The handful of cases of perforation reported in patients undergoing investigation with VCE have largely occurred in patients with capsule retention and an established diagnosis of Crohn's disease^[77]. Aspiration of the video capsule occurs rarely, and has been reported in 1 in 800 examinations^[78].

CONCLUSION

VCE has evolved into an important complementary tool to investigate the small bowel in patients with suspected or established Crohn's disease. It is a minimally invasive and well tolerated test with a high diagnostic yield. Its place in the monitoring of Crohn's disease and the implications of VCE findings for the treatment of Crohn's disease are becoming better understood. The more recent development of CCE has expanded the potential applications of capsule endoscopy to include assessment of UC and to provide a pan-enteric assessment of patients with Crohn's disease.

REFERENCES

- 1 Neumann H, Fry LC, Nägel A, Neurath MF. Wireless capsule endoscopy of the small intestine: a review with future directions. *Curr Opin Gastroenterol* 2014; **30**: 463-471 [PMID: 25029549 DOI: 10.1097/MOG.000000000000101]
- 2 Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltés P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: 25826168 DOI: 10.1055/s-0034-1391855]
- 3 Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, Despott EJ, Fortun PF, Heuschkel R, Kammermeier J, Leighton JA, Mantzaris GJ, Moussata D, Lo S, Paulsen V, Panés J, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger JM, Yamamoto H, Travis S, Colombel JF, Van Gossum A. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009; **41**: 618-637 [PMID: 19588292 DOI: 10.1055/s-0029-1214790]
- 4 Hartmann D. Capsule endoscopy and Crohn's disease. *Dig Dis* 2011; **29** Suppl 1: 17-21 [PMID: 22104747 DOI: 10.1159/000331124]
- 5 Rosa B, Moreira MJ, Rebelo A, Cotter J. Lewis score: a useful clinical tool for patients with suspected Crohn's Disease submitted to capsule endoscopy. *J Crohns Colitis* 2012; **6**: 692-697 [PMID: 22398099 DOI: 10.1016/j.crohns.2011.12.002]
- 6 Sidhu R, Brunt LK, Morley SR, Sanders DS, McAlindon ME. Undisclosed use of nonsteroidal anti-inflammatory drugs may underlie small-bowel injury observed by capsule endoscopy. *Clin Gastroenterol Hepatol* 2010; **8**: 992-995 [PMID: 20692369 DOI: 10.1016/j.cgh.2010.07.011]
- 7 Bar-Meir S. Review article: capsule endoscopy - are all small intestinal lesions Crohn's disease? *Aliment Pharmacol Ther* 2006; **24** Suppl 3: 19-21 [PMID: 16961739 DOI: 10.1111/j.1365-2036.2006.03054.x]
- 8 Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin Gastroenterol Hepatol* 2005; **3**: 133-141 [PMID: 15704047 DOI: 10.1016/S1542-3565(04)00619-6]
- 9 Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy* 2007; **39**: 895-909 [PMID: 17968807 DOI: 10.1055/s-2007-966930]
- 10 Niv Y, Ilani S, Levi Z, Herszkowitz M, Niv E, Fireman Z, O'Donnel S, O'Morain C, Eliakim R, Scapa E, Kalantzis N, Kalantzis C, Apostolopoulos P, Gal E. Validation of the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score): a multicenter prospective study. *Endoscopy* 2012; **44**: 21-26 [PMID: 22125196 DOI: 10.1055/s-0031-1291385]
- 11 Gralnek IM, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008; **27**: 146-154 [PMID: 17956598 DOI: 10.1111/j.1365-2036.2007.03556.x]
- 12 Monteiro S, Boal Carvalho P, Dias de Castro F, Magalhães J, Machado F, Moreira MJ, Rosa B, Cotter J. Capsule Endoscopy: Diagnostic Accuracy of Lewis score in Patients with Suspected Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 2241-2246 [PMID: 26197449 DOI: 10.1097/MIB.0000000000000517]
- 13 Van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, Ochsenkühn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010; **4**: 7-27 [PMID: 21122488 DOI: 10.1016/j.crohns.2009.12.003]
- 14 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]
- 15 Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010; **105**: 1240-1248; quiz 1249 [PMID: 20029412 DOI: 10.1038/ajg.2009.713]
- 16 Jensen MD, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CTE. *Clin Gastroenterol Hepatol* 2011; **9**: 124-129 [PMID: 21056692 DOI: 10.1016/j.cgh.2010.10.019]
- 17 Leighton JA, Gralnek IM, Cohen SA, Toth E, Cave DR, Wolf DC, Mullin GE, Ketover SR, Legnani PE, Seidman EG, Crowell MD, Bergwerk AJ, Peled R, Eliakim R. Capsule endoscopy is superior

- to small-bowel follow-through and equivalent to ileocolonoscopy in suspected Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 609-615 [PMID: 24075891 DOI: 10.1016/j.cgh.2013.09.028]
- 18 **Levesque BG**, Cipriano LE, Chang SL, Lee KK, Owens DK, Garber AM. Cost effectiveness of alternative imaging strategies for the diagnosis of small-bowel Crohn's disease. *Clin Gastroenterol Hepatol* 2010; **8**: 261-267, 267.e1-e4 [PMID: 19896559 DOI: 10.1016/j.cgh.2009.10.032]
 - 19 **Louis E**, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; **49**: 777-782 [PMID: 11709511 DOI: 10.1136/gut.49.6.777]
 - 20 **Kopylov U**, Nemeth A, Koulaouzidis A, Makins R, Wild G, Afif W, Bitton A, Johansson GW, Bessissow T, Eliakim R, Toth E, Seidman EG. Small bowel capsule endoscopy in the management of established Crohn's disease: clinical impact, safety, and correlation with inflammatory biomarkers. *Inflamm Bowel Dis* 2015; **21**: 93-100 [PMID: 25517597 DOI: 10.1097/MIB.0000000000000255]
 - 21 **Voderholzer WA**, Beinhöelzl J, Rogalla P, Murrer S, Schachschal G, Lochs H, Ortner MA. Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut* 2005; **54**: 369-373 [PMID: 15710985 DOI: 10.1136/gut.2004.040055]
 - 22 **Lazarev M**, Huang C, Bitton A, Cho JH, Duerr RH, McGovern DP, Proctor DD, Regueiro M, Rioux JD, Schumm PP, Taylor KD, Silverberg MS, Steinhardt AH, Hutfless S, Brant SR. Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. *Am J Gastroenterol* 2013; **108**: 106-112 [PMID: 23229423 DOI: 10.1038/ajg.2012.389]
 - 23 **Flamant M**, Trang C, Maillard O, Sacher-Huvelin S, Le Rhun M, Galmiche JP, Bourreille A. The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 1390-1396 [PMID: 23552764 DOI: 10.1097/MIB.0b013e31828133c1]
 - 24 **Liao Z**, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010; **71**: 280-286 [PMID: 20152309 DOI: 10.1016/j.gie.2009.09.031]
 - 25 **Modigliani R**, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. *Gastroenterology* 1990; **98**: 811-818 [PMID: 2179031]
 - 26 **Lewis JD**. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. *Gastroenterology* 2011; **140**: 1817-1826. e2 [PMID: 21530748 DOI: 10.1053/j.gastro.2010.11.058]
 - 27 **Burri E**, Beglinger C, Lehmann FS. Monitoring of therapy for inflammatory bowel disease. *Digestion* 2012; **86** Suppl 1: 1-5 [PMID: 23051719 DOI: 10.1159/000341953]
 - 28 **Kopylov U**, Rosenfeld G, Bressler B, Seidman E. Clinical utility of fecal biomarkers for the diagnosis and management of inflammatory bowel disease. *Inflamm Bowel Dis* 2014; **20**: 742-756 [PMID: 24562174 DOI: 10.1097/01.MIB.0000442681.85545.31]
 - 29 **Niv E**, Fishman S, Kachman H, Arnon R, Dotan I. Sequential capsule endoscopy of the small bowel for follow-up of patients with known Crohn's disease. *J Crohns Colitis* 2014; **8**: 1616-1623 [PMID: 24666976 DOI: 10.1016/j.crohns.2014.03.003]
 - 30 **Costa F**, Mumolo MG, Ceccarelli L, Bellini M, Romano MR, Sterpi C, Ricchiuti A, Marchi S, Bottai M. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut* 2005; **54**: 364-368 [PMID: 15710984 DOI: 10.1136/gut.2004.043406]
 - 31 **Jensen MD**, Kjeldsen J, Nathan T. Fecal calprotectin is equally sensitive in Crohn's disease affecting the small bowel and colon. *Scand J Gastroenterol* 2011; **46**: 694-700 [PMID: 21456899 DOI: 10.3109/00365521.2011.560680]
 - 32 **Koulaouzidis A**, Douglas S, Rogers MA, Arnott ID, Plevris JN. Fecal calprotectin: a selection tool for small bowel capsule endoscopy in suspected IBD with prior negative bi-directional endoscopy. *Scand J Gastroenterol* 2011; **46**: 561-566 [PMID: 21269246 DOI: 10.3109/00365521.2011.551835]
 - 33 **Koulaouzidis A**, Douglas S, Plevris JN. Lewis score correlates more closely with fecal calprotectin than Capsule Endoscopy Crohn's Disease Activity Index. *Dig Dis Sci* 2012; **57**: 987-993 [PMID: 22057284 DOI: 10.1007/s10620-011-1956-8]
 - 34 **Kopylov U**, Yablecovitch D, Lahat A, Neuman S, Levhar N, Greener T, Klang E, Rozendorn N, Amitai MM, Ben-Horin S, Eliakim R. Detection of Small Bowel Mucosal Healing and Deep Remission in Patients With Known Small Bowel Crohn's Disease Using Biomarkers, Capsule Endoscopy, and Imaging. *Am J Gastroenterol* 2015; **110**: 1316-1323 [PMID: 26215531 DOI: 10.1038/ajg.2015.221]
 - 35 **Khanna R**, Bouguen G, Feagan BG, D'Haens G, Sandborn WJ, Dubcenco E, Baker KA, Levesque BG. A systematic review of measurement of endoscopic disease activity and mucosal healing in Crohn's disease: recommendations for clinical trial design. *Inflamm Bowel Dis* 2014; **20**: 1850-1861 [PMID: 25029615 DOI: 10.1097/MIB.0000000000000131]
 - 36 **Dulai PS**, Levesque BG, Feagan BG, D'Haens G, Sandborn WJ. Assessment of mucosal healing in inflammatory bowel disease: review. *Gastrointest Endosc* 2015; **82**: 246-255 [PMID: 26005012 DOI: 10.1016/j.gie.2015.03.1974]
 - 37 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618 DOI: 10.1136/gutjnl-2012-302830]
 - 38 **Carvalho PB**, Rosa B, Cotter J. Mucosal healing in Crohn's disease - are we reaching as far as possible with capsule endoscopy? *J Crohns Colitis* 2014; **8**: 1566-1567 [PMID: 25023448 DOI: 10.1016/j.crohns.2014.06.008]
 - 39 **Kopylov U**, Ben-Horin S, Seidman EG, Eliakim R. Video Capsule Endoscopy of the Small Bowel for Monitoring of Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 2726-2735 [PMID: 26193349 DOI: 10.1097/MIB.0000000000000497]
 - 40 **Long MD**, Barnes E, Isaacs K, Morgan D, Herfarth HH. Impact of capsule endoscopy on management of inflammatory bowel disease: a single tertiary care center experience. *Inflamm Bowel Dis* 2011; **17**: 1855-1862 [PMID: 21830264 DOI: 10.1002/ibd.21571]
 - 41 **Dias de Castro F**, Boal Carvalho P, Monteiro S, Rosa B, Firmino-Machado J, Moreira MJ, Cotter J. Lewis score--Prognostic Value in Patients with Isolated Small Bowel Crohn's Disease. *J Crohns Colitis* 2015; **9**: 1146-1151 [PMID: 26377028 DOI: 10.1093/ecco-jcc/jjv166]
 - 42 **Dussault C**, Gower-Rousseau C, Salleron J, Vernier-Massouille G, Branche J, Colombel JF, Maunoury V. Small bowel capsule endoscopy for management of Crohn's disease: a retrospective tertiary care centre experience. *Dig Liver Dis* 2013; **45**: 558-561 [PMID: 23238033 DOI: 10.1016/j.dld.2012.11.004]
 - 43 **Cotter J**, Dias de Castro F, Moreira MJ, Rosa B. Tailoring Crohn's disease treatment: the impact of small bowel capsule endoscopy. *J Crohns Colitis* 2014; **8**: 1610-1615 [PMID: 24631311 DOI: 10.1016/j.crohns.2014.02.018]
 - 44 **Hall BJ**, Holleran GE, Smith SM, Mahmud N, McNamara DA. A prospective 12-week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. *Eur J Gastroenterol Hepatol* 2014; **26**: 1253-1259 [PMID: 25264865 DOI: 10.1097/MEG.0000000000000194]
 - 45 **Hall B**, Holleran G, Chin JL, Smith S, Ryan B, Mahmud N, McNamara D. A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. *J Crohns Colitis* 2014; **8**: 1601-1609 [PMID: 25257546 DOI: 10.1016/j.crohns.2014.09.005]
 - 46 **Efthymiou A**, Viazis N, Mantzaris G, Papadimitriou N, Tzourmakliotis D, Raptis S, Karamanolis DG. Does clinical response correlate with mucosal healing in patients with Crohn's disease of the small bowel? A prospective, case-series study using wireless capsule endoscopy. *Inflamm Bowel Dis* 2008; **14**: 1542-1547 [PMID: 18521929 DOI: 10.1002/ibd.20509]
 - 47 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease.

- Gastroenterology* 1990; **99**: 956-963 [PMID: 2394349]
- 48 **Jones GR**, Kennedy NA, Lees CW, Arnott ID, Satsangi J. Systematic review: The use of thiopurines or anti-TNF in post-operative Crohn's disease maintenance--progress and prospects. *Aliment Pharmacol Ther* 2014; **39**: 1253-1265 [PMID: 24738574 DOI: 10.1111/apt.12743]
 - 49 **Bourreille A**, Jarry M, D'Halluin PN, Ben-Soussan E, Maunoury V, Bulois P, Sacher-Huvelin S, Vahedy K, Lerebours E, Heresbach D, Bretagne JF, Colombel JF, Galmiche JP. Wireless capsule endoscopy versus ileocolonoscopy for the diagnosis of postoperative recurrence of Crohn's disease: a prospective study. *Gut* 2006; **55**: 978-983 [PMID: 16401689 DOI: 10.1136/gut.2005.081851]
 - 50 **Pons Beltrán V**, Nos P, Bastida G, Beltrán B, Argüello L, Aguas M, Rubin A, Pertejo V, Sala T. Evaluation of postsurgical recurrence in Crohn's disease: a new indication for capsule endoscopy? *Gastrointest Endosc* 2007; **66**: 533-540 [PMID: 17725942 DOI: 10.1016/j.gie.2006.12.059]
 - 51 **Eliakim R**. The impact of wireless capsule endoscopy on gastrointestinal diseases. *South Med J* 2007; **100**: 235-236 [PMID: 17396720 DOI: 10.1097/01.smj.0000257405.87268.48]
 - 52 **Guindi M**, Riddell RH. Indeterminate colitis. *J Clin Pathol* 2004; **57**: 1233-1244 [PMID: 15563659 DOI: 10.1136/jcp.2003.015214]
 - 53 **Öresland T**, Bemelman WA, Sampietro GM, Spinelli A, Windsor A, Ferrante M, Marteau P, Zmora O, Kotze PG, Espin-Basany E, Tirt E, Sica G, Panis Y, Faerden AE, Biancone L, Angriman I, Serclova Z, de Buck van Overstraeten A, Gionchetti P, Stassen L, Warusavitarne J, Adamina M, Dignass A, Eliakim R, Magro F, D'Hoore A. European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015; **9**: 4-25 [PMID: 25304060 DOI: 10.1016/j.crohns.2014.08.012]
 - 54 **Mow WS**, Lo SK, Targan SR, Dubinsky MC, Treyzon L, Abreu-Martin MT, Papadakis KA, Vasiliauskas EA, Voderholzer WA, Ortner M, Rogalla P, Beinhöhl J, Lochs H. Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. Diagnostic yield of wireless capsule enteroscopy in comparison with computed tomography enteroclysis. *Clin Gastroenterol Hepatol* 2004; **2**: 31-40 [DOI: 10.1016/S1542-3565(03)00289-1]
 - 55 **Mehdizadeh S**, Chen G, Enayati PJ, Cheng DW, Han NJ, Shaye OA, Ippoliti A, Vasiliauskas EA, Lo SK, Papadakis KA. Diagnostic yield of capsule endoscopy in ulcerative colitis and inflammatory bowel disease of unclassified type (IBDU). *Endoscopy* 2008; **40**: 30-35 [PMID: 18058654 DOI: 10.1055/s-2007-995359]
 - 56 **Maunoury V**, Savoye G, Bourreille A, Bouhnik Y, Jarry M, Sacher-Huvelin S, Ben Soussan E, Lerebours E, Galmiche JP, Colombel JF. Value of wireless capsule endoscopy in patients with indeterminate colitis (inflammatory bowel disease type unclassified). *Inflamm Bowel Dis* 2007; **13**: 152-155 [PMID: 17206697 DOI: 10.1002/ibd.20060]
 - 57 **Gralnek IM**, Cohen SA, Ephraim H, Napier A, Gobin T, Sherrod O, Lewis J. Small bowel capsule endoscopy impacts diagnosis and management of pediatric inflammatory bowel disease: a prospective study. *Dig Dis Sci* 2012; **57**: 465-471 [PMID: 21901253 DOI: 10.1007/s10620-011-1894-5]
 - 58 **Cohen SA**, Gralnek IM, Ephraim H, Saripkin L, Meyers W, Sherrod O, Napier A, Gobin T. Capsule endoscopy may reclassify pediatric inflammatory bowel disease: a historical analysis. *J Pediatr Gastroenterol Nutr* 2008; **47**: 31-36 [PMID: 18607266 DOI: 10.1097/MPG.0b013e318160df85]
 - 59 **Adler SN**, Metzger YC. PillCam COLON capsule endoscopy: recent advances and new insights. *Therap Adv Gastroenterol* 2011; **4**: 265-268 [PMID: 21765870 DOI: 10.1177/1756283X11401645]
 - 60 **Spada C**, Hassan C, Galmiche JP, Neuhaus H, Dumonceau JM, Adler S, Epstein O, Gay G, Pennazio M, Rex DK, Benamouzig R, de Franchis R, Delvaux M, Devière J, Eliakim R, Fraser C, Hagenmüller F, Herreras JM, Keuchel M, Macrae F, Munoz-Navas M, Ponchon T, Quintero E, Riccioni ME, Rondonotti E, Marmo R, Sung JJ, Tajiri H, Toth E, Triantafyllou K, Van Gossum A, Costamagna G. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2012; **44**: 527-536 [PMID: 22389230 DOI: 10.1055/s-0031-1291717]
 - 61 **D'Haens G**, Löwenberg M, Samaan MA, Franchimont D, Ponsioen C, van den Brink GR, Fockens P, Bossuyt P, Amininejad L, Rajamannar G, Lensink EM, Van Gossum AM. Safety and Feasibility of Using the Second-Generation Pillcam Colon Capsule to Assess Active Colonic Crohn's Disease. *Clin Gastroenterol Hepatol* 2015; **13**: 1480-6.e3 [PMID: 25804331 DOI: 10.1016/j.cgh.2015.01.031]
 - 62 **Remes-Troche JM**, Jiménez-García VA, García-Montes JM, Hergueta-Delgado P, Roesch-Dietlen F, Herreras-Gutiérrez JM. Application of colon capsule endoscopy (CCE) to evaluate the whole gastrointestinal tract: a comparative study of single-camera and dual-camera analysis. *Clin Exp Gastroenterol* 2013; **6**: 185-192 [PMID: 24068872 DOI: 10.2147/CEG.S45215]
 - 63 **Boal Carvalho P**, Rosa B, Dias de Castro F, Moreira MJ, Cotter J. PillCam COLON 2 in Crohn's disease: A new concept of pan-enteric mucosal healing assessment. *World J Gastroenterol* 2015; **21**: 7233-7241 [PMID: 26109810 DOI: 10.3748/wjg.v21.i23.7233]
 - 64 **Sung J**, Ho KY, Chiu HM, Ching J, Travis S, Peled R. The use of Pillcam Colon in assessing mucosal inflammation in ulcerative colitis: a multicenter study. *Endoscopy* 2012; **44**: 754-758 [PMID: 22696193 DOI: 10.1055/s-0032-1309819]
 - 65 **Ye CA**, Gao YJ, Ge ZZ, Dai J, Li XB, Xue HB, Ran ZH, Zhao YJ. PillCam colon capsule endoscopy versus conventional colonoscopy for the detection of severity and extent of ulcerative colitis. *J Dig Dis* 2013; **14**: 117-124 [PMID: 23134295 DOI: 10.1111/1751-2980.12005]
 - 66 **Hosoe N**, Matsuoka K, Naganuma M, Ida Y, Ishibashi Y, Kimura K, Yoneno K, Usui S, Kashiwagi K, Hisamatsu T, Inoue N, Kanai T, Imaeda H, Ogata H, Hibi T. Applicability of second-generation colon capsule endoscope to ulcerative colitis: a clinical feasibility study. *J Gastroenterol Hepatol* 2013; **28**: 1174-1179 [PMID: 23517279 DOI: 10.1111/jgh.12203]
 - 67 **Cave D**, Legnani P, de Franchis R, Lewis BS. ICCE consensus for capsule retention. *Endoscopy* 2005; **37**: 1065-1067 [PMID: 16189792 DOI: 10.1055/s-2005-870264]
 - 68 **Mitsui K**, Fujimori S, Tanaka S, Ehara A, Omori J, Akimoto N, Maki K, Suzuki M, Kosugi Y, Ensaka Y, Matsuura Y, Kobayashi T, Yonezawa M, Tatsuguchi A, Sakamoto C. Retrieval of Retained Capsule Endoscopy at Small Bowel Stricture by Double-Balloon Endoscopy Significantly Decreases Surgical Treatment. *J Clin Gastroenterol* 2016; **50**: 141-146 [PMID: 25930974 DOI: 10.1097/MCG.0000000000000335]
 - 69 **Nemeth A**, Kopylov U, Koulaouzidis A, Wurm Johansson G, Thorlacius H, Amre D, Eliakim R, Seidman EG, Toth E. Use of patency capsule in patients with established Crohn's disease. *Endoscopy* 2016; **48**: 373-379 [PMID: 26561918 DOI: 10.1055/s-0034-1393560]
 - 70 **Panes J**, Bouhnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, Danese S, Halligan S, Marincek B, Matos C, Peyrin-Biroulet L, Rimola J, Rogler G, van Assche G, Ardizzone S, Ba-Ssalamah A, Bali MA, Bellini D, Biancone L, Castiglione F, Ehehalt R, Grassi R, Kucharzik T, Maccioni F, Maconi G, Magro F, Martín-Comín J, Morana G, Pendsé D, Sebastian S, Signore A, Tolan D, Tielbeek JA, Weishaupt D, Wiarda B, Laghi A. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis* 2013; **7**: 556-585 [PMID: 23583097 DOI: 10.1016/j.crohns.2013.02.020]
 - 71 **Herreras JM**, Leighton JA, Costamagna G, Infantolino A, Eliakim R, Fischer D, Rubin DT, Manten HD, Scapa E, Morgan DR, Bergwerk AJ, Koslowsky B, Adler SN. Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. *Gastrointest Endosc* 2008; **67**: 902-909 [PMID: 18355824 DOI: 10.1016/j.gie.2007.10.063]
 - 72 **Assadsangabi A**, Blakeborough A, Drew K, Lobo AJ, Sidhu R, McAlindon ME. Small bowel patency assessment using the patency device and a novel targeted (limited radiation) computed tomography-based protocol. *J Gastroenterol Hepatol* 2015; **30**: 984-989 [PMID: 25594338 DOI: 10.1111/jgh.12891]
 - 73 **Al-Bawardy B**, Rajan E, Hansel S. A rare case of rapid patency capsule disintegration. *Am J Gastroenterol* 2015; **110**: 603-604 [PMID: 25853206 DOI: 10.1038/ajg.2015.25]

- 74 **Liatsos C**, Kyriakos N, Panagou E, Karagiannis S, Giakoumis M, Kalafatis E, Mavrogiannis C. An unusual presentation of obstructive ileus, due to impacted Agile® patency capsule, in a patient with Crohn's disease. *Ann Gastroenterol* 2011; **24**: 65-66 [PMID: 24714251]
- 75 **Okoli A**, Ammannagari N, Mazumder M, Nakkala K. When the dissolvable does not dissolve: an agile patency capsule mystery. *Am J Gastroenterol* 2014; **109**: 605-607 [PMID: 24698874 DOI: 10.1038/ajg.2013.435]
- 76 **Yadav A**, Heigh RI, Hara AK, Decker GA, Crowell MD, Gurudu SR, Pasha SF, Fleischer DE, Harris LA, Post J, Leighton JA. Performance of the patency capsule compared with nonenteroclysis radiologic examinations in patients with known or suspected intestinal strictures. *Gastrointest Endosc* 2011; **74**: 834-839 [PMID: 21839995 DOI: 10.1016/j.gie.2011.05.038]
- 77 **Van de Bruaene C**, De Looze D, Hindryckx P. Small bowel capsule endoscopy: Where are we after almost 15 years of use? *World J Gastrointest Endosc* 2015; **7**: 13-36 [PMID: 25610531 DOI: 10.4253/wjge.v7.i1.13]
- 78 **Lucendo AJ**, González-Castillo S, Fernández-Fuente M, De Rezende LC. Tracheal aspiration of a capsule endoscope: a new case report and literature compilation of an increasingly reported complication. *Dig Dis Sci* 2011; **56**: 2758-2762 [PMID: 21409372 DOI: 10.1007/s10620-011-1666-2]

P- Reviewer: Otowa Y, Toth E **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL



Endoscopic full thickness resection for gastric tumors originating from muscularis propria

Deepanshu Jain, Ejaz Mahmood, Aakash Desai, Shashideep Singhal

Deepanshu Jain, Ejaz Mahmood, Department of Internal Medicine, Albert Einstein Medical Center, Philadelphia, PA 19141, United States

Aakash Desai, Shashideep Singhal, Division of Gastroenterology, Hepatology and Nutrition, University of Texas Health Science Center at Houston, Houston, TX 77030, United States

Author contributions: Jain D contributed to literature review, interpretation of data and drafting of the manuscript; Mahmood E contributed in acquisition of data, interpretation of data and drafting of the manuscript; Desai A contributed in acquisition of data; Singhal S contributed to literature review and critical revision of the manuscript for important intellectual content.

Conflict-of-interest statement: None of the authors have any conflicts of interest.

Data sharing statement: Our article is a systematic review and thus it does not apply to our article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Shashideep Singhal, MD, Division of Gastroenterology, Hepatology and Nutrition, University of Texas Health Science Center at Houston, 6431 Fannin, MSB 4.234, Houston, TX 77030, United States. sdsinghal@gmail.com
Telephone: +1-713-5006677
Fax: +1-713-5006699

Received: March 6, 2016
Peer-review started: March 7, 2016
First decision: April 6, 2016
Revised: May 6, 2016
Accepted: May 31, 2016

Article in press: June 2, 2016
Published online: July 25, 2016

Abstract

AIM: To do systematic review of current literature for endoscopic full thickness resection (EFTR) technique for gastric tumors originating from muscularis propria.

METHODS: An extensive English literature search was done till December 2015; using PubMed and Google scholar to identify the peer reviewed original and review articles using keywords-EFTR, gastric tumor, muscularis propria. Human only studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered. For the purpose of review, data from individual studies was combined to calculate mean. No other statistical test was applied.

RESULTS: A total of 9 original articles were identified. Four articles were from same institute and the time frames of these studies were overlapping. To avoid duplication of data, only the study with patients over the longest time interval was included and other three were excluded. In total six studies were included in the final review. In our systematic review, the mean success rate for EFTR of gastric tumors originating from muscularis propria was 96.8%. The mean procedure time varied from a minimum of 37 min to a maximum of 105 min. There was no reported mortality from the technique itself. The most common histological diagnosis was gastrointestinal stromal tumors and leiomyoma. Gastric wall defect closure by either metallic clips or over the scope clip (OTSC) had similar outcomes although experience with OTSC was limited to smaller lesions (< 3 cm).

CONCLUSION: EFTR is a minimally invasive technique to resect gastric submucosal tumors originating from muscularis propria with a high success rate and low complication rate.

Key words: Endoscopic full thickness resection; Gastric tumor; Muscularis propria; Over the scope clip

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic submucosal dissection success for gastric submucosal tumors arising from muscularis propria has remained limited. Authors have reported success with endoscopic full thickness resection (EFTR) in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications. EFTR seems to be a reasonable replacement for laparoscopic technique for this subset of patients. Careful selection of candidates by preoperative imaging and endoscopy including endoscopic ultrasound to rule out metastatic disease and to confirm the size and location of lesion remains crucial.

Jain D, Mahmood E, Desai A, Singhal S. Endoscopic full thickness resection for gastric tumors originating from muscularis propria. *World J Gastrointest Endosc* 2016; 8(14): 489-495 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i14/489.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i14.489>

INTRODUCTION

Over the last decade, therapeutic options for gastric submucosal tumor (SMT) resection have drastically evolved. Gastric SMTs are mostly asymptomatic when small (< 2 cm) and are discovered incidentally on endoscopy or radiological investigations done for other indications but larger lesions are more likely to be symptomatic^[1]. The usual symptoms are bleeding, abdominal pain or obstruction. Abdominal mass and weight loss may be present especially if malignant^[2].

Gastrointestinal SMTs can be broadly classified in 4 main groups - gastrointestinal stromal tumors (GIST) which should be considered potentially malignant; smooth muscle derived SMTs like leiomyoma, leiomyosarcoma; SMTs of neurogenic origin like schwannoma, granular cell tumor, neurofibroma and vascular tumors like hemangioma, lymphangioma, kaposi sarcoma, etc^[3]. GISTs are further classified into groups based on their potential of recurrence and metastasis; very low risk, low risk, intermediate risk and high risk or overtly malignant with metastasis at diagnosis^[4]. Most of the tumors arising from muscularis propria are GISTs^[5]. National Comprehensive Cancer Network Guidelines recommend resection of GISTs larger than 2 cm^[6]. Gastric SMTs smaller than 2 cm without clinical

signs of malignancy can be managed conservatively with frequent follow up by endoscopic ultrasonography (EUS)^[7]. However, conservative management is limited by patient's anxiety about diagnosis and follow-up compliance. In addition, EUS cannot differentiate between benign and malignant tumor reliably and EUS-guided fine-needle aspiration is not always accurate since histology is not available^[8]. Due to these reasons some physicians and patients may prefer resection of these tumors over conservative management.

Surgically, gastric SMTs can be resected either by laparoscopic approach or open procedure. However, less invasive endoscopic techniques have been considered and used more often in the last few years. The endoscopic techniques include snare polypectomy or endoscopic submucosal dissection (ESD). Not all SMTs arising from muscularis propria may be luminal to be suitable for snare polypectomy and the success rate for complete resection of tumors originating from muscularis propria by ESD has been reported to vary from 68% to 75%^[9,10]. As tumors from muscularis propria are deep and are associated with risk of perforation and incomplete resection with ESD, newer techniques like full thickness resection followed by endoscopic closure of defect have evolved.

In this review article, we have summarized the studies describing endoscopic full thickness resection (EFTR) of gastric SMTs originating from muscularis propria. Indications, procedure techniques, outcomes and complications reported are discussed.

MATERIALS AND METHODS

An extensive English literature search was done till December 2015; using PubMed and Google scholar to identify the peer reviewed original and review articles using keywords-EFTR, gastric tumor, muscularis propria. Human only studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered.

RESULTS

A total of 9 original articles were identified. Four articles^[11-14] were from same institute and the time frames of these studies were overlapping. Only, the study^[11] which included the patients over the longest time interval was included in our review. Other three were excluded to avoid duplication of data^[12-14]. Out of the final 6 studies included, one was a prospective study^[15] from Germany and other 5 were retrospective studies^[11,16-19] from China. One study^[15] reported results for all gastric sub epithelial tumors. However, we included only those patients from this study who had tumors originating from muscularis propria^[15]. All studies have been summarized in Table 1.

Table 1 Descriptive summary of all studies

Ref. and location	Study type	Inclusion criterion	Exclusion criterion	No. of subjects	No. of lesions	Tumor location	Mean size of lesion (range) (cm)	Mean procedure time (range) (min)	Complications	Success rate (%)	Follow up
Ye <i>et al</i> ^[11] , 2014 China	Retro-spective Single Centre	(1) CT/EUS confirmation of MP origin (2) No extraluminal growth	(1) Size > 3.5 cm (2) Coagulation disorders (3) Unfit for GA (4) High risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci, heterogeneity)	51	51	(1) Fundus = 22 (2) Corpus = 28 (3) Antrum = 1	2.4 (1.3-3.5)	52 (30-125)	None	98	(1) Surveillance endoscopy for healing at 1, 3 and 6 mo PP (2) For GIST = Endoscopy/EUS/abdominal ultrasound/CT/chest radiography every 12 mo, indefinitely
Schlag <i>et al</i> ^[15] , 2013 Germany	Retro-spective Single Centre	(1) Age > 18 yr (2) Confirmed SET originating from MP on EUS	(1) Size > 3.0 cm (2) ASA class 4 or 5 (3) Coagulopathy (4) Pregnancy	EFTR group = 6 Lap group = 5	6 5	(1) Corpus = 4 (2) Antrum = 1 (3) Cardia = 1 (1) Fundus = 1 (2) Corpus = 4	1.3 (0.7-2.0) 1.88 (0.8-2.6)	37.3 (26-45) 55 (30-95)	None None	83.3 80	(1) Telephone interview or outpatient visit at 1 mo PP (2) Endoscopy at 3 mo PP
Feng <i>et al</i> ^[16] , 2014 China	Retro-spective Single Centre	(1) MP originating tumor confirmed on EUS or CT if size > 2.0 cm	(1) Size > 5.0 cm (2) Coagulopathy (3) Patients not suitable for GA	48	52	(1) Fundus = 40 (2) Corpus = 7 (3) Antrum = 1	1.59 (0.50-4.80)	59.72 (30-270)	(1) Abdominal distension = 5	100	(1) Endoscopy at 2, 6, 12 and 24 mo PP
Guo <i>et al</i> ^[17] , 2015 China	Retro-spective Single Centre	(1) CT and EUS confirming origin of tumor from MP	(1) Size > 2.0 cm (2) Enlarged lymph nodes (3) Malignant disease	23	23	(1) Fundus = 11 (2) Corpus = 9 (3) Antrum = 3	1.21 (0.6-2.0)	(1) Mean ETFR time = 40.5 (16-104) (2) Mean closure time = 4.9 (2-12)	(1) Localised peritonitis = 2 (managed conservatively) (2) Post op fever = 4	100	(1) Endoscopy at 1 wk, 1 and 6 mo PP
Wu <i>et al</i> ^[18] , 2015 China	Retro-spective analysis of clinical control study	(1) Single tumor (2) Absence of metastasis	(1) Size > 5.5 cm	EFTR group = 50 Lap group = 42	50 42	(1) Fundus = 14 (2) Corpus = 23 (3) Antrum = 13 (1) Fundus = 8 (2) Corpus = 19 (3) Antrum = 15	3.4 (2.5-5.0) 3.8 (3.0-5.0)	85 (55-155) 88 (45-215)	None (1) Gastroparesis = 2 (managed conservatively)	100 93	(1) Endoscopy at 1 mo PP
Zhou <i>et al</i> ^[19] , 2011 China	Retro-spective Single Centre	(1) MP originating tumors confirmed on EUS	(1) Size > 5.0 cm (2) Patients not fit for GA (3) Known abdominal adhesions	26	26	(1) Fundus = 12 (2) Corpus = 14	2.8 (1.2-4.5)	105 (60-145)	None	100	(1) Endoscopy at 2, 4 and 6 mo PP and then every 6 mo (2) EUS or CT scan was performed if tumor residual or recurrence was suspected

GA: General anesthesia; MP: Muscularis propria; PP: Post procedure; SET: Subepithelial tumor; EFTR: Endoscopic full thickness resection; Lap: Laparoscopic; CT: Computed tomography; EUS: Endoscopic ultrasonography; GIST: Gastrointestinal stromal tumors; ASA: American society of anesthesiologists.

DISCUSSION

Indications

All studies included patients with gastric SMTs originating from the muscularis propria confirmed on pre procedure imaging. Endoscopic EUS was the standard imaging technique used in all the studies to determine the layer of origin and size of tumor. Most studies^[11,17-19] also included computed tomography (CT) imaging to further assess the tumor and look for any metastasis. In one study, CT scan was performed only if the tumor size was > 2.0 cm on EUS^[16]. Small size gastric tumors arising from MP can be either benign or malignant. EUS does not allow definite discrimination of benign from malignant lesions^[20,21]. Even tissue sampling by EUS guided fine needle aspiration, trucut biopsy or other biopsy techniques fails to reliably differentiate between benign and malignant lesions^[22-29]. Hence, the only accurate way is complete resection of the target lesion. Nonetheless, authors from each study have used any potential sign of malignancy like large regional lymph nodes, metastatic disease on CT scan, large tumor size, high risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci or heterogeneity) as an exclusion criteria. In addition, subjects with coagulopathy and those unfit for endotracheal intubation or general anesthesia were also excluded.

The inclusion and exclusion criteria for subjects across each study have been summarized in Table 1.

Technique

Ye *et al*^[11], Feng *et al*^[16], Guo *et al*^[17], Wu *et al*^[18] and Zhou *et al*^[19], used similar technique with little variations to resect the gastric SMTs from muscularis propria. Both single and dual channel endoscopes were used to resect the tumor. Dual chamber endoscope was especially used for the broad based tumors. A transparent cap was applied to the tip of the endoscope to provide a constant endoscopic view during the procedure. The area around the lesion was marked either by needle knife^[11,19] or argon plasma coagulation^[18]. Submucosa in the area around the lesion was injected with a solution containing normal saline, 1% indigo carmine and epinephrine to make dissection easier. A hook knife^[11,16,18], IT knife^[16] or a triangle tipped knife^[17] was used to make incision in mucosa over the tumor. Dissection down to the serosa was done using hook knife and IT knife. Gastric fluid was aspirated and an active perforation was made through with a hook knife or IT knife. The tumor was dissected out *en bloc*. A needle paracentesis was often performed for decompression if there were signs of pneumoperitoneum.

Schlag *et al*^[15] performed EFTR *via* slightly different technique. EFTR was performed under the laparoscopic control in general anesthesia unless contraindicated, in which scenario procedural sedation was used. A 5 mm optic was used for laparoscopic control. A double channel endoscope was used in all cases. The tumor was grasped by the tissue anchor and lifted into the

snare. The snare was secured and resection performed using blended electrosurgical current. Some of the cases developed perforation during resection, which was treated with tissue twin grasper and over the scope clip (OTSC).

Sarker *et al*^[30] attempted EFTR for gastric tumors ($n = 2$, both were less than 2 cm in size) using OTSC. Although the study was excluded from the review secondary to the site of tumor origin (above the level of muscularis propria), the technique used by the author deserves a mention. The target gastric lesion was suctioned into the cap, followed by deployment of OTSC. Following clip application the scope was removed and reintroduced to snare the lesion above the closed clip. In both cases, author was able to achieve tumor free margin but was unable to achieve full thickness resection. With further improvisation, OTSC holds a promising future for achieving EFTR for local gastric tumors. For larger defects post resection two OTSC placed side by side can be helpful^[31].

Closure

It is extremely important and challenging to achieve effective closure of the gastric perforation for the success of procedure to prevent peritonitis and surgical intervention. There were two main methods for gastric defect closure-metal clips^[11,16,18,19] and OTSC^[15,17].

Metal clips have been commonly used to close the gastric wall defect. They can be easily applied when the perforation is small. For wider defects, air suctioning was used to narrow the size of defect and then clips were applied to close the defect^[11,18,19]. In few cases across the studies, omental patch method^[18,19] was used in which the omentum was sucked into the gastric cavity and clips were used to seal the wound by clipping the omentum to the gastric mucosa. This technique is useful especially for larger defects. Ye *et al*^[11] used endoloop to further strengthen the closure with clips. The endoloop was placed to trap all clips, the loop was tightened and all the clips were tied together with a ligature^[11]. The number of clips used for gastric wall closure were higher for the tumors located in the gastric corpus^[16].

OTSC closure system has been used in the past for the treatment of gastrointestinal bleeding, fistulas and perforations. Guo *et al*^[17] and Schlag *et al*^[15] used OTSC system to close the perforation after tumor resection. Gastric tissues adjacent to the perforation were clamped and then drawn into the transparent cap of the OTSC device. The OTSC system was then released to close the defect. Metal clips were used for any remaining perforation. Both closure methods-clips and OTSC have been found to be effective in the studies. OTSC system is simple to use, convenient and quick however the maximum tumor size for which it has been used till now is 3 cm in the study by Schlag *et al*^[15]. The use of OTSC for gastric perforations arising from EFTR of larger gastric SMTs originating from muscularis propria has not yet been reported.

The protocols to check for leak varied in different studies. Contrast roentgenography was routinely conducted on day 3 by Ye *et al.*^[11]. In the study where, EFTR was performed under laparoscopic control, methylene blue was used at the end of the procedure to perform leakage test^[15]. Feng *et al.*^[16] and Guo *et al.*^[17] did not report any routine post op investigations to check for the adequacy of closure. Two other studies reported use of contrast roentgenography on day 3 to check for contrast leakage in addition to abdominal and pelvic ultrasound to check for any fluid collections^[18,19].

As there is no uniform protocol, it needs to be established what type of investigations need to be performed routinely if any.

Procedure time

The mean procedure time varied from a minimum of 37 min^[15] to a maximum of 105 min^[19]. It was noted that EFTR for SMT > 2.0 cm and for gastric corpus located SMTs took longer time^[16]. Schlag *et al.*^[15] who used grasp and snare technique had shorter procedure time as compared to the other studies who used dissection for full thickness resection. Wu *et al.*^[18] had a mean time of 85 min for EFTR as compared to 88 min for laparoscopic surgery for gastric SMT originating from muscularis propria. A number of factors including size of tumor, location, technique used and experience of operator may effect the procedure time.

Post op care

The immediate post op care in most studies included GI decompression with nasogastric tube, NPO for 1 to 3 d, Proton Pump Inhibitors and antibiotics. Zhou *et al.*^[19] used hemocoagulase injections in addition to the above mentioned post op management.

Outcome

The success of procedure was considered as the complete resection of the tumor and closure of the perforation endoscopically without the need to convert into surgical operation during or after the procedure. R0 is complete resection of tumor with clear margins microscopically while R1 is macroscopic complete resection but positive margins on histology. In our systematic review, the mean success rate for EFTR of gastric tumors originating from muscularis propria was 96.8%.

Ye *et al.*^[11] reported a success rate of 98% for the 51 patients included in the study. One patient in this study needed laparoscopy to retrieve the tumor as it fell in the peritoneal cavity^[11]. Feng *et al.*^[16] reported a tumor free margin resection rate of 100%. A total of 52 lesions in 48 patients were resected in this study with a mean tumor size of 1.59 cm (0.50-4.80 cm)^[16]. Guo *et al.*^[17] also reported a success rate of 100% for tumor free margins for all 23 lesions. The mean size of the tumor was 1.21 cm (0.6-2.0 cm)^[17]. Wu *et al.*^[18] included 50 patients in their study who had EFTR of SMTs with

a mean size of 3.4 cm (2.0-5.0 cm) and 42 patients who had laparoscopic procedure for gastric SMTs with a mean size of 3.8 cm (3.0-5.0 cm). They reported a success rate of 100% for EFTR as compared to 93% for laparoscopic resection. In 3/42 patients, the laparoscopic procedure needed to be converted to laparotomy due to the location of the tumors^[18]. Zhou *et al.*^[19] also achieved a success rate of 100% for their 26 patients with a mean tumor size of 2.8 cm (1.2-4.5 cm). Schlag *et al.*^[15] who performed grasp and snare technique had 20 patients in their study. Eleven out of 20 patients had muscularis propria originating tumors with mean size of 1.56 cm (0.7-2.6 cm). In 5/11 patients, a pure endoscopic approach appeared impossible and a switch to laparoscopic gastric wedge resection was made. The main reasons were extraluminal growth and large size. So endoscopic resection was performed in 6/11 patients. Of these 6 patients, R0 resection was achieved in 5/6 patients (83.3%) and R1 in 1/6. R0 resection rate in laparoscopic group was 80% (4/5 patients). One patient had acute myeloid leukemia (AML) and histology showed diffuses infiltration of AML recurrence in gastric wall. Routine CT scanning in the pre procedure workup was not included in the protocol of this study. The high conversion rate to laparoscopy due to location and size of tumor may suggest the need of extensive pre procedure imaging to better define the size and location of the tumor to plan the resection modality.

Complications

Most studies^[11,15,18,19] did not report any major complications and the post procedure recovery was unremarkable. Feng *et al.*^[16] reported abdominal distension in 5 patients. It was relieved with paracentesis in 3 patients and resolved in 2 d in the rest of the patients. Guo *et al.*^[17] reported post op fever in 4 patients and localised peritonitis in 2 patients, which was managed conservatively. Overall, the complication rate was low with no mortality and no major complications.

Histopathology

The most common diagnosis was GIST and leiomyoma. Out of 51 total lesions, Ye *et al.*^[11] found 30 lesions to be GIST (7 - very low risk and 23 - low risk) and 21 to be leiomyoma. Schlag *et al.*^[15] removed 11 tumors arising from muscularis propria. The histopathologic examination showed GIST in 4, ectopic pancreas in 2, lipoma in 1, accessory spleen in 1, leiomyoma in 1, angioma in 1 and acute myeloid infiltration in 1 specimen. Feng *et al.*^[16] reported a diagnosis of GIST in 43 patients (29 - benign; 8 - very low risk and 6 - low risk), leiomyoma in 4 and schwannoma in 1. In the study by Guo *et al.*^[17] the histology of 23 cases revealed GISTs in 19 (18 - very low risk and 1 - high risk) and Leiomyoma in 4 cases. Zhou *et al.*^[19] resected 26 lesions. Of these 16 were GIST (2 - benign; 12 - low risk; 2 - malignant), 6 were leiomyoma, 3 were glomus tumor and 1 was schwannoma.

GISTs can be malignant but imaging techniques including EUS and CT scan cannot reliably estimate the malignant potential. Thus, resection of these gastric SMTs with minimal invasive techniques is necessary to make a histological diagnosis and estimate risk of malignancy without increasing the morbidity.

Follow up

All authors performed upper GI endoscopy on follow up visits, however timing varied across the studies^[11,15-19]. None of the authors reported any recurrence on the follow up visits. Currently, there is no uniform agreed follow up protocol after EFTR of gastric SMTs arising from muscularis propria. Although endoscopy alone is used in all studies for follow up, there may be a role of EUS to detect recurrence in deeper layers, which may be missed on routine endoscopy.

ESD success for gastric SMTs arising from muscularis propria has remained limited. Incomplete resection and high incidence of perforation seen with ESD is likely secondary to deep location of the tumor. Authors have reported success with EFTR in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications. EFTR seems to be a reasonable replacement for laparoscopic technique for this subset of gastric SMTs. Careful selection of candidates by preoperative imaging and endoscopy including EUS to rule out metastatic disease and to confirm the size and location of lesion remains crucial. Gastric wall defect closure by either metallic clips or OTSC had similar outcomes although experience with OTSC was limited to smaller lesions (< 3 cm). Post resection follow up by EUS in addition to endoscopy is contemplated. The overall evidence for EFTR for gastric SMTs originating from muscularis propria is small but promising and more experience is awaited.

COMMENTS

Background

Minimally invasive resection of local gastric lesions has remained a challenge for endoscopists. Over the last decade, newer techniques like endoscopic mucosal resection (EMR), piecemeal EMR (EMR), endoscopic submucosal dissection (ESD) have come up.

Research frontiers

For subset of gastric tumors originating from muscularis propria, the success of ESD remains limited due to deeper location resulting in incomplete resection and increased incidence of perforation. Endoscopic full thickness resection (EFTR) seems to have overcome these pitfalls.

Innovations and breakthroughs

Authors have reported high success rate with EFTR in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications.

Applications

EFTR seems to be a reasonable replacement for laparoscopic technique for resection of gastric submucosal tumors. Careful selection of candidates by

preoperative imaging and endoscopy including endoscopic ultrasonography to rule out metastatic disease and to confirm the size and location of lesion remains crucial.

Terminology

EFTR is a minimally invasive method for *en bloc* resection of gastrointestinal lesions.

Peer-review

This is a good summarization of classification and option of therapeutic method of submucosal tumors (SMTs). The necessity of EFTR for SMTs is convincing and the outcome of EFTR is satisfactory and promising.

REFERENCES

- 1 Ludwig DJ, Traverso LW. Gut stromal tumors and their clinical behavior. *Am J Surg* 1997; **173**: 390-394 [PMID: 9168073 DOI: 10.1016/S0002-9610(97)00064-0]
- 2 Nishida T, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. *Dig Endosc* 2013; **25**: 479-489 [PMID: 23902569 DOI: 10.1111/den.12149]
- 3 Ponsaing LG, Kiss K, Hansen MB. Classification of submucosal tumors in the gastrointestinal tract. *World J Gastroenterol* 2007; **13**: 3311-3315 [PMID: 17659669 DOI: 10.3748/wjg.v13.i24.3316]
- 4 Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer* 2005; **103**: 821-829 [PMID: 15648083 DOI: 10.1002/cncr.20862]
- 5 Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005; **29**: 52-68 [PMID: 15613856 DOI: 10.1097/01.pas.0000146010.92933.de]
- 6 Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetz S, Sundar HM, Trent JC, Wayne JD. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 2010; **8** Suppl 2: S1-S41; quiz S42-S44 [PMID: 20457867]
- 7 Sato T, Peiper M, Fritscher-Ravens A, Gocht A, Soehendra N, Knoefel WT. Strategy of treatment of submucosal gastric tumors. *Eur J Med Res* 2005; **10**: 292-295 [PMID: 16055400]
- 8 Sakamoto H, Kitano M, Kudo M. Diagnosis of subepithelial tumors in the upper gastrointestinal tract by endoscopic ultrasonography. *World J Radiol* 2010; **2**: 289-297 [PMID: 21160683 DOI: 10.4329/wjr.v2.i8.289]
- 9 Bialek A, Wiechowska-Kozłowska A, Pertkiewicz J, Polkowski M, Milkiewicz P, Karpińska K, Ławniczak M, Starzyńska T. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). *Gastrointest Endosc* 2012; **75**: 276-286 [PMID: 22032850 DOI: 10.1016/j.gie.2011.08.029]
- 10 Lee IL, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. *Endoscopy* 2006; **38**: 1024-1028 [PMID: 17058168 DOI: 10.1055/s-2006-944814]
- 11 Ye LP, Yu Z, Mao XL, Zhu LH, Zhou XB. Endoscopic full-thickness resection with defect closure using clips and an endoloop for gastric subepithelial tumors arising from the muscularis propria. *Surg Endosc* 2014; **28**: 1978-1983 [PMID: 24619327 DOI: 10.1007/s00464-014-3421-1]
- 12 Huang LY, Cui J, Wu CR, Zhang B, Jiang LX, Xian XS, Lin SJ, Xu N, Cao XL, Wang ZH. Endoscopic full-thickness resection and laparoscopic surgery for treatment of gastric stromal tumors. *World J Gastroenterol* 2014; **20**: 8253-8259 [PMID: 25009400 DOI: 10.3748/wjg.v20.i25.8253]

- 13 **Huang LY**, Cui J, Lin SJ, Zhang B, Wu CR. Endoscopic full-thickness resection for gastric submucosal tumors arising from the muscularis propria layer. *World J Gastroenterol* 2014; **20**: 13981-13986 [PMID: 25320536 DOI: 10.3748/wjg.v20.i38.13981]
- 14 **Zhang B**, Huang LY, Wu CR, Cui J, Jiang LX, Zheng HT. Endoscopic full-thickness resection of gastric stromal tumor arising from the muscularis propria. *Chin Med J (Engl)* 2013; **126**: 2435-2439 [PMID: 23823814]
- 15 **Schlag C**, Wilhelm D, von Delius S, Feussner H, Meining A. EndoResect study: endoscopic full-thickness resection of gastric subepithelial tumors. *Endoscopy* 2013; **45**: 4-11 [PMID: 23254401 DOI: 10.1055/s-0032-1325760]
- 16 **Feng Y**, Yu L, Yang S, Li X, Ding J, Chen L, Xu Y, Shi R. Endolumenal endoscopic full-thickness resection of muscularis propria-originating gastric submucosal tumors. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 171-176 [PMID: 24555874 DOI: 10.1089/lap.2013.0370]
- 17 **Guo J**, Liu Z, Sun S, Liu X, Wang S, Ge N, Wang G, Qi Y. Endoscopic full-thickness resection with defect closure using an over-the-scope clip for gastric subepithelial tumors originating from the muscularis propria. *Surg Endosc* 2015; **29**: 3356-3362 [PMID: 25701060 DOI: 10.1007/s00464-015-4076-2]
- 18 **Wu CR**, Huang LY, Guo J, Zhang B, Cui J, Sun CM, Jiang LX, Wang ZH, Ju AH. Clinical Control Study of Endoscopic Full-thickness Resection and Laparoscopic Surgery in the Treatment of Gastric Tumors Arising from the Muscularis Propria. *Chin Med J (Engl)* 2015; **128**: 1455-1459 [PMID: 26021500 DOI: 10.4103/0366-6999.157651]
- 19 **Zhou PH**, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW, Liu JZ. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surg Endosc* 2011; **25**: 2926-2931 [PMID: 21424195 DOI: 10.1007/s00464-011-1644-y]
- 20 **Hwang JH**, Saunders MD, Rulyak SJ, Shaw S, Nietsch H, Kimmey MB. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. *Gastrointest Endosc* 2005; **62**: 202-208 [PMID: 16046979 DOI: 10.1016/S0016-5107(05)01567-1]
- 21 **Karaca C**, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc* 2010; **71**: 722-727 [PMID: 20171632 DOI: 10.1016/j.gie.2009.10.019]
- 22 **Hunt GC**, Smith PP, Faigel DO. Yield of tissue sampling for submucosal lesions evaluated by EUS. *Gastrointest Endosc* 2003; **57**: 68-72 [PMID: 12518134 DOI: 10.1067/mge.2003.34]
- 23 **Cantor MJ**, Davila RE, Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. *Gastrointest Endosc* 2006; **64**: 29-34 [PMID: 16813799 DOI: 10.1016/j.gie.2006.02.027]
- 24 **Hoda KM**, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. *Gastrointest Endosc* 2009; **69**: 1218-1223 [PMID: 19394006 DOI: 10.1016/j.gie.2008.09.045]
- 25 **Ji JS**, Lee BI, Choi KY, Kim BW, Choi H, Huh M, Chung WC, Chae HS, Chung IS. Diagnostic yield of tissue sampling using a bite-on-bite technique for incidental subepithelial lesions. *Korean J Intern Med* 2009; **24**: 101-105 [PMID: 19543487 DOI: 10.3904/kjim.2009.24.2.101]
- 26 **Polkowski M**, Gerke W, Jarosz D, Nasierowska-Guttmejer A, Rutkowski P, Nowecki ZI, Ruka W, Regula J, Butruk E. Diagnostic yield and safety of endoscopic ultrasound-guided trucut [corrected] biopsy in patients with gastric submucosal tumors: a prospective study. *Endoscopy* 2009; **41**: 329-334 [PMID: 19340737 DOI: 10.1055/s-0029-1214447]
- 27 **Mekky MA**, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA, Osman AM, Koshikawa T, Yatabe Y, Bhatia V. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. *Gastrointest Endosc* 2010; **71**: 913-919 [PMID: 20226456 DOI: 10.1016/j.gie.2009.11.044]
- 28 **Philipp M**, Hollerbach S, Gabbert HE, Heikau S, Böcking A, Pomjanski N, Neuhaus H, Frieling T, Schumacher B. Prospective comparison of endoscopic ultrasound-guided fine-needle aspiration and surgical histology in upper gastrointestinal submucosal tumors. *Endoscopy* 2010; **42**: 300-305 [PMID: 20306384 DOI: 10.1055/s-0029-1244006]
- 29 **Fernández-Esparrach G**, Sendino O, Solé M, Pellisé M, Colomo L, Pardo A, Martínez-Pallí G, Argüello L, Bordas JM, Llach J, Ginès A. Endoscopic ultrasound-guided fine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: a randomized crossover study. *Endoscopy* 2010; **42**: 292-299 [PMID: 20354939 DOI: 10.1055/s-0029-1244074]
- 30 **Sarker S**, Gutierrez JP, Council L, Brazelton JD, Kyanam Kabir Baig KR, Mönkemüller K. Over-the-scope clip-assisted method for resection of full-thickness submucosal lesions of the gastrointestinal tract. *Endoscopy* 2014; **46**: 758-761 [PMID: 24830398 DOI: 10.1055/s-0034-1365513]
- 31 **Kirtane T**, Singhal S. Endoscopic closure of iatrogenic duodenal perforation using dual over-the-scope clips. *Gastrointest Endosc* 2016; **83**: 467-468 [PMID: 26284744 DOI: 10.1016/j.gie.2015.08.014]

P- Reviewer: Blevé C, İlhan E, Lee HW, Zhang QS

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL



Splenic artery aneurysm presenting as a submucosal gastric lesion: A case report

Jenny Tannoury, Khalil Honein, Bassam Abboud

Jenny Tannoury, Khalil Honein, Department of Gastroenterology and Hepatology, Hotel Dieu de France Hospital, Faculty of Medicine, Saint-Joseph University, Beirut 16-6830, Lebanon

Bassam Abboud, Department of General Surgery, Hotel Dieu de France Hospital, Faculty of Medicine, Saint-Joseph University, Beirut 16-6830, Lebanon

Author contributions: All authors contributed to the acquisition of data, writing, and revision of this manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Saint Joseph University.

Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Bassam Abboud, MD, Department of General Surgery, Hotel Dieu de France Hospital, Faculty of Medicine, Saint-Joseph University, Alfred Naccache Street, Beirut 16-6830, Lebanon. dbabboud@yahoo.fr
Telephone: +961-1-15300
Fax: +961-1-615295

Received: March 18, 2016

Peer-review started: March 21, 2016

First decision: May 17, 2016

Revised: May 23, 2016

Accepted: June 14, 2016

Article in press: June 16, 2016

Published online: July 25, 2016

Abstract

We are reporting the rare case of splenic artery aneurysm of 4 cm of diameter presenting as a sub mucosal lesion on gastro-duodenal endoscopy. This aneurysm was treated by endovascular coil embolization and stent graft implantation. The procedure was uneventful. On day 1, the patient presented an acute severe epigastric pain and cardiovascular arrest. Abdominal computed tomography scan showed an active leak of the intravenous contrast dye in the peritoneum from the splenic aneurysm. We performed an emergent resection of the aneurysm, and peritoneal lavage. Postoperatively, hemorrhagic choc was refractory to large volumes replacement, and intravenous vaso-active drugs. On day 2, he presented massive hematochezia. We performed a total colectomy with splenectomy and cholecystectomy for ischemic colitis, with spleen and gallbladder infarction. Despite vaso-active drugs and aggressive treatment with Factor VIIa, the patient died after uncontrolled disseminated intravascular coagulation.

Key words: Gastroscopy; Splenic artery aneurysm; Rupture; Endo-vascular treatment; Surgery

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Recently, a per-cutaneous endovascular embolization procedure has become the first-line treatment for splenic artery aneurysm. This rare presentation, in this case, as sub-mucosal gastric lesion and bleeding after embolization of the aneurysm showed the gravity of this entity when the diameter of aneurysm is > 2 cm. Although the risk of rupture is low, ruptured splenic artery aneurysm carry a high mortality rate.

Tannoury J, Honein K, Abboud B. Splenic artery aneurysm presenting as a submucosal gastric lesion: A case report. *World J Gastrointest Endosc* 2016; 8(14): 496-500 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i14/496.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i14.496>

INTRODUCTION

Splenic artery aneurysms (SAA) are a rare clinical entity that carry the risk of rupture and fatal hemorrhage (particularly those sized > 2 cm). SAA accounts for up to 60% of all splanchnic artery aneurysms and is the third most common intra-abdominal aneurysm following those of the aorta and the iliac arteries^[1-7]. The diagnosis is often incidental on abdominal radiologic exams^[7-12]. Symptomatic SAA (20%) may present with abdominal pain in the epigastrium or left upper quadrant. A more dramatic mode of presentation is spontaneous rupture of the aneurysm which is reported to occur in 2%-10% of patients as the initial presentation^[1-12]. We report here a case of an 82-year-old man with SAA presenting as a sub mucosal lesion on upper gastro-duodenal endoscopy. We will discuss diagnosis tools of SAA, management and potential complications.

CASE REPORT

An 82-year-old male patient with a history of hypertension and smoking presented with vague epigastric pain. General physical examination was unremarkable. All labs were within normal limits. He underwent a diagnostic upper gastro-intestinal endoscopy and it showed a 5-cm firm non pulsating submucosal lesion in the fundus suggesting gastrointestinal stromal tumor (GIST) (Figure 1). Endoscopic ultrasound was then performed to characterize the sub mucosal lesion and to perform biopsies. It showed a round anechoic cystic mass measuring 3.5 cm in diameter, communicating with the splenic vessels and showing positive flow on Doppler ultrasound, suggesting a splenic artery aneurysm. Abdominal enhanced computed tomography (CT) scan and angioscan revealed a dilated and tortuous course of the splenic artery with a first saccular aneurysm of 20 mm of diameter behind the stomach lesser curvature, and a second saccular aneurysm of 43 mm of diameter projecting into the stomach (Figure 2). *Via* a femoral artery catheterization, the patient underwent an endovascular coil embolization and stent graft implantation to treat the aneurysms. The angiographic series taken after the procedure was satisfactory. The procedure was uneventful, and the patient was hemodynamically stable for the first few hours after endovascular repair. On day 1 post embolization, the patient presented an acute severe epigastric pain with rapid drop in arterial pressure and cardiovascular arrest. He was successfully resuscitated and intubated. An urgent abdominal enhancing CT scan revealed active

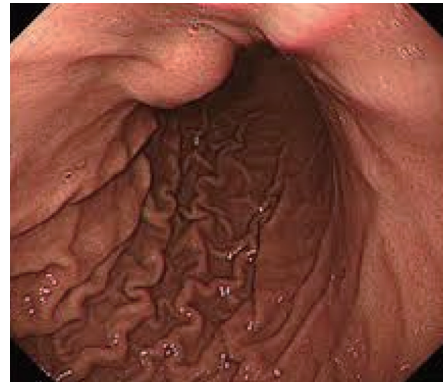


Figure 1 Gastrodudenal endoscopy showing a 5-cm firm non pulsating sub mucosal lesion in the fundus.

extravasation of the intravenous contrast dye in the peritoneum from the splenic aneurysm confirming the diagnosis of ongoing peritoneal bleeding (Figure 3). We performed an emergent laparotomy with resection of the aneurysm, and peritoneal lavage. The patient is transferred to the intensive care unit. His hemorrhagic choc was refractory to large volumes of isotonic saline, multiple transfusions of packed red blood cells, fresh frozen plasma, platelets, and intravenous vaso-active drugs. On day 2, he presented massive hematochezia. A second laparotomy revealed an extensive ischemic colitis, with spleen and gallbladder infarction, as well as some hypo-perfused regions of the small intestine. We performed a total colectomy with splenectomy and cholecystectomy. Despite vaso-active drugs and aggressive treatment with Factor VIIa, the patient died after uncontrolled disseminated intravascular coagulation.

DISCUSSION

SAA diagnosis is nearly always a fortuitous discovery by abdominal imaging (CT scan and ultrasound). In our case, the initial presentation was a sub-mucosal non pulsatile lesion detected on an upper gastro-duodenal endoscopy. At our knowledge, this type of presentation has not been described in the literature. Endoscopic ultrasound was initially done with the purpose of performing a fine needle aspiration of the lesion, thought to be a gastric sub-mucosal tumor as GIST. However, the positive Doppler flow detected shifted the diagnosis to a vascular lesion instead of a sub-mucosal tumor, and therefore fine needle aspiration was not performed. The prevalence of SAA is reported to be 0.1%-2%; however, the number of undetected SAAs may be much higher. The clinical presentation is nonspecific in most cases, and the diagnosis of SAA is often an incidental finding^[5]. SAAs account for up to 75% of all visceral artery aneurysms and are more commonly reported in female patients than in male patients at a ratio of 4:1. Why SAAs predominate in women is not exactly clear, but a hormonal contribution has been postulated^[13]. The pathophysiology of SAA is not fully understood,

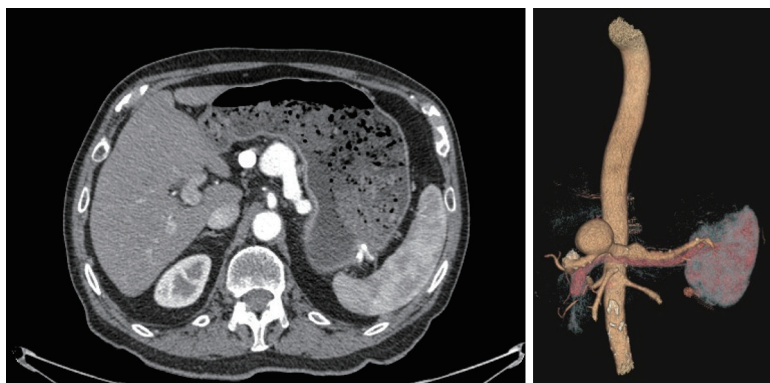


Figure 2 Abdominal enhanced computed tomography scan and angioscan showing a double aneurysm of splenic artery.



Figure 3 Abdominal enhanced computed tomography scan showing a peritoneal leak of contrast material from splenic aneurysm.

but local failure of the connective tissue of the arterial wall to maintain the integrity of the blood vessel could be playing a major role. Multiple risk factors have been listed including atherosclerosis, autoimmune diseases, collagen vascular diseases, pancreatitis, portal hypertension, traumatism, fibromuscular dysplasia, female gender, and history of multiple pregnancies^[11-16]. Nearly 70% of the SAA are saccular and situated at splenic hilum bifurcation^[6]. Although the risk of rupture is low (nearly 2% of cases), ruptured SAA carry a high mortality rate, approaching 50%. Risk factors for rupture of the aneurysms include pregnancy, development of symptoms, expanding aneurysms, a diameter greater than 2 cm, portal hypertension, porto-caval shunt and liver transplantation^[1,3,5,7,12]. Therefore, patients having one or more risk factor should undergo active treatment. Once the diagnosis of SAA is made, the essential goal of the physician remains to choose the adequate patient to treat as well as the right timing of any intervention. It is the general consensus that symptomatic SAA should be treated immediately, since rupture is associated with a high mortality rate. According to the guidelines, treatment is suggested for SAA with diameters > 2 cm or if the SAA is three times greater in diameter than the respective normal artery^[5]. To treat symptoms and prevent complications, SAA repair is often required^[4]. Various therapeutic options are available for patients with SAA, including conventional open surgery, endovascular

treatment and, most recently, laparoscopic surgery^[17-26]. Endovascular techniques (EV), including trans-catheter embolization and covered stent placement, can be used to treat most SAA regardless of the clinical presentation, etiology, or location of the aneurysm. If endovascular treatment is technically unavoidable, surgery should be considered given both good results and low morbidity. Open surgical treatment has traditionally been performed. The surgical procedures included ligation of the splenic artery, resection of the aneurysm and vascular reconstruction and/or bypass, and resection of the aneurysm with splenectomy. Complications rate of surgical treatment of non-ruptured aneurysm was 14.3%, and reached 25% in case with rupture^[5]. The 30-d mortality rate of surgical treatment was 2.6% in non-ruptured aneurysm and 20.4% in rupture cases^[13]. Recently, a per-cutaneous endovascular embolization procedure has become the first-line treatment for SAA. Packing of the aneurysmal sac with embolic agents (most commonly with coils, but also with detachable balloons and inert particles) and exclusion of the aneurysmal neck are the recommended techniques for treating splenic artery aneurysms. In our case, the patient had a 4 cm aneurysm and he was therefore treated with coil embolization and stent graft placement. Although trans-catheter arterial embolization (TAE) is associated with significantly lower morbidity and mortality than are surgical procedures, the possibility of organ ischemia or hemorrhagic events should not be underestimated. The success rate of TAE varies between 75% and 100%, with complication rate (aneurysm re-permeabilization, hemorrhage) ranging from 14% to 25%. The most common complications include acute pancreatitis, splenic infarction, splenic abscess, or intra-peritoneal hemorrhage. In case of an intra-peritoneal hemorrhage with hemodynamic instability, emergent laparotomy with resection of the aneurysm is the treatment of choice, with, however, high morbidity and mortality rate^[5]. EV is the most cost-effective treatment for most patient groups with SAAs, independent of the sex and risk profile of the patient. EV is superior over OPEN in costs and effect for all age groups^[4]. The results of meta-analysis show that EV of SAA has better short-term results than OPEN. However, OPEN is associated with fewer late complications and re-interventions during

follow-up. The results of this meta-analysis show that SAAs > 2 cm should be treated, given the good short-term and long-term results. EV repair has the best outcomes and should be the treatment of choice if the splenic artery has a suitable anatomy for EV repair^[13]. In our case, the patient had peritoneal hemorrhage at day 1 post embolization requiring emergent laparotomy. Despite aggressive treatment, the patient died after uncontrolled disseminated intravascular coagulation. In a large cohort evaluating prognostic factors associated with the clinical outcomes after TAE, multivariate analysis confirmed advanced patient age, post procedure thrombocytopenia, post procedure hydrothorax, and the need for a second intervention to be significant prognostic factors for overall 30-d morbidity^[13]. In our case, the patient's advanced age and the need for a second intervention after TAE were two prognostic factors associated with high short term morbidity and mortality.

In conclusion, SAA may be incidentally discovered on an upper gastro-duodenal endoscopy as a sub-mucosal lesion of the stomach. Caution must be made in order not to perform biopsies or fine needle aspiration to such lesions before checking for Doppler flow on endoscopic ultrasound. Treatment of choice for SAA of more than 2 cm of diameter is trans-catheter arterial embolization with a complication rate of around 20%. Intra-peritoneal hemorrhage after EV for SAA carry a high mortality rate despite emergent laparotomy and aggressive medical treatment.

COMMENTS

Case characteristics

An 82-year-old male patient with a history of hypertension and smoking presented with vague epigastric pain.

Clinical diagnosis

General physical examination was unremarkable.

Differential diagnosis

Gastrointestinal stromal tumor, pancreatic mass, gastric tumor.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Upper endoscopy showed a 5-cm firm non pulsating submucosal lesion in the fundus, and computed tomography showed two splenic artery aneurysms (SAAs).

Treatment

Endovascular coil embolization and stent graft implantation, and surgical excision.

Related reports

SAAs are a rare clinical entity that carry the risk of rupture and fatal hemorrhage (particularly those sized > 2 cm). The diagnosis is often incidental on abdominal radiologic exams. Symptomatic SAA (20%) may present with abdominal pain in the epigastrium or left upper quadrant. A more dramatic mode of presentation is spontaneous rupture of the aneurysm which is reported to occur in 2%-10% of

patients as the initial presentation.

Experiences and lessons

SAA may be incidentally discovered on an upper gastro-duodenal endoscopy as a sub-mucosal lesion of the stomach. Caution must be made in order not to perform biopsies or fine needle aspiration to such lesions before checking for Doppler flow on endoscopic ultrasound.

Peer-review

The case is well presented though the language needs to be refined a little. It would be prudent if the authors elaborate a bit on the treatment options including operative mortality (elective vs emergent) and success rates of radiological interventions.

REFERENCES

- 1 **Al-Habbal Y**, Christophi C, Muralidharan V. Aneurysms of the splenic artery - a review. *Surgeon* 2010; **8**: 223-231 [PMID: 20569943 DOI: 10.1016/j.surge.2009.11.011]
- 2 **Pasha SF**, Gloviczki P, Stanson AW, Kamath PS. Splanchnic artery aneurysms. *Mayo Clin Proc* 2007; **82**: 472-479 [PMID: 17418076 DOI: 10.4065/82.4.472]
- 3 **Akbulut S**, Otan E. Management of Giant Splenic Artery Aneurysm: Comprehensive Literature Review. *Medicine* (Baltimore) 2015; **94**: e1016 [PMID: 26166071 DOI: 10.1097/MD.0000000000001016]
- 4 **Hogendoorn W**, Lavidia A, Hunink MG, Moll FL, Geroulakos G, Muhs BE, Sumpio BE. Cost-effectiveness of endovascular repair, open repair, and conservative management of splenic artery aneurysms. *J Vasc Surg* 2015; **61**: 1432-1440 [PMID: 25827968 DOI: 10.1016/j.jvs.2014.12.064]
- 5 **Pitton MB**, Dappa E, Jungmann F, Kloeckner R, Schotten S, Wirth GM, Mittler J, Lang H, Mildenerberger P, Kreitner KF, Oberholzer K, Dueber C. Visceral artery aneurysms: Incidence, management, and outcome analysis in a tertiary care center over one decade. *Eur Radiol* 2015; **25**: 2004-2014 [PMID: 25693662 DOI: 10.1007/s00330-015-3599-1]
- 6 **Telfah MM**. Splenic artery aneurysm: pre-rupture diagnosis is life saving. *BMJ Case Rep* 2014; **2014**: pii: bcr2014205115 [PMID: 25427929 DOI: 10.1136/bcr-2014-205115]
- 7 **Frasnelli A**. Successful resuscitation after splenic artery aneurysm rupture. *J Emerg Trauma Shock* 2016; **9**: 38-39 [PMID: 26957826 DOI: 10.4103/0974-2700.173863]
- 8 **Tétreau R**, Beji H, Henry L, Valette PJ, Pilleul F. Arterial splanchnic aneurysms: Presentation, treatment and outcome in 112 patients. *Diagn Interv Imaging* 2016; **97**: 81-90 [PMID: 26292616 DOI: 10.1016/j.diii.2015.06.014]
- 9 **Liu B**, Zhou L, Liu M, Xie X. Giant peripancreatic artery aneurysm with emphasis on contrast-enhanced ultrasound: report of two cases. *J Med Ultrason* (2001) 2015; **42**: 103-108 [PMID: 26578497 DOI: 10.1007/s10396-014-0572-6]
- 10 **Lo WL**, Mok KL. Ruptured splenic artery aneurysm detected by emergency ultrasound-a case report. *Crit Ultrasound J* 2015; **7**: 26 [PMID: 26069053 DOI: 10.1186/s13089-015-0026-4]
- 11 **Badour S**, Mukherji D, Faraj W, Haydar A. Diagnosis of double splenic artery pseudoaneurysm: CT scan versus angiography. *BMJ Case Rep* 2015; **2015**: pii: bcr2014207014 [PMID: 25920735 DOI: 10.1136/bcr-2014-207014]
- 12 **Wang CX**, Guo SL, Han LN, Jie Y, Hu HD, Cheng JR, Yu M, Xiao YY, Yin T, Chu FT, Liang FQ. Computed Tomography Angiography in Diagnosis and Treatment of Splenic Artery Aneurysm. *Chin Med J (Engl)* 2016; **129**: 367-369 [PMID: 26831243 DOI: 10.4103/0366-6999.174506]
- 13 **Hogendoorn W**, Lavidia A, Hunink MG, Moll FL, Geroulakos G, Muhs BE, Sumpio BE. Open repair, endovascular repair, and conservative management of true splenic artery aneurysms. *J Vasc Surg* 2014; **60**: 1667-76.e1 [PMID: 25264364 DOI: 10.1016/j.jvs.2015.08.052]
- 14 **Parrish J**, Maxwell C, Beecroft JR. Splenic Artery Aneurysm in

- Pregnancy. *J Obstet Gynaecol Can* 2015; **37**: 816-818 [PMID: 26605452 DOI: 10.1016/S1701-2163(15)30153-5]
- 15 **Velupillai C**, Perre S, de Kerviler B, Ducarme G. Splenic arterial aneurysm and pregnancy: A review. *Presse Med* 2015; **44**: 991-994 [PMID: 26404648 DOI: 10.1016/j.lpm.2015.06.009]
- 16 **Corey EK**, Harvey SA, Sauvage LM, Bohrer JC. A case of ruptured splenic artery aneurysm in pregnancy. *Case Rep Obstet Gynecol* 2014; **2014**: 793735 [PMID: 25574408 DOI: 10.1155/2014/793735]
- 17 **Pietrabissa A**, Ferrari M, Berchiolli R, Morelli L, Pugliese L, Ferrari V, Mosca F. Laparoscopic treatment of splenic artery aneurysms. *J Vasc Surg* 2009; **50**: 275-279 [PMID: 19631859 DOI: 10.1016/j.jvs.2009.03.015]
- 18 **Naganuma M**, Matsui H, Koizumi J, Fushimi K, Yasunaga H. Short-term outcomes following elective transcatheter arterial embolization for splenic artery aneurysms: data from a nationwide administrative database. *Acta Radiol Open* 2015; **4**: 2047981615574354 [PMID: 26443101 DOI: 10.1177/2047981615574354]
- 19 **Gaba RC**, Katz JR, Parvinian A, Reich S, Omene BO, Yap FY, Owens CA, Knuttinen MG, Bui JT. Splenic artery embolization: a single center experience on the safety, efficacy, and clinical outcomes. *Diagn Interv Radiol* 2013; **19**: 49-55 [PMID: 22875411 DOI: 10.4261/1305-3825]
- 20 **Zhang W**, Fu YF, Wei PL, E B, Li DC, Xu J. Endovascular Repair of Celiac Artery Aneurysm with the Use of Stent Grafts. *J Vasc Interv Radiol* 2016; **27**: 514-518 [PMID: 26922007 DOI: 10.1016/j.jvir.2015.12.024]
- 21 **Guang LJ**, Wang JF, Wei BJ, Gao K, Huang Q, Zhai RY. Endovascular Treatment of Splenic Artery Aneurysm With a Stent-Graft: A Case Report. *Medicine (Baltimore)* 2015; **94**: e2073 [PMID: 26717355 DOI: 10.1097/MD.0000000000002073]
- 22 **Reed NR**, Oderich GS, Manunga J, Duncan A, Misra S, de Souza LR, Fleming M, de Martino R. Feasibility of endovascular repair of splenic artery aneurysms using stent grafts. *J Vasc Surg* 2015; **62**: 1504-1510 [PMID: 26365664 DOI: 10.1016/j.jvs.2015.07.073]
- 23 **Yoon T**, Kwon T, Kwon H, Han Y, Cho Y. Transcatheter Arterial Embolization of Splenic Artery Aneurysms: A Single-Center Experience. *Vasc Specialist Int* 2014; **30**: 120-124 [PMID: 26217630 DOI: 10.5758/vsi.2014.30.4.120]
- 24 **Jiang R**, Ding X, Jian W, Jiang J, Hu S, Zhang Z. Combined Endovascular Embolization and Open Surgery for Splenic Artery Aneurysm with Arteriovenous Fistula. *Ann Vasc Surg* 2016; **30**: 311.e1-311.e4 [PMID: 26522588 DOI: 10.1016/j.avsg.2015.07.036]
- 25 **Sticco A**, Aggarwal A, Shapiro M, Pratt A, Rissuci D, D'Ayala M. A comparison of open and endovascular treatment strategies for the management of splenic artery aneurysms. *Vascular* 2015 Oct 22; Epub ahead of print [PMID: 26500136 DOI: 10.1177/1708538115613703]
- 26 **Dorigo W**, Pulli R, Azas L, Fargion A, Angiletta D, Pratesi G, Alessi Innocenti A, Pratesi C. Early and Intermediate Results of Elective Endovascular Treatment of True Visceral Artery Aneurysms. *Ann Vasc Surg* 2016; **30**: 211-218 [PMID: 26381325 DOI: 10.1016/j.avsg.2015.06.097]

P- Reviewer: Arora A, Vennarecci G **S- Editor:** Gong ZM

L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 August 10; 8(15): 501-545





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hirotoshi Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hirotoshi Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Pulli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

ORIGINAL ARTICLE

Observational Study

- 501 Performance characteristics of retrograde single-balloon endoscopy: A single center experience

Christian KE, Kapoor K, Goldberg EM

- 508 Sensory characterization of bowel cleansing solutions

Sharara AI, Daroub H, Georges C, Shayto R, Nader R, Chlahoub J, Olabi A

META-ANALYSIS

- 517 Endoscopic submucosal dissection of gastric tumors: A systematic review and meta-analysis

Akintoye E, Obaitan I, Muthusamy A, Akanbi O, Olusunmade M, Levine D

CASE REPORT

- 533 Endoscopic multiple metal stenting for the treatment of enteral leaks near the biliary orifice: A novel effective rescue procedure

Mutignani M, Dioscoridi L, Dokas S, Aseni P, Carnevali P, Forti E, Manta R, Sica M, Tringali A, Pugliese F

- 541 Standardized technique for single-incision laparoscopic-assisted stoma creation

Miyoshi N, Fujino S, Ohue M, Yasui M, Noura S, Wada Y, Kimura R, Sugimura K, Tomokuni A, Akita H, Kobayashi S, Takahashi H, Omori T, Fujiwara Y, Yano M

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 15 August 10, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Chia-Long Lee, MD, Assistant Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hsinchu Cathay General Hospital, Hsinchu 30060, Taiwan

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jin-Xin Kong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herreras Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lei Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
August 10, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Observational Study

Performance characteristics of retrograde single-balloon endoscopy: A single center experience

Kaci E Christian, Karan Kapoor, Eric M Goldberg

Kaci E Christian, Karan Kapoor, Eric M Goldberg, Department of Medicine, Division of Gastroenterology, University of Maryland Medical Center, Baltimore, MD 21201, United States

Author contributions: Christian KE, Kapoor K and Goldberg EM contributed equally to this work; Christian KE collected and analyzed the data and drafted the manuscript; Kapoor K analyzed the data and assisted with drafting the manuscript; Goldberg EM designed and supervised the study.

Institutional review board statement: This study was reviewed and approved by the University of Maryland Medical Center Institutional Review Board. Please see the attached document.

Informed consent statement: All study participants, or their legal guardian, provided informed consent (written or verbal, as appropriate) prior to undergoing the procedures retrospectively described in this study.

Conflict-of-interest statement: Christian, KE and Kapoor K have no conflicts of interest to report. Goldberg EM has served as a consultant for both Olympus and Boston Scientific. Please see the attached signed document.

Data sharing statement: No additional data are available. Please see the attached signed document.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Kaci E Christian, MD, Department of Medicine, Division of Gastroenterology, University of Maryland Medical Center, 21 South Greene Street, Baltimore, MD 21201, United States. kchristian1@medicine.maryland.edu
Telephone: +1-570-3282370

Fax: +1-410-3282977

Received: September 22, 2015

Peer-review started: October 3, 2015

First decision: December 28, 2015

Revised: April 6, 2016

Accepted: May 7, 2016

Article in press: May 9, 2016

Published online: August 10, 2016

Abstract

AIM: To evaluate the technical success, diagnostic yield (DY) and therapeutic potential of retrograde single balloon enteroscopy (rSBE).

METHODS: A retrospective review of 136 rSBE procedures performed at a tertiary academic referral center from January 2006 and September 2013 was completed. Patient characteristics including age, gender and in-patient status were collected. The indication for the procedure was categorized into one of three groups: Obscure gastrointestinal bleeding (GIB), evaluation for Crohn's disease and abnormal imaging. Procedural characteristics including insertion depth (ID), procedure time, concordance with pre-procedural imaging and complications were also recorded. Lastly, DY, defined as the percentage of cases producing either a definitive diagnosis or findings that could explain clinical symptoms and therapeutic yield (TY), defined as the percentage of cases in which a definitive intervention was performed, were determined. Mucosal tattooing and biopsy alone were not included in the TY.

RESULTS: A total of 136 rSBE procedures were identified. Mean patient age was 57.5 (\pm 16.2) years, 67 (49.2%) were male, and 110 (80.9%) procedures were performed on an outpatient basis. Indications for rSBE included GIB in 55 (40.4%), evaluation of inflammatory bowel disease

(IBD) in 29 (21.3%), and imaging suggestive of pathology other than GIB or IBD in 43 (31.6%). Nine (6.6%) rSBEs were performed for other indications. Mean ID was 68.3 (\pm 39.3) cm proximal to the ileocecal valve and mean time to completion was 41.7 (\pm 15.5) min. Overall, 73 (53.7%) cases were diagnostic and 25 (18.4%) cases were therapeutic in which interventions (argon plasma coagulation, stricture dilatation, polypectomy, *etc.*) were performed. Pre-procedural imaging was performed in 88 (64.7%) patients. Endoscopic concordance of positive imaging findings was seen in 31 (35.2%) cases. Follow up data was available in 93 (68.4%) patients; 2 (2.2%) reported post-procedural abdominal pain within 30 d following rSBE. There were no other reported complications.

CONCLUSION: rSBE exhibits an acceptable diagnostic and TY, rendering it a safe and effective procedure for the evaluation and treatment of small bowel diseases.

Key words: Retrograde; Single-balloon; Enteroscopy; Endoscopy

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Disorders of the small intestine account for an increasing number of hospital discharges and aggregate healthcare cost. Single-balloon enteroscopy (SBE) represents a novel approach to diagnose and treat small bowel disease and can be performed *via* the antegrade or retrograde approach. SBE has different performance characteristics depending upon the route chosen, but most studies combine the information. Little data exists on the retrograde approach alone, a notoriously difficult procedure. This study constitutes the largest published cohort to date of retrograde SBE, with a focus on patient and procedural characteristics, diagnostic and therapeutic yield.

Christian KE, Kapoor K, Goldberg EM. Performance characteristics of retrograde single-balloon endoscopy: A single center experience. *World J Gastrointest Endosc* 2016; 8(15): 501-507 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i15/501.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i15.501>

INTRODUCTION

Since its release in 2006, single-balloon endoscopy (SBE) has emerged as a therapeutic option for small bowel lesions visualized by noninvasive tests such as wireless capsule endoscopy. The small bowel can be deeply intubated *via* the antegrade (mouth) or retrograde approach (anus) depending on the probable location of the suspected lesion. The retrograde approach to SBE has been described as more technically challenging than the antegrade approach for multiple reasons, including:

The length and tortuosity of the colon, difficulty traversing the ileocecal valve (ICV) and potential for colonic contents to interfere with the function of the overtube^[1]. Limited data is available on performance metrics of retrograde single-balloon endoscopy (rSBE), such as success, complications, diagnostic yield (DY) and therapeutic yield (TY).

In cases where lesions are diffuse or the exact location of a lesion is not clear, many endoscopists will initially perform antegrade enteroscopy, largely because it is technically easier to perform. The retrograde approach is typically chosen when imaging suggests a very distal small bowel lesion. Other indications for retrograde procedures include a non-diagnostic antegrade examination, or as a complimentary procedure to an antegrade examination when complete enteroscopy (CE) is desired^[2]. In addition to its more challenging nature, there may also be a longer learning curve^[1]. Average insertion depths proximal to the ICV *via* the retrograde approach have been reported from 73 to 199 cm, but these studies are limited by a relatively small sample size of retrograde cases^[2-4]. The purpose of this report is to describe our center's experience with rSBE, the largest published cohort to date.

MATERIALS AND METHODS

We performed a retrospective analysis of all rSBEs performed at the University of Maryland Medical Center from January 2006 to April 2015. All cases of rSBE were performed by one of three therapeutic endoscopists, who began performing the procedure in 2006 without any formal training. Patient and procedural data were obtained from electronic medical records and the electronic endoscopy reporting system, ProVation MD® (MN). The study was approved by the University of Maryland Medical Center Institutional Review Board.

All patients underwent SBE for accepted indications after signed informed consent was obtained. All patients underwent bowel cleansing prior to the procedure with standard preparations, most receiving four liters of polyethylene glycol. Most cases were performed with monitored anesthesia care, although some were performed under conscious sedation. Few cases were conducted under general anesthesia. The anesthesiologist determined the type of sedation utilized. Fluoroscopy was utilized in select cases, most often in the context of retrieval of a retained capsule.

The indication for rSBE was categorized into one of three groups: Obscure gastrointestinal bleeding (OGIB), abnormal imaging or evaluation of Crohn's disease. OGIB was defined as persistent or recurrent bleeding whose source was not identified by conventional studies, such as colonoscopy or esophagogastroduodenoscopy (EGD). Abnormal imaging was defined as any abnormality detected *via* video capsule endoscopy (VCE) or noninvasive radiological study. rSBEs performed for the evaluation of Crohn's included both cases of previously established

**Table 1 Patient characteristics and pre-procedural characteristics
n (%)**

Factor	Value
Age (yr)	57.5
Female	69 (50.7)
Outpatient	110 (80.9)
Pre-procedural imaging	88 (64.7)
Indication	
Gastrointestinal bleeding	55 (40.4)
Suspected or known CD	29 (21.3)
Abnormal imaging	43 (31.6)
Other	9 (6.6)
ASA classification	
Class I	8 (5.9)
Class II	109 (80.1)
Class III	19 (14.0)

CD: Crohn's disease; ASA: American Society for Anesthesiologists.

disease and suspected, but yet undiagnosed, Crohn's disease.

Insertion depth (ID) was determined quantitatively, in terms of centimeters (cm) beyond the ICV in some cases, and qualitatively, in terms of the anatomic extent reached, in others. Quantitatively determined ID was estimated during withdrawal of the scope by adding 5 cm increments, similar to the technique described by Efthymiou *et al*^[5]. Procedure time was determined by the time at which the enteroscope was passed through the anus to the time at which it was completely withdrawn. Technical failure was defined as the inability to advance the enteroscope beyond 20 cm proximal to the ICV. Positive findings were defined as any abnormality that explained the patient's presentation or that required therapeutic intervention. Cases in which positive findings were not observed were categorized as normal exams or technically difficult studies (due either to poor bowel preparation or technical failure). For rSBEs performed due to abnormal imaging, endoscopic concordance was defined as ability of enteroscopy to corroborate the abnormality seen on imaging. DY was defined by the percentage of cases producing either a definitive diagnosis or findings that could explain clinical symptoms. TY was defined as the percentage of cases in which a definitive intervention was performed. Excluded from this definition were cases in which only tissue specimens or mucosal tattooing were achieved. Post-procedure complications were defined as any symptomatic complaint or hospital re-admission within 30 d following rSBE.

Single-balloon system

The Olympus SIF-Q180® (Olympus, Center Valley, Pennsylvania, USA) is a 200-cm high-resolution enteroscope with a 2.8 mm working channel that uses a 140-cm long × 13.2-mm outer diameter flexible overtube. The silicone balloon at the tip of the over tube can be inflated and deflated *via* an external balloon control module, conventionally within a pressure range of 6-16 kPa. The

Table 2 Procedural characteristics and findings

Factor	Value
Anesthesia	
Monitored anesthesia care	103 (75.7)
Conscious sedation	28 (20.6)
General anesthesia	5 (3.7)
Fluoroscopy	5 (3.7)
Time to completion (min)	41.7 (15.5)
Insertion depth	
Quantitative (cm) ¹	68.3 (39.3)
Qualitative	
Distal ileum	29 (51.8)
Mid ileum	17 (30.4)
Proximal ileum	5 (8.9)
Distal jejunum	4 (7.1)
Mid jejunum	1 (1.8)
Findings	
Ulcer	22 (31.9)
Angiectasia	8 (11.6)
Erosion	3 (4.3)
Stricture	12 (17.4)
Polyp	14 (20.3)
Inflammation	9 (13.0)
Other	6 (8.7)

¹As measured from the ileocecal valve. Values presented as mean (SD) for time and quantitative depth, and *n* (%) otherwise.

technique of rSBE has been described previously and is widely recognized^[6].

Biostatistics

The statistical methods of this study were reviewed only by the authors listed above and no one else.

RESULTS

Patient demographics and pre-procedural characteristics are presented in Table 1. A total of 136 rSBEs were performed. Mean age was 57.5 years. Sixty-nine (50.7%) patients were female, and 110 (80.9%) cases were on outpatients. Eighteen (13.2%) cases were conducted in patients with post-surgical anatomy due to prior intestinal surgery. Procedural data is presented in Table 2. Fluoroscopy was utilized in only 5 (3.7%) cases. Monitored anesthesia with propofol was the anesthetic strategy in 103 (75.7%) cases. Conscious sedation and generalized anesthesia were utilized in 28 (20.6%) and 5 (3.7%) cases, respectively.

Primary indications for rSBE were 55 (40.4%) cases for OGIB, 29 (21.3%) for evaluation of Crohn's disease and 43 (31.6%) for abnormal radiographic or endoscopic findings observed during the workup of GI complaints unrelated to OGIB or suspected Crohn's, such as a possible small bowel mass. Another 9 (6.6%) procedures were conducted in patients varied symptoms unrelated to the above three categories, such as diarrhea (Table 1). Imaging data was available in 88 (64.7%) patients. Among them, 69 (78.4%) underwent VCE, 9 (10.22%) computed tomography (CT), 5 (5.7%) magnetic resonance enterography (MRE), 4 (4.5%) small bowel series

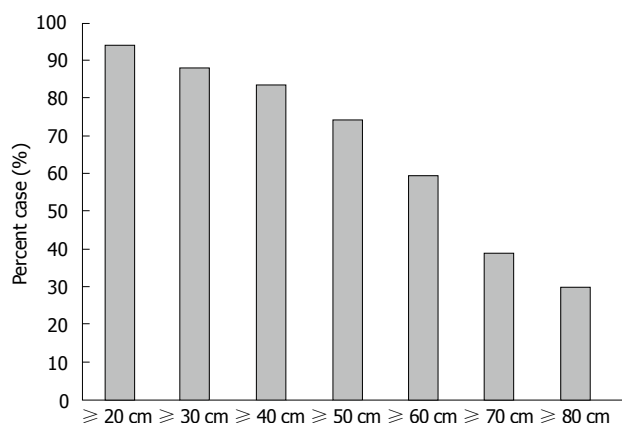


Figure 1 Insertion depth beyond the ileocecal valve.

(SBS) and 1 (1.1%) Meckel's scan.

ID was estimated quantitatively in 67 (49.3%) cases. Mean ID in these cases was 68.3 ± 39.3 cm. Sixty-three (94.0%) of the cases met criteria for technical success with ID at least 20 cm beyond the ICV. Fifty (74.6%) cases reached at least 50 cm beyond the ICV, and 20 (29.9%), at least 80 cm (Figure 1). Among 56 (41.2%) cases in which ID was qualitatively described on the basis of anatomic extent reached, 29 (51.8%) cases reached the distal ileum, 17 (30.4%) cases reached the mid-ileum and 5 (8.9%) reached the proximal ileum. The jejunum was reached in 5 (8.9%) cases.

Overall, 73 cases were diagnostic, producing a DY of 53.7%. The 63 non-diagnostic cases were due to a normal examination in 45 (71.4%) cases, technical failure in 11 (17.5%), and poor preparation or fresh blood in the intestinal lumen in 7 (11.1%). Concordance between abnormalities detected on imaging and rSBE was seen in 31 of the 88 (35.2%) cases in which prior imaging was available. Positive endoscopic findings were present in 69 (50.7%) of all cases, including 22 (31.9%) ulcers, 14 (20.3%) polyps, 12 (17.4%) strictures, 8 (11.6%) arteriovenous malformations (AVMs), and 9 (13.0%) cases with chronic inflammatory changes. One (1.4%) Dieulafoy lesion, 3 (4.3%) diverticuli, 3 (4.3%) erosions and 2 (2.9%) mass lesions accounted for the remaining 6 (13.0%) cases.

There were 25 (18.4 %) therapeutic cases. Argon plasma coagulation (APC) was utilized in 6 (24.0%), stricture dilatation in 8 (32.0%), hemoclippling in 2 (8.0%), polypectomy and removal in 9 (36.0%). Tissue specimens and/or mucosal tattooing were obtained in 48 (35.3%) cases, but these were not included in the overall TY. Eighteen (13.2%) cases were technical failures. However, in one such case, an ileal stricture was diagnosed within 20 cm of the ICV, and in four, a colonic source was identified as the most probable etiology, despite inability to intubate the ICV.

DY per indication for rSBE was 16 of 55 (29.1%) cases for OGIB, 12 of 43 (27.9%) cases for abnormal imaging and 1 of 9 (11.1%) rSBEs indicated due to other reasons. Twelve new diagnoses of Crohn's disease were

established. Similarly, TY per indication was 8 (14.5%) cases for OGIB, 5 (17.2%) for Crohn's, 10 (23.3%) for abnormal imaging and 2 (22.2%) for rSBE indicated due to other reasons. Post-procedural symptomatic complaints were observed only in 2 among 93 (2.2%) cases in which this data was available. Both of these patients had self-limiting pain and neither required medical intervention or were readmitted to the hospital within 30 d of the procedure. There were no major adverse events. Finally, procedural characteristics were analyzed according to year in which the procedure was conducted, with no significant trends noted in terms of ID, procedure time, diagnostic or TY or failure rates from 2006 to 2013.

DISCUSSION

Disorders of the small intestine account for an increasing number of hospital discharges and aggregate healthcare cost^[7]. Continuing to develop the expertise and technical proficiency to safely and effectively visualize and treat disorders of the small bowel remains a challenge. Deep enteroscopy techniques have helped to open what has long been considered the endoscopist's "black box"^[5]. SBE has emerged as a feasible alternative to double-balloon endoscopy in the evaluation of these disorders, due to its increased ease of setup^[8], wider availability^[1,9], and similar DY^[2,5]. A less studied topic has been route selection. The antegrade approach is preferred in cases of suspected small bowel pathology with no localizing evidence, because diagnostic and TYs have been shown to be superior^[10-12]. This is likely the result of the proximal (*i.e.*, jejunal) location of most small bowel pathology^[13]. The technical challenges of the retrograde approach, in both single and double-balloon platforms, is also well documented^[1,11,14]. However, because CE is seldom achieved *via* one route alone^[13], and because capsule endoscopy's ability to accurately localize lesions is notoriously poor^[15,16], facility with the retrograde approach is important. Our study evaluated the efficacy and safety of retrograde enteroscopy in 136 patients, the largest case series of rSBE reported to date.

The primary indications for rSBE in our population were similar to those in other studies^[2,3,17], and included OGIB (40.4%), abnormal imaging (31.6%), and evaluation of Crohn's disease (21.3%). Our concordance rate between abnormalities detected on imaging and enteroscopy was 35.2%, slightly lower than 2 prior studies^[3,17]. One explanation for our overall low concordance rate is that erosions and ulcers on capsule studies can be transient and false positives are common^[3]. Since ulcers were the most prevalent finding in our population, a lower concordance was expected.

There are multiple methods to determine ID, including fold counting and the 40 cm push-pull cycles described by May *et al*^[8]. Our endoscopists routinely determine ID by addition of 5 cm increments upon withdrawal of the scope. Prior studies have reported a range of IDs from 73-199 cm for rSBE^[2-4,18,19]. In our population, 26 (38.8%)

retrograde exams were at least 70 cm beyond the ICV. Although no strict correlation exists between ID and DY^[20,21], reproducible IDs support the technical feasibility of rSBE.

Average procedure time in our population was 41.7 ± 15.5 min. Previous studies report a range of 48-78 min for rSBE and 38-82 min for the antegrade approach^[2-4,17-19,22]. Our observed mean procedure time also compares favorably to previously reported procedure times for retrograde double-balloon endoscopy, which ranges from 59 to 90 min^[11,23]. To our knowledge, no studies have demonstrated a relationship between procedure time and DY. Operator experience and patient anatomy are among several factors that may affect procedure time. Shorter procedure time may lend itself to increased cost-effectiveness, and should be a topic for future study.

A definitive diagnosis was established in 73 (53.7%) cases. One prior study of 34 rSBE cases reported a similar DY of 47.0%^[17]. The DY of SBE ranges from 41% to 65%^[2-4,8,18,19,22,24-26]. In our study, pathology limited to the colon was included in the overall DY, and in all 13 (9.6%) such cases, patients' symptoms were deemed attributable to a colonic source. DYs were 29.1% and 27.9% in cases of OGIB and abnormal imaging, respectively. For those cases in which Crohn's disease was suspected, rSBE established that diagnosis in 41.4% of cases. Prior studies predominantly examining the antegrade approach have reported yields of 42.9%-60.0% for OGIB and 25.0%-65.0% for abnormal imaging^[4,17].

Twenty-five (18.4%) cases were therapeutic. APC was performed in 6 (24.0%), stricture dilatation in 8 (32.0%), hemoclippping in 2 (8.0%), and polypectomy in 9 (36.0%). TY has never been reported in the isolated context of rSBE, but overall TY for SBE is highly variable ranging from 7%-50%^[2-4,8,18,19,22,24-26]. Tissue specimens were obtained where appropriate in 48 (35.3%) cases, but were not considered in the overall TY.

Technical failure, defined in this study as inability to traverse at least 20 cm beyond the ICV, occurred in 18 (13.2%) cases. However, six such cases remained diagnostic either because pathology was found within 20 cm of the ICV or symptoms were attributed to a colonic source. Most technical failures were caused by inability to deeply intubate the ICV. Previous studies have reported failure rates for rSBE ranging from 10%-16%^[3,4]. Failure rates in retrograde DBE are more highly variable, occurring in up to 30% of cases^[11,23,24,27].

The types of endoscopic findings in our study also merit discussion. Specifically, only 8 (11.6%) had vascular lesions, whereas 22 (31.9%) had ulcers, 12 (17.4%) had strictures and 14 (20.3%) had polyps. One study reported a similar distribution of endoscopic lesions^[17], whereas two others reported vascular lesions as the most common^[3,22]. The relatively high prevalence of Crohn's disease in our population may explain this finding. These findings are also consistent with the categorization proposed by one author of typically

"jejunal" processes (including obscure overt GIB presenting as melena, among others) vs typically "ileal" processes (including ileal Crohn's disease, among others)^[13].

The limitations of this study include the absence of long-term follow-up data and the retrospective single-center setting. Furthermore, imaging and endoscopy reports that lead to the decision to pursue rSBE were not available in all patients, and so it is possible that our concordance rate may be skewed. Additionally, ID was not quantitatively determined in all cases. Larger prospective studies of rSBE with specific emphasis on long term outcomes and cost-effectiveness are needed to fully define its role in daily clinical gastroenterology.

The niche for SBE in the evaluation of disorders of the small bowel continues to develop. In the correct clinical context and with radiographic or capsule findings to suggest distal pathology, the retrograde approach is appropriate. Therefore, facility with this procedure is important for endoscopists involved in the care of these patients. Inherently, this approach poses a technical challenge because the tortuosity of the colon induces significant looping of the enteroscopy and ICV is often retroverted. To date, studies describing experience with rSBE have dealt with relatively few cases. Our study demonstrates that rSBE is a technically feasible, safe and effective procedure with acceptable diagnostic and TYs.

COMMENTS

Background

Single-balloon enteroscopy (SBE) represents a novel approach to diagnose and treat small bowel disease. The small bowel can be deeply intubated via the antegrade (mouth) or retrograde (anus) approach depending on the probable location of the suspected lesion. SBE has different performance characteristics depending upon the route chosen, but most studies combine the information. This study constitutes the largest published cohort to date of retrograde single-balloon enteroscopy (rSBE).

Research frontiers

Limited data is available on performance metrics of rSBE, such as success, complications, diagnostic yield (DY) and therapeutic yield (TY). Many studies include both antegrade and retrograde approach for SBE in the study sample, which typically is of a small size. Regarding double vs single-balloon technique, there is evidence to suggest that there is no difference between the two in terms of DY, TY, insertion depth and procedure time.

Innovations and breakthroughs

As previously mentioned, this study adds to the small body of literature on rSBE. Results demonstrate that rSBE is a technically feasible, safe and effective procedure with acceptable diagnostic and TYs.

Applications

Developing the expertise and technical proficiency to safely and effectively visualize and treat disorders of the small bowel remains a challenge, but deep enteroscopy techniques have helped to open what has long been considered the endoscopist's "black box". Given that disorders of the small intestine account for an increasing number of hospital discharges and aggregate healthcare cost, research into the most beneficial type of procedure with the appropriate route selection is important. Larger prospective studies of rSBE with specific emphasis on long term outcomes and cost-effectiveness are needed to fully define its role in daily clinical gastroenterology.

Terminology

Antegrade: Approach into the small bowel via the mouth; Retrograde: Approach into the small bowel via the anus; Enteroscopy: Procedure with an enteroscope to directly visualize the small bowel.

Peer-review

rSBE is a very useful interventional procedure of notorious difficulty though. Authors are presenting their experience that is quite impressive for both numbers and results. Manuscript, written in fluent and understandable English is very concise and explanatory.

REFERENCES

- Manno M, Barbera C, Bertani H, Manta R, Mirante VG, Dabizzi E, Caruso A, Pigo F, Olivetti G, Conigliaro R. Single balloon enteroscopy: Technical aspects and clinical applications. *World J Gastrointest Endosc* 2012; **4**: 28-32 [PMID: 22347529 DOI: 10.4253/wjge.v4.i2.28]
- Domagk D, Mensink P, Aktas H, Lenz P, Meister T, Luegering A, Ullerich H, Aabakken L, Heinecke A, Domschke W, Kuipers E, Bretthauer M. Single- vs. double-balloon enteroscopy in small-bowel diagnostics: a randomized multicenter trial. *Endoscopy* 2011; **43**: 472-476 [PMID: 21384320 DOI: 10.1055/s-0030-1256247]
- Upchurch BR, Sanaka MR, Lopez AR, Vargo JJ. The clinical utility of single-balloon enteroscopy: a single-center experience of 172 procedures. *Gastrointest Endosc* 2010; **71**: 1218-1223 [PMID: 20409544 DOI: 10.1016/j.gie.2010.01.012]
- Ramchandani M, Reddy DN, Gupta R, Lakhtakia S, Tandan M, Rao GV, Darisetty S. Diagnostic yield and therapeutic impact of single-balloon enteroscopy: series of 106 cases. *J Gastroenterol Hepatol* 2009; **24**: 1631-1638 [PMID: 19686408 DOI: 10.1111/j.1440-1746.2009.05936.x]
- Efthymiou M, Desmond PV, Brown G, La Nauze R, Kaffes A, Chua TJ, Taylor AC. SINGLE-01: a randomized, controlled trial comparing the efficacy and depth of insertion of single- and double-balloon enteroscopy by using a novel method to determine insertion depth. *Gastrointest Endosc* 2012; **76**: 972-980 [PMID: 22980289 DOI: 10.1016/j.gie.2012.06.033]
- Buscaglia JM, Okolo PI. Deep enteroscopy: training, indications, and the endoscopic technique. *Gastrointest Endosc* 2011; **73**: 1023-1028 [PMID: 21429487 DOI: 10.1016/j.gie.2011.01.026]
- Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibanaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-1187.e1-3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]
- May A, Färber M, Aschmoneit I, Pohl J, Manner H, Lotterer E, Möschler O, Kunz J, Gossner L, Mönkemüller K, Ell C. Prospective multicenter trial comparing push-and-pull enteroscopy with the single- and double-balloon techniques in patients with small-bowel disorders. *Am J Gastroenterol* 2010; **105**: 575-581 [PMID: 20051942 DOI: 10.1038/ajg.2009.712]
- Upchurch BR, Vargo JJ. Single-balloon enteroscopy. *Gastrointest Endosc Clin N Am* 2009; **19**: 335-347 [PMID: 19647643 DOI: 10.1016/j.giec.2009.04.010]
- Akyüz Ü, Pata C, Kalayci M, Özdl K, Altun H, Karip B, Akyüz F. Route selection for double balloon enteroscopy in patients with obscure gastrointestinal bleeding: experience from a single center. *Turk J Gastroenterol* 2012; **23**: 670-675 [PMID: 23794303]
- Sanaka MR, Navaneethan U, Kosuru B, Yerneni H, Lopez R, Vargo JJ. Antegrade is more effective than retrograde enteroscopy for evaluation and management of suspected small-bowel disease. *Clin Gastroenterol Hepatol* 2012; **10**: 910-916 [PMID: 22610006 DOI: 10.1016/j.cgh.2012.04.020]
- Dutta AK, Sajith KG, Joseph AJ, Simon EG, Chacko A. Learning curve, diagnostic yield and safety of single balloon enteroscopy. *Trop Gastroenterol* 2012; **33**: 179-184 [PMID: 23600047]
- Mönkemüller K. Should we illuminate the black box of the small bowel mucosa from above or below? *Clin Gastroenterol Hepatol* 2012; **10**: 917-919 [PMID: 22610001 DOI: 10.1016/j.cgh.2012.04.017]
- Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, Despott EJ, Fortun PF, Heuschkel R, Kammermeier J, Leighton JA, Mantzaris GJ, Moussata D, Lo S, Paulsen V, Panés J, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger JM, Yamamoto H, Travis S, Colombel JF, Van Gossum A. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009; **41**: 618-637 [PMID: 19588292 DOI: 10.1055/s-0029-1214790]
- Ahmad NA, Iqbal N, Joyce A. Clinical impact of capsule endoscopy on management of gastrointestinal disorders. *Clin Gastroenterol Hepatol* 2008; **6**: 433-437 [PMID: 18325843 DOI: 10.1016/j.cgh.2007.12.035]
- Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010; **71**: 280-286 [PMID: 20152309 DOI: 10.1016/j.gie.2009.09.031]
- Prachayakul V, Deesomsak M, Aswakul P, Leelakulsolvong S. The utility of single-balloon enteroscopy for the diagnosis and management of small bowel disorders according to their clinical manifestations: a retrospective review. *BMC Gastroenterol* 2013; **13**: 103 [PMID: 23800178 DOI: 10.1186/1471-230X-13-103]
- Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, Senoh K, Hayafuji K, Ogawa A, Nakahara T, Sasaki M, Fujiyama Y. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. *Endoscopy* 2008; **40**: 11-15 [PMID: 18058613 DOI: 10.1055/s-2007-966976]
- Khashab MA, Lennon AM, Dunbar KB, Singh VK, Chandrasekhara V, Giday S, Canto MI, Buscaglia JM, Kapoor S, Shin EJ, Kalloo AN, Okolo PI. A comparative evaluation of single-balloon enteroscopy and spiral enteroscopy for patients with mid-gut disorders. *Gastrointest Endosc* 2010; **72**: 766-772 [PMID: 20619404 DOI: 10.1016/j.gie.2010.04.043]
- Albert JG. Interventional balloon-enteroscopy. *J Interv Gastroenterol* 2012; **2**: 42-50 [PMID: 22586550 DOI: 10.4161/jig.20134]
- Xin L, Gao Y, Liao Z, Li ZS. The reasonable calculation of complete enteroscopy rate for balloon-assisted enteroscopy. *Endoscopy* 2011; **43**: 832; author reply 832 [PMID: 21894584 DOI: 10.1055/s-0030-1256569]
- Frantz DJ, Dellon ES, Grimm IS, Morgan DR. Single-balloon enteroscopy: results from an initial experience at a U.S. tertiary-care center. *Gastrointest Endosc* 2010; **72**: 422-426 [PMID: 20541189 DOI: 10.1016/j.gie.2010.03.1117]
- Di Caro S, May A, Heine DG, Fini L, Landi B, Petruzzello L, Cellier C, Mulder CJ, Costamagna G, Ell C, Gasbarrini A. The European experience with double-balloon enteroscopy: indications, methodology, safety, and clinical impact. *Gastrointest Endosc* 2005; **62**: 545-550 [PMID: 16185969 DOI: 10.1016/j.gie.2005.04.029]
- Aktas H, de Ridder L, Haringsma J, Kuipers EJ, Mensink PB. Complications of single-balloon enteroscopy: a prospective evaluation of 166 procedures. *Endoscopy* 2010; **42**: 365-368 [PMID: 20178072 DOI: 10.1055/s-0029-1243931]
- Kawamura T, Yasuda K, Tanaka K, Uno K, Ueda M, Sanada K, Nakajima M. Clinical evaluation of a newly developed single-balloon enteroscope. *Gastrointest Endosc* 2008; **68**: 1112-1116 [PMID: 18599052 DOI: 10.1016/j.gie.2008.03.1063]
- Takano N, Yamada A, Watabe H, Togo G, Yamaji Y, Yoshida H, Kawabe T, Omata M, Koike K. Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial. *Gastrointest Endosc* 2011; **73**: 734-739 [PMID: 21272875 DOI: 10.1016/j.gie.2010.10.047]
- Mehdizadeh S, Ross A, Gerson L, Leighton J, Chen A, Schembre D, Chen G, Semrad C, Kamal A, Harrison EM, Binmoeller K, Waxman

I, Kozarek R, Lo SK. What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience

in 6 U.S. tertiary care centers. *Gastrointest Endosc* 2006; **64**: 740-750 [PMID: 17055868 DOI: 10.1016/j.gie.2006.05.022]

P- Reviewer: Giannopoulos GA, Skok P, Sharma SS
S- Editor: Song XX **L- Editor:** A **E- Editor:** Lu YJ



Observational Study

Sensory characterization of bowel cleansing solutions

Ala I Sharara, Hamza Daroub, Camille Georges, Rani Shayto, Ralph Nader, Jean Chalhoub, Ammar Olabi

Ala I Sharara, Rani Shayto, Ralph Nader, Jean Chalhoub, Division of Gastroenterology, Department of Internal Medicine, American University of Beirut Medical Center, American University of Beirut, Beirut 1107 2020, Lebanon

Hamza Daroub, Camille Georges, Ammar Olabi, Nutrition and Food Sciences Department, Faculty of Agricultural and Food Sciences, American University of Beirut, Beirut 1107 2020, Lebanon

Author contributions: Sharara AI and Olabi A designed the research study, wrote the protocol, and drafted the manuscript; Nader R and Chalhoub J conducted literature searches and provided summaries of previous research studies; Daroub H, Georges C and Shayto R contributed equally to this work; Daroub H and Georges C recruited subjects, conducted experimental trials, collected data, and executed tables and figures; Shayto R interpreted the data; Olabi A performed the statistical data analysis; all authors contributed to and approved the final manuscript.

Institutional review board statement: The study protocol was reviewed and approved by the American University of Beirut Institutional Review Board on June 29, 2015 and the study was registered with clinicaltrials.gov identifier: NCT02642783.

Informed consent statement: All study participants provided written informed consent for descriptive analysis and verbal consent for hedonic evaluation.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: No additional data available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Ammar Olabi, Associate Professor, Nutrition and Food Sciences Department, Faculty of Agricultural and Food Sciences, American University of Beirut, Riad El-Solh, Beirut 1107 2020, Lebanon. ammar.olabi@aub.edu.lb
Telephone: +961-1-374374-4500
Fax: +961-1-744460

Received: January 16, 2016
Peer-review started: January 18, 2016
First decision: February 22, 2016
Revised: February 29, 2016
Accepted: May 7, 2016
Article in press: May 9, 2016
Published online: August 10, 2016

Abstract

AIM: To evaluate the sensory characteristics of commercial bowel cleansing preparations.

METHODS: Samples of 4 commercially available bowel cleansing preparations, namely polyethylene glycol electrolyte solution (PEG), PEG + ascorbic acid (PEG-Asc), sodium picosulfate (SPS), and oral sodium sulfate (OSS) were prepared according to the manufacturer's instructions. Descriptive analysis was conducted ($n = 14$) using a 15-cm line scale with the Compusense at-hand® sensory evaluation software. Acceptability testing ($n = 80$) was conducted using the 9-point hedonic scale. In addition, a Just-About-Right (JAR) scale was included for the four basic tastes to determine their intensity compatibility with acceptability levels in the products.

RESULTS: Samples were significantly different, in descriptive analysis, for all attributes ($P < 0.05$) except for sweetness. SPS received the highest ratings for turbidity, viscosity appearance, orange odor and orange flavor; PEG-Asc for citrus odor and citrus flavor; OSS for sweetener taste, sweet aftertaste, bitterness, astringency, mouthcoating, bitter aftertaste and throatburn, and along with PEG-Asc, the highest ratings for saltiness, sourness and adhesiveness. Acceptability results showed

significant differences between the various samples ($P < 0.05$). SPS received significantly higher ratings for overall acceptability, acceptability of taste, odor and mouthfeel ($P < 0.05$). JAR ratings showed that PEG and PEG-Asc were perceived as slightly too salty; SPS and OSS were slightly too sweet, while SPS, PEG-Asc and OSS were slightly too sour and OSS slightly too bitter. While using small sample volumes was necessary to avoid unwanted purgative effects, acceptability ratings do not reflect the true effect of large volumes intake thus limiting the generalization of the results.

CONCLUSION: Further improvements are needed to enhance the sensory profile and to optimize the acceptability for better compliance with these bowel cleansing solutions.

Key words: Laxatives; Acceptability; Sensory evaluation; Taste; Preparation; Colonoscopy

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Bowel preparation is an important quality indicator in colonoscopy. Purgative solutions are generally poorly tolerated and may serve as an impediment to colorectal cancer screening and surveillance. The need for rapid ingestion of these solutions is perceived as a major disadvantage concerning patient adherence as these solutions are often considered unpleasant. To date, no major studies have investigated the sensory properties of bowel cleansing solutions using comprehensive sensory evaluation techniques. This study showed major differences in sensory characteristics and the need for product development to optimize patient acceptability for better compliance with bowel cleansing solutions.

Sharara AI, Daroub H, Georges C, Shayto R, Nader R, Chlahoub J, Olabi A. Sensory characterization of bowel cleansing solutions. *World J Gastrointest Endosc* 2016; 8(15): 508-516 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i15/508.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i15.508>

INTRODUCTION

Colonoscopy is the preferred screening method for colorectal cancer (CRC) due to its high diagnostic sensitivity and specificity. An adequate bowel preparation is crucial to perform a good colonoscopy exam. Bowel laxative preparations are generally poorly tolerated, disliked and as a result often serve as an impediment to CRC screening and surveillance. Patients who have had a colonoscopy often consider the bowel preparation as the worst part of their experience, and are, as a result, sometimes reluctant to undergo the procedure again or recommend it to others^[1,2]. In addition, patients commonly experience adverse events of the

bowel preparation, including bloating, nausea, vomiting and abdominal pain which may lead to interruption or incomplete adherence of the preparation. This may result in suboptimal bowel cleansing leading to incomplete examination, poor visualization of the mucosa, missed colon pathology, and possibly increased procedural complications and cost^[3]. Despite the above, inadequate bowel preparation occurs surprisingly often and in as many as 25% of patients^[4]. Predictors of an inadequate bowel preparation include medical factors like chronic constipation, use of opioids and tricyclics, diabetes mellitus, and obesity as well as other patient-related factors such as education, health literacy, and motivation^[5]. Clearly, adherence with the prescribed laxative regimen including diet is an essential step to an effective bowel preparation. A recent study investigated the burden of the bowel preparation on pre-procedural quality of life by examining 7 variables including hunger, taste, volume, adverse events (AE), and the effect on sleep, social, and work functioning^[6]. Except for work and AE, all variables scored negatively by greater than one fifth of patients (range 20.4-34.2). Overall, volume, taste, hunger, and sleep disturbances were considered the worst aspect of the preparation. To date, no major studies have investigated the sensory properties of bowel cleansing solutions using comprehensive sensory evaluation techniques. This may lead to a better understanding of the favorable and unfavorable characteristics of each preparation and provide a framework for comparing commercially available products and guide future development strategies.

MATERIALS AND METHODS

Sample preparation

Four commercial bowel cleansing laxative solutions namely polyethylene glycol electrolyte solution (PEG)-electrolyte + ascorbic acid (PEG-Asc, lime flavor, Moviprep®, Norgine, United Kingdom), PEG-electrolyte (PEG, no flavor, Fortrans® IPSEN, France), sodium picosulfate/magnesium citrate (SPS, orange flavor, Picoprep®, Ferring, Switzerland), and oral sodium sulfate (OSS, exotic fruits flavor, Izinova®, IPSEN, France) were used in the study. Samples were prepared according to manufacturer's instructions: PEG-Asc, PEG, and SPS powdered samples were dissolved in mineral water; while OSS liquid sample was diluted to volume with mineral water.

Descriptive analysis

Descriptive analysis was conducted on the bowel cleansing solutions as described in previous studies^[7]. The descriptive panel consisted of 14 judges (12 females and 2 males, age 19-26) recruited from the American University of Beirut. Panelists attended 4 one-hour training sessions during which a 15-cm unstructured line scale descriptive ballot was generated using 19 descriptive sensory attributes, anchor points and reference standards (Table 1). Subjects also attended 3 evaluation

Table 1 Terms used in the descriptive analysis of the bowel cleansing laxative solutions

Attribute	Definition as worded on score sheet	Anchor words (low to high)
Appearance		
Turbidity	The level of haze present in sample when holding the sample at eye level ¹	Clear to turbid
Viscosity	The resistance to flow when swirling the sample in the cup ²	Thin to thick
Odor		
Orange	Odor of orange juice ³	Not at all to very
Citrus	Odor of lemonade ⁴	Not at all to very
Flavor		
Saltiness	Taste elicited by table salt	Not at all to very
Sweetness	Taste elicited by sugar (sucrose)	Not at all to very
Sourness	Taste elicited by citric acid	Not at all to very
Sweetener	Taste elicited by the sweetener solution ⁵	Not at all to very
Bitterness	Taste elicited by caffeine ⁶	Not at all to very
Orange	Flavor of orange juice ³	Not at all to very
Citrus	Flavor of lemonade ⁴	Not at all to very
Mouthfeel		
Adhesiveness	The level of cling to surface of tongue when swirling sample in mouth	Not at all to very
Astringency	Dryness and puckering on tongue and palate ⁶	Not at all to very
Mouthcoating	Layer of sample left on palate after swallowing	Not at all to very
Aftertaste		
Sweet	Aftertaste elicited by sugar solution	Not at all to very
Sour	Aftertaste elicited by citric acid solution	Not at all to very
Astringent	Dryness and puckering on tongue and palate after swallowing ⁷	Not at all to very
Bitter	Aftertaste elicited by caffeine solution ⁶	Not at all to very
Throatburn	Burn in throat after swallowing sample ⁷	Not at all to very

¹Mineral water (low level), Rim, bottled at source by Rim Natural Spring Mineral Water SAL - Mount Sannine, Lebanon; ²Mineral water, Rim, bottled at source by Rim Natural Spring Mineral Water SAL - Mount Sannine, Lebanon, for low level *vs* pineapple juice, Tropicana, bottled by société moderne Libanaise pour le commerce SAL, Beirut, Lebanon, for high level; ³Orange juice (high level), Mr. Juicy, bottled by société moderne Libanaise pour le commerce SAL, Beirut, Lebanon; ⁴Lemonade (high level), Balkis, Balkis SAL, Beirut, Lebanon; ⁵Sweetener solution (high level), prepared by dissolving 2 tea spoons artificial sweetener (Sweet *n* low, Dietary foods, Soham Cambs, United Kingdom) in 500 mL mineral water; ⁶Cold tea (high level), prepared by soaking 2 bags of black tea (Lipton, Unilever Mashreq tea company, New Borj El Arab, Alexandria, Egypt) in 500 mL hot mineral water, then cooled down to room temperature; ⁷Baking soda solution (high level), prepared by dissolving 2 tea spoons of baking soda (Arm and Hammer, Harrison Street, Princeton New Jersey, United States) in 500 mL of mineral water.

sessions over 3 d. All bowel cleansing solutions were prepared on the same day of training/evaluation sessions. Samples were evaluated in triplicates over 3 sessions with 4 samples per session using the Compusense at-hand® (Compusense Inc., Guelph, ON, Canada) sensory evaluation software. Serving sequence was randomized and counterbalanced based on William's design for 4 treatments as generated by the software.

Hedonic evaluation

An acceptability test was carried out by 80 untrained panelists (49 females and 31 males, age 18-28). Four samples were assessed in one session during which subjects rated overall acceptability, and acceptability of odor, taste and mouthfeel on a 9-point hedonic scale^[8] ranging from 1 (dislike extremely) to 9 (like extremely) using the Compusense at-hand® (Compusense Inc., Guelph, ON, Canada) sensory evaluation software. In addition, a Just-About-Right (JAR) scale^[8] (-3: too little, 0: just about right, 3: too much) was included for the basic tastes (saltiness, sweetness, sourness, and bitterness) to determine the compatibility of their intensity in the samples with optimum acceptability levels. Moreover, panelists were asked to identify any additional flavor perceived other than the four basic tastes. Serving sequence was randomized and counterbalanced based

on William's design for 4 treatments as generated by the software.

Statistical analysis

Analysis of variance using the GLM procedure of SPSS statistics for windows software (version 23, IBM Corporation, Armonk, NY, United States) was performed. In the statistical model for descriptive analysis, the response variable was the sensory attribute. Factors in the model included sample, panelist, replicate and their two-way interactions. Panelist was considered as random effect and sample and replicate were fixed effects. The sensory acceptability model did not include replicate. Significant means were separated by Tukey's honestly significant difference (HSD) test. Significance was pre-established at $\alpha < 0.05$.

RESULTS

Descriptive analysis

The analysis of variance results for the descriptive analysis are summarized in Table 2. As expected the panelist effect was significant for most attributes, with 12 out of the 19 attributes having a significant panelist effect ($P < 0.05$). Significant differences between samples were obtained for 18 out of the 19 attributes, specifically for turbidity,

Table 2 Significance of effects (*F* and *P*-values) for descriptive attributes for the bowel cleansing laxative solutions

Attributes	Panelist (df = 13)	Sample ¹ (df = 3)	Replicate (df = 2)	S × P (df = 39)	R × P (df = 26)	S × R (df = 6)
Appearance						
Turbidity	5.6 ^d	9.1 ^d	3.1	1.4	1.5	0.5
Viscosity	5.4 ^d	4.2 ^a	4.5 ^a	1.5	1.7 ^a	0.1
Odor						
Orange	2.0	15.9 ^d	0.0	2.3 ^b	0.4	1.3
Citrus	2.0	35.0 ^d	4.7 ^a	2.1 ^b	0.6	1.3
Flavor						
Saltiness	2.9 ^b	8.8 ^d	0.7	2.7 ^d	1.3	0.9
Sweetness	6.3 ^d	2.8	5.3 ^a	5.7 ^d	1.2	0.8
Sourness	4.5 ^d	18.5 ^d	0.6	2.5 ^d	1.2	1.4
Sweetener	8.4 ^d	3.7 ^a	3.5 ^a	4.7 ^d	1.6	1.6
Bitterness	2.0	8.5 ^d	0.2	4.8 ^d	1.0	0.9
Orange	1.6	10.9 ^d	0.7	6.1 ^d	1.4	0.6
Citrus	1.3	11.4 ^d	2.3	3.7 ^d	1.2	0.7
Mouthfeel						
Adhesiveness	4.8 ^d	4.3 ^b	1.3	3.9 ^d	2.0 ^a	1.4
Astringency	2.2 ^a	11.0 ^d	1.2	2.0 ^b	2.6 ^b	0.1
Mouthcoating	3.7 ^d	4.8 ^b	0.9	2.4 ^d	1.6	0.7
Aftertaste						
Sweet	10.2 ^d	8.6 ^d	2.6	1.8 ^a	2.4 ^d	1.6
Sour	6.3 ^d	16.3 ^d	2.1	2.4 ^d	0.9	0.8
Astringent	1.3	9.1 ^d	2.1	2.4 ^d	2.1 ^b	0.9
Bitter	2.0	15.2 ^d	0.3	2.2 ^d	1.5	0.7
Throatburn	3.5 ^b	7.9 ^d	0.9	1.9 ^b	1.4	0.4

¹Bowel cleansing laxative solutions. *P* > 0.05 not significant (no superscript) vs ^a*P* < 0.05; ^b*P* < 0.01; ^d*P* < 0.001.

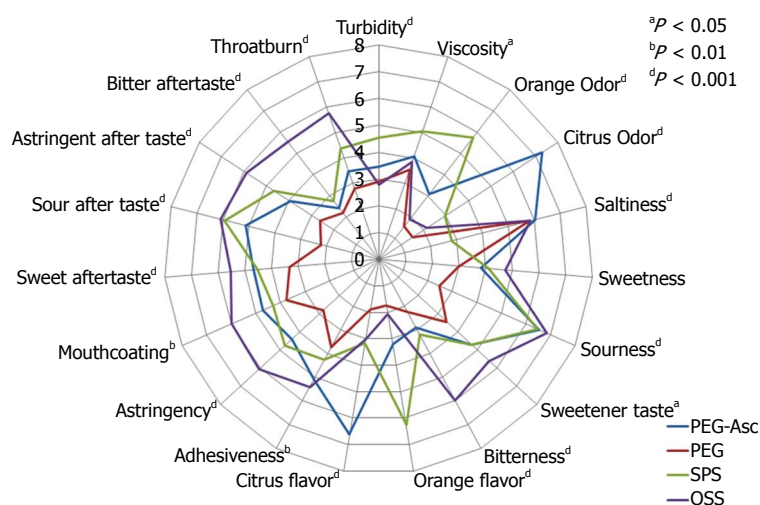


Figure 1 Sensory profiles for the 4 bowel cleansing laxative solutions. Individual attributes are positioned like the spokes of a wheel around a center (zero or not detected) point, with the spokes representing attribute intensity scales, with higher (more intense) values radiating outward. PEG: Polyethylene glycol; PEG-Asc: PEG + ascorbic acid; SPS: Sodium picosulfate; OSS: Oral sodium sulfate.

orange and citrus odors and flavors, saltiness, sourness, bitterness, astringency, sweet, sour, astringent, bitter aftertastes and throatburn (*P* < 0.001); adhesiveness, mouthcoating (*P* < 0.01) and viscosity-appearance and sweetener taste (*P* < 0.05). Replicate effect existed for only viscosity-appearance, citrus odor, sweetness and sweetener tastes (*P* < 0.05) indicating a high level of reliability. The same was true for sample × replicate interaction which was not significant for all attributes (*P* > 0.05). However, this was not the case for sample × panelist which was significant for many attributes (*P* < 0.05) and to a lesser extent for panelist × replicate. Means for the different samples are summarized in Table 3 and in Figure 1, which also include the level of significance for the different attributes. PEG-Asc had

significantly higher ratings than other samples for citrus odor and flavor and adhesiveness (*P* < 0.05), which was not significantly different from OSS. PEG had significantly lower values for bitterness, astringency, sweet, sour and astringent aftertastes (*P* < 0.05). On the other hand, SPS had significantly higher values for turbidity, viscosity-appearance, orange odor and flavor, sourness and sour aftertaste (*P* < 0.05) while OSS had significantly higher values for sweetener taste, bitterness, astringency, mouthcoating, bitter, astringent aftertastes and throatburn (*P* < 0.05).

Hedonic evaluation

Acceptability ratings: The analysis of variance results for the acceptability test are summarized in Table 4.

Table 3 Least squares means of descriptive sensory attributes (rated on a 15 cm line scale) for the bowel cleansing laxative solutions

Attribute	Bowel cleansing laxative solution			
	PEG-Asc (mean \pm SD)	PEG (mean \pm SD)	SPS (mean \pm SD)	OSS (mean \pm SD)
Appearance				
Turbidity	3.5 \pm 2.3 ^c	2.9 \pm 1.8 ^c	4.5 \pm 2.4 ^a	2.8 \pm 1.6 ^c
Viscosity	4.1 \pm 2.7 ^c	3.5 \pm 2.0 ^c	5.0 \pm 2.8 ^a	3.8 \pm 2.3 ^c
Odor				
Orange	3.1 \pm 3.1 ^c	1.6 \pm 0.4 ^e	5.8 \pm 3.4 ^a	1.9 \pm 1.4 ^e
Citrus	7.3 \pm 3.7 ^a	1.5 \pm 0.4 ^e	3.0 \pm 2.3 ^c	2.2 \pm 1.8 ^{ce}
Flavor				
Saltiness	6.0 \pm 3.1 ^a	5.8 \pm 3.2 ^a	2.8 \pm 1.9 ^c	5.8 \pm 3.4 ^a
Sweetness	3.8 \pm 2.4	3.0 \pm 1.9	4.1 \pm 2.6	4.7 \pm 3.4
Sourness	6.6 \pm 3.0 ^a	2.5 \pm 1.4 ^c	6.5 \pm 3.2 ^a	6.9 \pm 3.8 ^a
Sweetener	4.7 \pm 3.5 ^c	3.5 \pm 2.5 ^e	4.7 \pm 3.4 ^c	5.6 \pm 3.3 ^a
Bitterness	2.9 \pm 1.9 ^{ce}	2.2 \pm 1.7 ^e	3.2 \pm 2.1 ^c	6.0 \pm 4.2 ^a
Orange	3.2 \pm 3.3 ^c	1.8 \pm 0.9 ^e	6.3 \pm 4.1 ^a	2.1 \pm 2.0 ^e
Citrus	6.6 \pm 3.9 ^a	1.9 \pm 1.3 ^e	3.2 \pm 2.6 ^c	3.0 \pm 3.2 ^{ce}
Mouthfeel				
Adhesiveness	5.1 \pm 2.6 ^a	3.7 \pm 1.9 ^c	4.3 \pm 2.2 ^c	5.4 \pm 2.6 ^a
Astringency	4.4 \pm 2.6 ^c	2.8 \pm 2.0 ^e	4.5 \pm 2.2 ^c	6.1 \pm 3.4 ^a
Mouthcoating	4.7 \pm 2.8 ^c	3.8 \pm 2.3 ^c	4.3 \pm 2.5 ^c	6.0 \pm 3.2 ^a
Aftertaste				
Sweet	4.7 \pm 3.2 ^{ac}	3.3 \pm 2.3 ^e	4.5 \pm 3.3 ^c	5.5 \pm 3.3 ^a
Sour	5.1 \pm 2.6 ^a	2.2 \pm 1.4 ^c	5.9 \pm 3.1 ^a	6.1 \pm 3.9 ^a
Astringent	4.0 \pm 2.2 ^c	2.6 \pm 1.5 ^e	4.6 \pm 2.6 ^c	5.9 \pm 3.5 ^a
Bitter	2.4 \pm 1.4 ^c	2.2 \pm 1.7 ^c	2.8 \pm 1.6 ^c	5.5 \pm 3.7 ^a
Throatburn	3.5 \pm 2.5 ^{ce}	2.8 \pm 2.1 ^e	4.4 \pm 2.8 ^c	5.7 \pm 3.8 ^a

^{a,c,e}Means within each row with different superscripts are significantly different ($P < 0.05$). PEG: Polyethylene glycol; PEG-Asc: PEG + ascorbic acid; SPS: Sodium picosulfate; OSS: Oral sodium sulfate.

Table 4 Significance of effects (F and P -values) for acceptability attributes for the bowel cleansing solutions

Attributes	Panelist (df = 79)	Sample ¹ (df = 3)
Overall acceptability	1.8 ^d	22.3 ^d
Odor	1.3	4.2 ^b
Taste	1.6 ^b	22.2 ^d
Mouthfeel	1.9 ^d	14.5 ^d

¹Bowel cleansing laxative solutions. $P > 0.05$ not significant (no superscript) vs ^a $P < 0.05$; ^b $P < 0.01$; ^d $P < 0.001$.

Panelist effect was significant for overall acceptability and the acceptability of mouthfeel ($P < 0.001$), taste ($P < 0.01$) but not for odor ($P > 0.05$). Significant differences between samples existed for overall acceptability and acceptability of taste, mouthfeel ($P < 0.001$) and odor ($P < 0.01$). The means of the acceptability variables are summarized in Table 5. SPS was significantly more liked for overall acceptability and the acceptability of taste and mouthfeel ($P < 0.05$) and although it obtained the highest rating for acceptability of odor, it was not significantly different from PEG-Asc or OSS.

Just about right ratings and sample flavor: The JAR scale ratings for the different samples on saltiness, sweetness, sourness and bitterness are illustrated in Figure 2. A high percentage of ratings in the -1 to +1 range is indicative of an optimum level of taste intensity

to the liking of panelists while a high skew to lower or upper ratings is indicative of low or high intensity with respect to the liking of taste, respectively. SPS seems to be the best sample in terms of percentage of subjects who found it to have the optimal taste to their liking. This applied to all four tastes. PEG seemed to have a tilt for higher percentages of subjects who gave higher ratings for saltiness and sourness and the opposite was true for sweetness while a spread of percentages across all ratings for bitterness. PEG-Asc exhibited the same trends as PEG while OSS had a tilt for higher percentages of subjects who gave higher ratings for sweetness, sourness and bitterness. Table 6 summarizes the percentage of subjects who indicated the presence of a certain flavor in the different samples. It is clear, and expected, that none of the subjects noticed any flavor in the PEG sample. PEG-Asc, which is expected to have a lemon-citrus flavor, had only 28% of the subjects who indicated this flavor, while 60% did not indicate any and smaller percentages were given to other flavors, such as orange, fruity, strawberry, green tea and pomegranate. SPS, which is expected to have an orange flavor, also had 28% who indicated the above flavor, while 56% did not indicate any, 13% indicated lemon and 4% indicated fruity. OSS, which is expected to have tropical/exotic fruits, had 55% who did not indicate any flavor, 13% for strawberry, 10% for medicinal, 9% for bubble gum and smaller percentages for other flavors.

Table 5 Least squares means of acceptability variables (rated using the 9-point hedonic scale) for the bowel cleansing laxative solutions

Acceptability variable	Bowel cleansing laxative solution			
	PEG-Asc (mean \pm SD)	PEG (mean \pm SD)	SPS (mean \pm SD)	OSS (mean \pm SD)
Overall acceptability	3.8 \pm 2.1 ^c	3.1 \pm 1.6 ^c	5.5 \pm 2.1 ^a	3.8 \pm 2.4 ^c
Odor	5.5 \pm 2.1 ^{ac}	4.9 \pm 0.9 ^c	5.9 \pm 1.8 ^a	5.5 \pm 2.5 ^{ac}
Taste	3.5 \pm 2.1 ^c	2.9 \pm 1.6 ^c	5.1 \pm 2.3 ^a	3.1 \pm 2.2 ^c
Mouthfeel	4.2 \pm 1.9 ^c	3.8 \pm 1.7 ^{ce}	5.1 \pm 2.0 ^a	3.4 \pm 2.0 ^e

^{a,c,e}Means within each row with different superscripts are significantly different ($P < 0.05$). PEG: Polyethylene glycol; PEG-Asc: PEG + ascorbic acid; SPS: Sodium picosulfate; OSS: Oral sodium sulfate.

Table 6 Percentage of participants' responses to the additional flavor perceived in the different bowel cleansing laxative solutions

Flavor	Bowel cleansing laxative solution			
	PEG-Asc	PEG	SPS	OSS
None	60%	100%	56%	55%
Lemon	28%	0%	13%	1%
Orange	6%	0%	28%	1%
Strawberry	1%	0%	0%	13%
Bubble gum	0%	0%	0%	9%
Cherry	0%	0%	0%	5%
Medicinal	0%	0%	0%	10%
Mint	0%	0%	0%	1%
Green tea	1%	0%	0%	0%
Fruity	3%	0%	4%	4%
Pomegranate	1%	0%	0%	1%

PEG: Polyethylene glycol; PEG-Asc: PEG + ascorbic acid; SPS: Sodium picosulfate; OSS: Oral sodium sulfate.

DISCUSSION

Our study is the first of its kind to analyze the sensory attributes of commercially available bowel preparations commonly used today in an effort to improve the understanding of patients' taste preferences and acceptability of these different bowel cleansing solutions. The study describes 19 different sensory attributes, demonstrating a significant difference in 18 of the 19 under five major categories: Appearance, odor, flavor, mouthfeel and aftertaste. Additionally, our results demonstrated a significant difference of overall acceptability, taste, odor and mouthfeel assessment between the four cleansing solutions as rated on a 9-point hedonic scale.

Based on previous sensory descriptive studies^[7], this study findings introduce a detailed description of the different sensory attributes that bowel cleansing solutions share. Cleansing solutions can be assessed based on appearance (turbidity and viscosity), odor and flavor (orange and citrus), basic tastes (saltiness, bitterness, sourness, sweetness), mouthfeel and aftertaste, characteristics that have not been fully described during palatability interpretation in the literature^[9-14]. Our results demonstrate that characteristics such as orange and citrus odor/flavor and saltiness, sourness and bitterness are strongly noticeable and differentiated when con-

sumed in a low volume, while other attributes such as sweetness are less differentiated. These descriptive analysis sample differences are indicative of the ease of differentiating between samples for panelists due to major differences in the sensory nature of samples. In addition, they can serve as a stepping-stone to create and improve more focused validated instruments aimed at assessing bowel-cleansing solutions. For example, and due to the lack of validated instruments to assess tolerability of bowel cleansing solutions^[6], Patel *et al.*^[14] proposed the Mayo Clinic Bowel Prep Tolerability Questionnaire that, although comprehensive, only slightly touches on the aspect of taste by asking about the severity of bad taste bother during consumption.

Flavoring of bowel cleansing solutions is one of the techniques used to alter palatability and improve patient tolerability. Orange flavor and odor were significantly more noticeable in SPS compared to the three other solutions while citrus flavor and odor were significantly more noticeable in PEG-Asc compared to the three other solutions (Table 3). When sampled by 80 subjects and scaled on a 9 point hedonic scale, SPS (orange-flavored) was significantly more accepted in terms of overall acceptability, taste and mouthfeel compared to the three other samples. These results might indicate that orange and citrus flavors are more effective in improving palatability compared to other flavors. A recent study investigating the addition of 100% orange juice to 2 L PEG-Asc found that palatability scores were higher (2.36 ± 0.76 vs 1.78 ± 0.88 ; $P = 0.005$) when orange juice was added, as was willingness to repeat the same process^[9]. This effect was hypothesized to be due to the intense sourness which offsets the bitter taste of PEG solutions, and the fact that orange juice was kept in the mouth for 5 s prior to solution intake^[9]. Similarly, the addition of citrus reticulate peel to conventional low dose PEG + bicasodol demonstrated higher taste acceptability and lower rates of difficulty swallowing when compared to PEG + bicasodol regimen^[10]. Again, citrus peel was required to stay in the mouth in between solution consumption every 10-15 min. A study by Sharara *et al.*^[12] investigated the role of sugar free menthol drops used with 4 L split dose PEG regimen. Patients instructed to suck on the candy while drinking the solution had significantly higher palatability score and increased willingness to take the same preparation

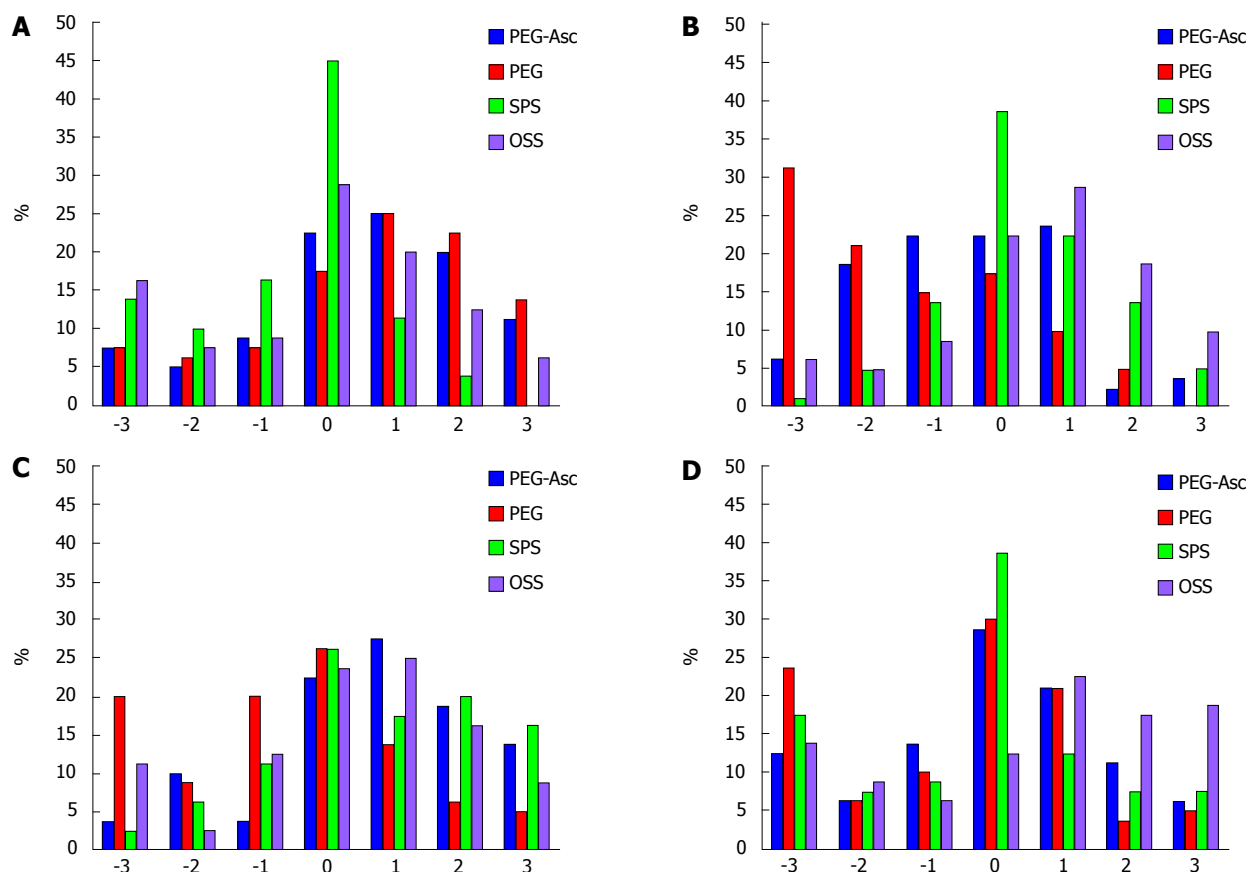


Figure 2 Just-About-Right ratings for saltiness (A), sweetness (B), sourness (C) and bitterness (D) for PEG-Asc (blue), PEG (red), SPS (green) and OSS (violet) samples. -3: Too little; 0: Just about right; 3: Too much; PEG: Polyethylene glycol; PEG-Asc: PEG + ascorbic acid; SPS: Sodium picosulfate; OSS: Oral sodium sulfate.

in the future (92% vs 80%; $P = 0.091$) compared to PEG without menthol^[12]. This regimen was also found to be superior to reduced volume PEG-Asc, in terms of palatability (76% vs 62%; $P = 0.03$) and willingness to retake the solution compared to low volume PEG-Asc (54% vs 40%; $P = 0.047$)^[13]. Of interest, 1 L of pineapple juice demonstrated no change in patient-rated tolerability when added to 4 L and 2 L PEG respectively and compared to each other as well as PEG^[11].

One interesting observation is the low percentage of study participants who correctly perceived the flavor of the solutions tested. While SPS was deemed the most acceptable overall -taste-, odor- and mouthfeel-wise-, only 28% of participants picked up on the orange taste, while 56% indicated that the solution had no flavor. Similarly, only 28% of participants detected lemon flavor in PEG-Asc samples while 60% indicated that the solution had no flavor. Similar results were also true for OSS. Only PEG was correctly perceived to have no flavor in 100% of the cases. This could indicate the possibility that higher flavor concentrations or different flavor ingredients are required in order to make the solutions taste and smell closer to the original attributes marketed. Another possibility for the discordance between marketed and perceived taste could be due to the mechanism of flavor introduction and taste

alteration. Menthol drops for example were kept in the mouth during solution intake instead of being dissolved in an attempt to flavor the solution itself^[12]. Similarly in the citrus study, citrus peel was kept between the tongue and hard palate every 10-15 min in between solution intake and was not swallowed or mixed with the solution^[10]. Pineapple juice however was dissolved in the entire solution volume of 2 L and 4 L^[11] and could have resulted in a dilution effect, compromising the intensity and palatability. The mechanism of action of the former two interventions could have more effectively affected taste transduction leading to significant improvement in palatability, a possibly crucial observation that can add to future clinical trials and introduce a new and different approach to manufacturers manipulating cleansing solution taste for an improved palatability.

Our study has few limitations. It was conducted at a single center with volunteers as panelists thus limiting the generalizability of the results. The study focuses on taste and palatability assessment, thus using a small sample volume of cleansing solution which does not reflect the true effect of large volume intake in real settings. In a previous study investigating the burden of bowel preparation in patients undergoing colonoscopy, patients reported that volume is considered one of the worst aspects of bowel preparation^[6]. Using small

volume samples might have masked some taste aversions that would otherwise have occurred with larger or repeated ingestions^[6]. However, our use of small volumes was necessary to avoid the unwanted purgative effects that would have invariably occurred. Unlike colonoscopy patients who are required to follow dietary restrictions, panelists in our study had no such additional burden that may impact tolerability and possibly allowing more room for observational error and variation in the ability to differentiate and properly rate the sensory attributes under investigation. Low volume split-dose SPS regimens for example are associated with increased hunger secondary to longer dietary restrictions and modifications^[6] that also add to the burden and tolerability of bowel cleansing consumption when taken under realistic measures.

In summary, our study is the first to assess different sensory attributes in regards to bowel cleansing solutions. While previous literature has focused on overall tolerability and willingness to retake solution as a marker for improved palatability, our study introduces taste, odor, flavor and other attributes that interplay in affecting overall tolerability. Sensory evaluation results revealed that SPS (orange flavored) bowel cleansing solution was the most palatable and tolerable by the subjects. The use of a JAR scale and spider plot illustrating the different attributes of each solution is an important visual aid for consumers and physicians, allowing for better customization of a bowel cleansing solution tailored to patients' personal preference. Shedding light on noticeable attributes other than taste and flavor, as well as different mechanisms of taste alteration could also aid bowel cleansing solution manufacturers in the process of product development and lead to new and better modified bowel cleansing.

ACKNOWLEDGMENTS

The authors would like to thank Hani Chaar (PharmD) and Roy Nassif for technical assistance; Soraya Ghantous and Sara Issa for assistance with subjects' recruitment.

COMMENTS

Background

Bowel preparation is an important quality indicator in colonoscopy. Patient adherence can be poor given that these solutions are often considered unpleasant.

Research frontiers

Evaluating the sensory characteristics of commercial bowel cleansing preparations is necessary to optimize consumer acceptability for better compliance with pre-colonoscopy procedures.

Innovations and breakthroughs

Sodium picosulfate (SPS, orange flavored) preparation received higher acceptability ratings than other commercial bowel cleansing solutions, with an optimal level of taste acceptability for saltiness, bitterness and sweetness. SPS might be associated with better palatability and tolerability among other solutions.

Applications

Orange flavored bowel cleansing solutions appear to be more palatable and tolerable by panelists than bland or other flavored preparations.

Peer-review

This is an interesting article that presents novel data on the palatability of various bowel preparations.

REFERENCES

- 1 **Burke CA**, Church JM. Enhancing the quality of colonoscopy: the importance of bowel purgatives. *Gastrointest Endosc* 2007; **66**: 565-573 [PMID: 17725947 DOI: 10.1016/j.gie.2007.03.1084]
- 2 **Dykes C**, Cash BD. Key safety issues of bowel preparations for colonoscopy and importance of adequate hydration. *Gastroenterol Nurs* 2008; **31**: 30-35; quiz 36-37 [PMID: 18300822 DOI: 10.1097/01.SGA.0000310933.54551.ca]
- 3 **Johnson DA**, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, Robertson DJ, Richard Boland C, Giardello FM, Lieberman DA, Levin TR, Rex DK. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2014; **109**: 1528-1545 [PMID: 25223578 DOI: 10.1038/ajg.2014.272]
- 4 **Sharara AI**, Abou Mrad RR. The modern bowel preparation in colonoscopy. *Gastroenterol Clin North Am* 2013; **42**: 577-598 [PMID: 23931861 DOI: 10.1016/j.gtc.2013.05.010]
- 5 **Rex DK**. Bowel preparation for colonoscopy: entering an era of increased expectations for efficacy. *Clin Gastroenterol Hepatol* 2014; **12**: 458-462 [PMID: 24239858 DOI: 10.1016/j.cgh.2013.11.003]
- 6 **Sharara AI**, El Reda ZD, Harb AH, Abou Fadel CG, Sarkis FS, Chalhoub JM, Mrad RA. The burden of bowel preparations in patients undergoing elective colonoscopy. *United Eur Gastroent* 2016; **4**: 314-318 [DOI: 10.1177/2050640615594550]
- 7 **Srouf N**, Daroub H, Toufeili I, Olabi A. Developing a carob-based milk beverage using different varieties of carob pods and two roasting treatments and assessing their effect on quality characteristics. *J Sci Food Agric* 2016; **96**: 3047-3057 [PMID: 26416256 DOI: 10.1002/jsfa.7476]
- 8 **Lawless HT**, Heymann H. Sensory evaluation of food: principles and practices. 2nd ed. Berlin: Springer Science and Business Media, 2010: 325-344
- 9 **Choi HS**, Shim CS, Kim GW, Kim JS, Lee SY, Sung IK, Park HS, Kim JH. Orange juice intake reduces patient discomfort and is effective for bowel cleansing with polyethylene glycol during bowel preparation. *Dis Colon Rectum* 2014; **57**: 1220-1227 [PMID: 25203380 DOI: 10.1097/dcr.0000000000000195]
- 10 **Lan HC**, Liang Y, Hsu HC, Shu JH, Su CW, Hung HH, Hou MC, Lin HC, Lee SD, Wang YJ. Citrus reticulata peel improves patient tolerance of low-volume polyethylene glycol for colonoscopy preparation. *J Chin Med Assoc* 2012; **75**: 442-448 [PMID: 22989539 DOI: 10.1016/j.jcma.2012.06.022]
- 11 **Altınbas A**, Aktas B, Yılmaz B, Ekiz F, Deveci M, Basar O, Simsek Z, Coban S, Tuna Y, Uyar MF, Yuksel O. Adding pineapple juice to a polyethylene glycol-based bowel cleansing regime improved the quality of colon cleaning. *Ann Nutr Metab* 2013; **63**: 83-87 [PMID: 23949576 DOI: 10.1159/000354094]
- 12 **Sharara AI**, El-Halabi MM, Abou Fadel CG, Sarkis FS. Sugar-free menthol candy drops improve the palatability and bowel cleansing effect of polyethylene glycol electrolyte solution. *Gastrointest Endosc* 2013; **78**: 886-891 [PMID: 23769143 DOI: 10.1016/j.gie.2013.05.015]
- 13 **Sharara AI**, Harb AH, Sarkis FS, Chalhoub JM, Badreddine R, Mourad FH, Othman M, Masri O. Split-dose menthol-enhanced PEG vs PEG-ascorbic acid for colonoscopy preparation. *World J Gastroenterol* 2015; **21**: 1938-1944 [PMID: 25684963 DOI: 10.3748/wjg.v21.i6.1938]
- 14 **Patel M**, Staggs E, Thomas CS, Lukens F, Wallace M, Almansa C. Development and validation of the Mayo Clinic Bowel Prep



Endoscopic submucosal dissection of gastric tumors: A systematic review and meta-analysis

Emmanuel Akintoye, Itegbemie Obaitan, Arunkumar Muthusamy, Olalekan Akanbi, Mayowa Olusunmade, Diane Levine

Emmanuel Akintoye, Arunkumar Muthusamy, Diane Levine, Department of Internal Medicine, Wayne State University School of Medicine/Detroit Medical Center, Detroit, MI 48201, United States

Itegbemie Obaitan, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States

Olalekan Akanbi, Department of Internal Medicine, Presence Saint Joseph Hospital, Chicago, IL 60657, United States

Mayowa Olusunmade, School of Public Health, Harvard University, Boston, MA 02115, United States

Author contributions: All authors contributed to this paper.

Conflict-of-interest statement: The authors have no conflict of interest.

Data sharing statement: Dataset and statistical code available from the first author at eakintoy@med.wayne.edu.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Diane Levine, MD, Department of Internal Medicine, Wayne State University School of Medicine/Detroit Medical Center, 4201 St. Antoine St, Detroit, MI 48201, United States. dlllevine@med.wayne.edu
Telephone: +1-313-7457003

Received: March 26, 2016

Peer-review started: March 27, 2016

First decision: May 13, 2016

Revised: June 23, 2016

Accepted: July 11, 2016

Article in press: July 13, 2016

Published online: August 10, 2016

Abstract

AIM: To systematically review the medical literature in order to evaluate the safety and efficacy of gastric endoscopic submucosal dissection (ESD).

METHODS: We performed a comprehensive literature search of MEDLINE, Ovid, CINAHL, and Cochrane for studies reporting on the clinical efficacy and safety profile of gastric ESD.

RESULTS: Twenty-nine thousand five hundred and six tumors in 27155 patients (31% female) who underwent gastric ESD between 1999 and 2014 were included in this study. R0 resection rate was 90% (95%CI: 87%-92%) with significant between-study heterogeneity ($P < 0.001$) which was partly explained by difference in region ($P = 0.02$) and sample size ($P = 0.04$). Endoscopic *en bloc* and curative resection rates were 94% (95%CI: 93%-96%) and 86% (95%CI: 83%-89%) respectively. The rate of immediate and delayed perforation rates were 2.7% (95%CI: 2.1%-3.3%) and 0.39% (95%CI: 0.06%-2.4%) respectively while rates of immediate and delayed major bleeding were 2.9% (95%CI: 1.3-6.6) and 3.6% (95%CI: 3.1%-4.3%). After an average follow-up of about 30 mo post-operative, the rate of tumor recurrence was 0.02% (95%CI: 0.001-1.4) among those with R0 resection and 7.7% (95%CI: 3.6%-16%) among those without R0 resection. Overall, irrespective of the resection status, recurrence rate was 0.75% (95%CI: 0.42%-1.3%).

CONCLUSION: Our meta-analysis, the largest and most comprehensive assessment of gastric ESD till date, showed that gastric ESD is safe and effective for gastric

tumors and warrants consideration as first line therapy when an expert operator is available.

Key words: Endoscopic submucosal dissection; Gastric neoplasms; Meta-analysis

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Our meta-analysis, the largest and most comprehensive assessment of gastric endoscopic submucosal dissection (ESD) to date, showed that gastric ESD is safe and effective for gastric tumors when an expert operator is available. The most compelling evidence is from Asian countries and we recommend the consideration of the procedure as first line therapy in Western countries.

Akintoye E, Obaitan I, Muthusamy A, Akanbi O, Olusunmade M, Levine D. Endoscopic submucosal dissection of gastric tumors: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2016; 8(15): 517-532 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i15/517.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i15.517>

INTRODUCTION

Advances in diagnostic techniques and an improved understanding of gastric tumors has led to a deepening interest in new management techniques aimed to improve outcomes with minimal complications. In the past, open gastrectomy was the standard of care for gastric tumor but open surgery is typically associated with increased morbidity and mortality rates. Laparoscopy-assisted gastrectomy has also been explored as another option but despite being less invasive, there are known issues with accurately locating the lesion and resection of unnecessary quantities of normal tissue. Endoscopic submucosal dissection (ESD) is an alternative and advance way of managing early-stage lesions in the gastrointestinal tract. It allows for complete resection of early-state lesions with the aim of providing tissue for accurate histological diagnosis as well as preventing the reoccurrence of tumors. While somewhat similar to endoscopic mucosal resection (EMR), ESD is as feasible but more effective^[1]. As a minimally invasive management technique developed in Japan in the mid-1990s, ESD has gradually become very widely used in Asia and some part of Europe and America. There is an increasing need to synthesize all the literature currently available to evaluate ESD thoroughly for efficacy and safety profile. We therefore conducted a systematic review and meta-analysis of studies reporting on safety and efficacy of gastric ESD, and evaluated for potential sources of heterogeneity with the aim of elucidating factors affecting these outcomes while utilizing this technique.

MATERIALS AND METHODS

We performed meta-analysis of proportion similar to what has been done in prior studies^[2-9]. We followed the recommendations of the meta-analysis of observational studies in epidemiology during all stages of the design, implementation, and reporting of this meta-analysis^[10].

Search strategy

We performed a comprehensive literature search of MEDLINE, Ovid, CINAHL, and Cochrane for studies published up to October 2014. Our search query for MEDLINE was ("endoscopic submucosal dissection"[tiab] OR "endoscopic submucosal resection"[tiab] OR "submucosal dissection"[tiab] OR "ESD"[tiab]) AND ("stomach"[Mesh] OR gastr*[tiab] OR "foregut"[tiab]). Similar search terms were adapted for the other databases (Table 1).

Study selection

One investigator screened all titles and abstracts for relevance to our study. Two investigators reviewed full text of these articles and applied our pre-defined inclusion/exclusion criteria independently and in duplicate (Figure 1). Hand searching of reference list of the articles was also done in order to retrieve other articles that might have been missed by our search strategy. We included all full-text publications reporting clinical outcome(s) after gastric ESD. Our exclusion criteria were: Animal studies; case reports; commentaries or general reviews; or overlapping publications from the same center. However, review papers and overlapping publications from the same center were included in the initial screening for further assessment of the full-text and reference list after which, for the overlapping publications, only the most updated and comprehensive publication was retained. For the multicenter studies, we excluded all individual studies from the contributing centers if their sample size is comparable or less than that contributed to the multicenter study. Otherwise, we excluded the multicenter study if there are more updated studies from individual centers that provided more information. Articles in foreign language were translated *via* Google translator.

Data extraction

Data from each study were extracted using a standardized data extraction sheet. These included publication information such as author name, year of publication; characteristics of study cohort such as country, name of medical center, study design, number of patients, year of data collection, demographics, setting (single or multi center); characteristics of tumor such as anatomical location, number of tumors, average tumor size, macroscopic or microscopic detail; ESD procedural details such as duration of the procedure and number of failed procedure; and number of patients with clinical success and adverse outcomes.

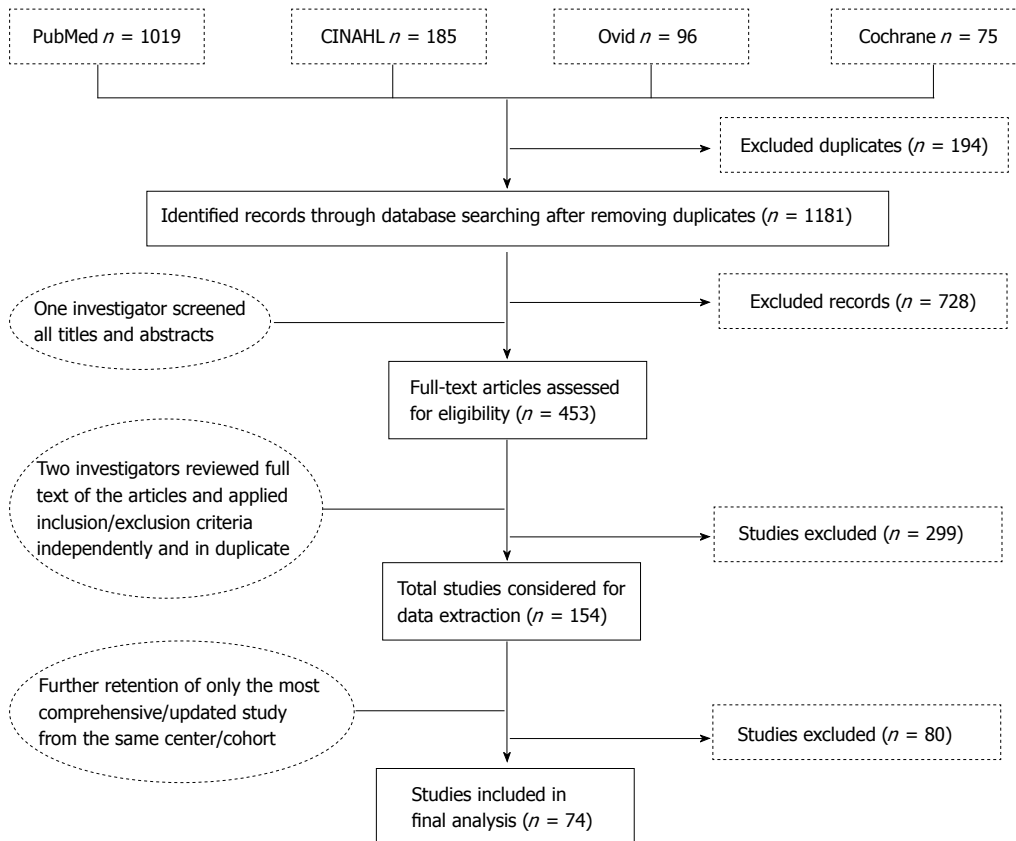


Figure 1 Screening and selection process.

Table 1 Search query

Medline	("endoscopic submucosal dissection"[tiab] OR "endoscopic submucosal resection"[tiab] OR "submucosal dissection"[tiab] OR "ESD"[tiab]) AND ("stomach"[Mesh] OR gastr*[tiab] OR "foregut"[tiab])
Ovid	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissection OR ESD) AND (stomach OR gastr* OR foregut)
CINAHL	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissection OR ESD) AND (stomach OR gastr* OR foregut)
Cochrane	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissection OR ESD) AND (stomach OR gastr* OR foregut)

Endpoints

We assessed both measures of efficacy and adverse outcomes associated with gastric ESD. Our primary measure of efficacy was complete (R0) resection defined as *en bloc* (i.e., one-piece) resection with histologically confirmed tumor-free lateral and vertical margins. In addition, we evaluated endoscopic *en bloc* (i.e., one-piece resection without histological confirmation) and curative resection rate as secondary endpoints. Curative resection was defined as resections with both tumor-free lateral and vertical resection margins, minimal submucosal invasion (< 500 μ m from the muscularis mucosa), and with no lymphovascular invasion or poorly differentiated component. Adverse outcomes include viscus perforation, major bleeding requiring intervention, and tumor recurrence. Immediate adverse events refers to those occurring within 24 h of the procedure

while delayed refers to those occurring after 24 of the procedure. For all endpoints, the rates were evaluated as percentage of number of tumors operated.

Statistical analysis

Proportions from each study were pooled together using logistic-normal random effect model. Study-specific confidence intervals were based on the exact method while confidence intervals for the pooled estimates were based on the Wald method with logit transformation and back transformation. Heterogeneity between studies were assessed *via* visual inspection of the forest plot and χ^2 statistic of the likelihood ratio test comparing the random effect model with its corresponding fixed effect model; Evaluation for potential sources of heterogeneity such as study design, setting, year of data collection (evaluated based on the last year of data collection),

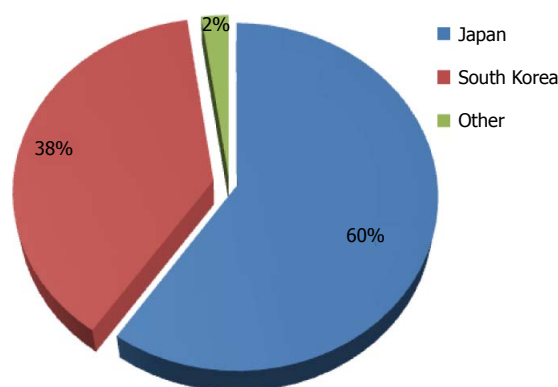


Figure 2 Percentage distribution of 27155 patients who underwent gastric endoscopic submucosal dissection between 1999 and 2014 in 11 countries. Others include China, Taiwan, Australia, Germany, Italy, Poland, Portugal, Brazil and Uruguay that contributed $\leq 1\%$ each.

region (Asia vs Western world), average age, sex distribution, number of tumors, epithelial vs subepithelial tumor, average tumor size, and duration of the procedure were assessed *via* meta-regression. Evaluation for publication bias was assessed *via* visual inspection of the funnel plot and Egger's test. Potential impact of the bias was evaluated with a cumulative meta-analysis after sorting studies in decreasing order of precision (roughly corresponding to largest to smallest study)^[11].

In a subgroup analysis, we evaluated same endpoints in studies reporting outcomes exclusively among patients with cancers, *i.e.*, we excluded studies reporting benign tumors or mixed population of benign and malignant tumors.

Analyses were performed using STATA (Version 13; StataCorp, College Station, TX), 2-tailed $\alpha = 0.05$.

RESULTS

Of the 1181 citations retrieved through database searching, 728 were excluded because they reported no clinical outcome after ESD procedure in human (Figure 1). Four hundred and fifty-three studies underwent full text review using our pre-defined inclusion and exclusion criteria, after which 74 studies published between 2003 and 2014 were retained for data synthesis.

A total of 29506 tumors in 27155 patients (31% female) with average age 67 years (range: 18-95 years) underwent gastric ESD between 1999 and 2014 (Table 2). The majority of these procedures were performed in the Asian countries of Japan and South Korea with very few experiences in the Western world (Figure 2). Average tumor size was 18 mm (range: 1-150 mm), and the procedures were completed in an average time of 73 min (range: 4-750 min).

Efficacy

R0 resection rate was reported in 53 studies across which meta-analysis yielded a pooled estimate of 90% (95%CI: 87%-92%) (Figure 3). There was significant between-study heterogeneity ($P < 0.001$) which was partly

explained by difference in region ($P = 0.02$) and sample size ($P = 0.04$), but not by any of the other pre-specified variables. Specifically, R0 resection rate was higher in Asia compared to the western world, and an increase in number of tumors operated by 100 is associated with 0.7% higher rate. Although significant asymmetry in the funnel plot was apparent ($P = 0.001$) (Figure 4), further exploration with a cumulative meta-analysis suggests that this asymmetry is not likely due to publication bias (Figure 5): The result from high-precision studies (*e.g.*, first 25 studies in Figure 5) did not substantially differ from the overall estimate. In addition, lower estimates were reported in the low-precision studies which is the reverse of what we would expect for a publication bias. Rather, our analysis suggests that the asymmetry is due to true heterogeneity based on sample size. This notion is further supported by finding of sample size as a source of heterogeneity, and lack of asymmetry across quartile of sample size (Figure 6)^[12].

Endoscopic *en bloc* and curative resection rates were reported in 60 and 20 studies respectively. Across studies, meta-analysis yielded a pooled estimate of 94% (95%CI: 93%-96%) (Figure 7) for endoscopic *en bloc* resection rate and 86% (95%CI: 83%-89%) (Figure 8) for curative resection rate. Evaluation for heterogeneity, publication bias, and the result of a cumulative meta-analysis for the secondary endpoints were generally similar to those of R0 resection.

Adverse outcomes

Perforation and major bleeding requiring intervention were the most common peri-operative complications reported (Table 3). Immediate and delayed perforation rates were 2.7% (95%CI: 2.1%-3.3%) and 0.39% (95%CI: 0.06%-2.4%) respectively while rates of immediate and delayed major bleeding were 2.9% (95%CI: 1.3-6.6) and 3.6% (95%CI: 3.1%-4.3%). Evaluation for potential sources of heterogeneity showed that the rate (95%CI) of immediate perforation was significantly lower with epithelial [2.7% (2.2%-3.6%)] compared with subepithelial tumors [8.9% (2.7-15%)] ($P = 0.02$) and has declined by 0.29% (0.05%-0.54%) per year over the duration of study ($P = 0.02$). Similarly, the rate (95%CI) of immediate bleeding has declined by 2.3% (0.72%-3.9%) per year over the duration of study ($P = 0.007$). Lastly, we found that the rate (95%CI) of delayed bleeding increases by 1.3% (0.07%-2.5%) for every 10 years increase in age.

After an average follow up of about 30 mo post-operative, the rate of tumor recurrence was 0.02% (95%CI: 0.001-1.4) among those with R0 resection and 7.7% (95%CI: 3.6%-16%) among those without R0 resection (Table 3). Overall, irrespective of the resection status, recurrence rate was 0.75% (95%CI: 0.42%-1.3%). The rate (95%CI) of recurrence decreases by 0.4% (0.1%-0.7%) for every 10 year increase in age ($P = 0.01$) and there was a trend towards higher rate in Western countries [5.1% (0.5%-11%)] compared with Asia [0.5% (0.3%-0.6%)], $P = 0.06$.

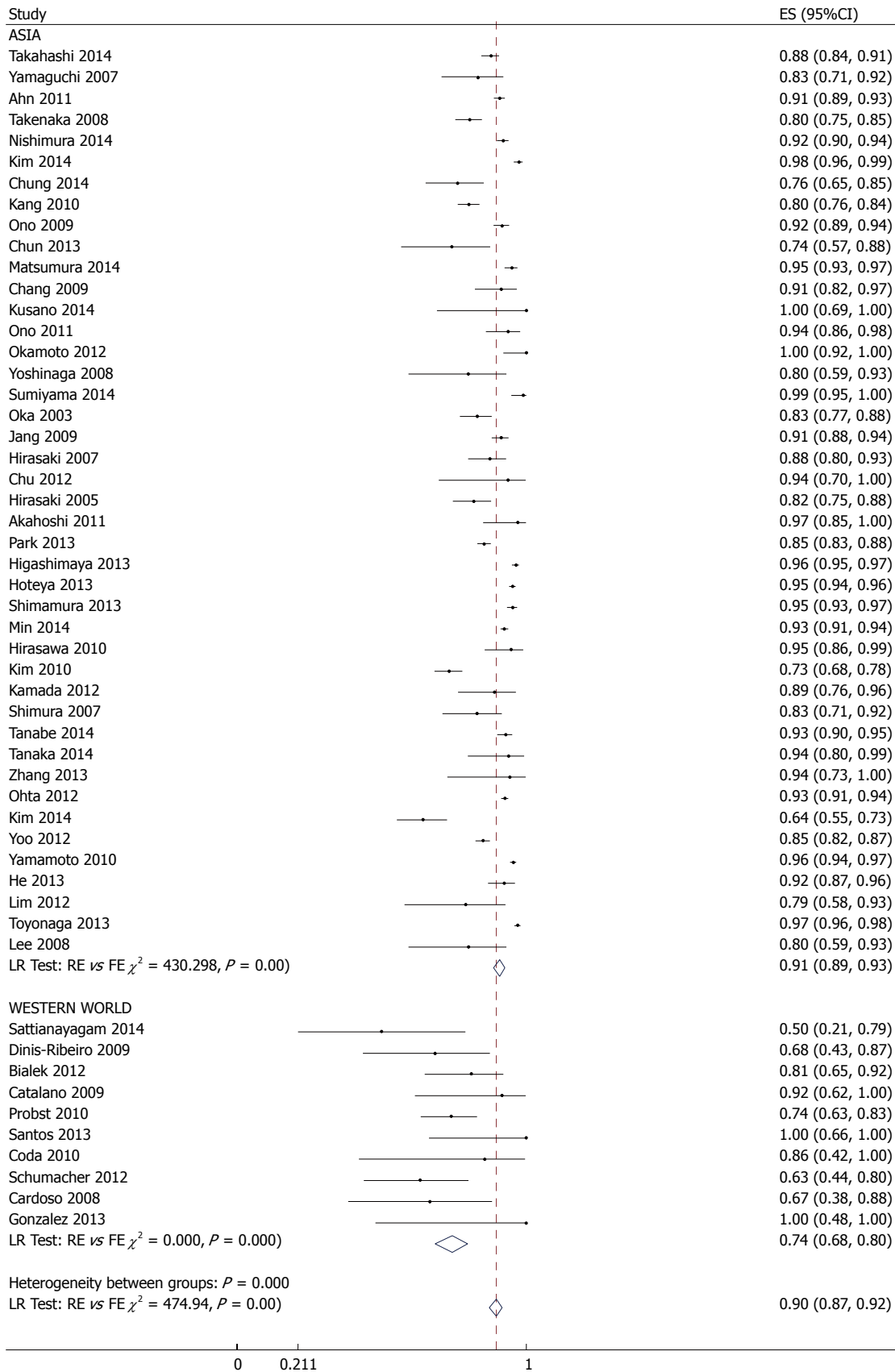


Figure 3 Meta-analysis of histologic *en bloc* resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection, stratified by region. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. ES: Estimate.

Table 2 Characteristics of studies included in the meta-analysis of gastric endoscopic submucosal dissection

Ref.	Data period, yr	Country	Patients, n	Age, mean (range), yr	Female, %	Tumor, n	Tumor size, mean (range), mm	Procedure length, mean (range), min
Sattianayagam <i>et al</i> ^[21]	2008-2012	Australia	10	75 (43-86)	NA	12	35 (15-65)	NA
Cardoso <i>et al</i> ^[22]	2005-2007	Brazil	12	71.2 (27-91)	50	15	16.8 (8-20)	140
Chaves <i>et al</i> ^[23]	2007-2009	Brazil	15	67.1 (32-81)	20	16	16.2 (6-35)	85 (20-150)
Santos <i>et al</i> ^[24]	2010-2011	Brazil	9	65 (58-73)	0	9	28.6 (20-45)	103 (60-240)
Xu <i>et al</i> ^[25]	2006-2009	China	120	51.5 (26-75)	40	120	18.8 (8-30)	64.6 (30-120)
He <i>et al</i> ^[26]	2008-2012	China	144	55.8 (18-78)	72	145	15.14	63.4 (20-180)
Zhang <i>et al</i> ^[27]	2008-2011	China	18	65.3 (30-71)	61	18	26 (10-35)	90 (50-120)
Probst <i>et al</i> ^[28]	2003-2010	Germany	83	68.6 (41-87)	40	91	NA	142 (60-420)
Schumacher <i>et al</i> ^[29]	2008-2010	Germany	30	61 (35-93)	43	30	25 (20-70)	74 (15-402)
Catalano <i>et al</i> ^[30]	2005-2007	Italy	12	68 (38-83)	100	12	NA	111 (62-150)
Coda <i>et al</i> ^[31]	2007-2009	Italy	7	72 (61-83)	43	7	26 (15-50)	123 (50-360)
Hirasaki <i>et al</i> ^[32]	2000-2004	Japan	144	70 (45-91)	NA	144	13	73
Yokoi <i>et al</i> ^[33]	1999-2003	Japan	46	67 (45-89)	9	46	NA	NA
Ono <i>et al</i> ^[34]	2000-2007	Japan	408	67	NA	444	NA	NA
Hirasawa <i>et al</i> ^[35]	2000-2009	Japan	58	69.3	21	58	20.3 (3-50)	82 (22-275)
Yoshinaga <i>et al</i> ^[36]	2001-2006	Japan	24	61.7 (37-85)	8	25	16.5 (3-60)	NA
Takenaka <i>et al</i> ^[37]	2001-2005	Japan	275	NA	NA	306	NA	NA
Miyahara <i>et al</i> ^[38]	2001-2010	Japan	1082	71.7 (36-92)	29	1190	NA	99.8 (10-675)
Ohnita <i>et al</i> ^[39]	2001-2010	Japan	1209	72 (33-95)	27	1322	NA	NA
Oka <i>et al</i> ^[40]	2002-2004	Japan	185	NA	NA	195	19.4 (5-100)	84.4
Shimura <i>et al</i> ^[41]	2002-2005	Japan	55	71.4 (46-91)	22	59	15.5	58 (7-640)
Hirasaki <i>et al</i> ^[42]	2002-2006	Japan	112	70 (45-89)	NA	112	19	69
Ohta <i>et al</i> ^[43]	2002-2010	Japan	1500	NA	NA	1795	NA	NA
Kamada <i>et al</i> ^[44]	2002-2010	Japan	46	65.5 (29-90)	48	46	NA	NA
Toyonaga <i>et al</i> ^[45]	2002-2007	Japan	821	71 (31-93)	34	1136	13 (1-105)	NA
Kosaka <i>et al</i> ^[46]	2002-2007	Japan	438	69.4	26	438	14.6	47 (8-345)
Yamaguchi <i>et al</i> ^[47]	2003-2005	Japan	54	NA	NA	54	19.1 (30-70)	129 (29-440)
¹ Akasaka <i>et al</i> ^[48]	2003-2008	Japan	1188	71	27	1188	20 (2-105)	90 (6-750)
Ono <i>et al</i> ^[49]	2003-2011	Japan	80	69.6	20	80	NA	83.7
¹ Toyokawa <i>et al</i> ^[50]	2003-2010	Japan	967	NA	32	1123	18	98
Tanabe <i>et al</i> ^[51]	2003-2007	Japan	421	69 (41-91)	23	421	NA	67 (7-360)
Shimamura <i>et al</i> ^[52]	2004-2012	Japan	521	NA	NA	616	NA	NA
Takahashi <i>et al</i> ^[53]	2004-2013	Japan	459	71.4	25	459	17.2	NA
Yamamoto <i>et al</i> ^[54]	2005-2011	Japan	1430	69.6	28	1520	15.3	101
Higashimaya <i>et al</i> ^[55]	2005-2011	Japan	891	69.1	27	1027	18.3	NA
Hoteya <i>et al</i> ^[56]	2005-2010	Japan	1224	68	24	1463	21	89
Matsumura <i>et al</i> ^[57]	2005-2014	Japan	413	72.1	30	425	18.4	NA
Sohara <i>et al</i> ^[58]	2006-2011	Japan	681	70.9 (45-91)	40	850	20.8 (2-150)	42 (4-360)
¹ Nishimura <i>et al</i> ^[59]	2006-2012	Japan	669	71	27	750	NA	NA
Tsuji <i>et al</i> ^[60]	2007-2009	Japan	328	68	29	398	43	69
Akahoshi <i>et al</i> ^[61]	2007-2009	Japan	35	72 (52-85)	34	35	15.6	104 (33-264)
Mukai <i>et al</i> ^[62]	2007-2010	Japan	142	72.4	32	161	NA	81
Tanaka <i>et al</i> ^[63]	2008-2011	Japan	32	71 (56-84)	63	33	17 (4-67)	111 (23-399)
Okamoto <i>et al</i> ^[64]	2009-2010	Japan	45	69 (49-83)	29	45	14 (10-35)	80
Watari <i>et al</i> ^[65]	2010-2012	Japan	94	70.9 (48-87)	24	98	NA	NA
Sumiyama <i>et al</i> ^[66]	2010-2012	Japan	100	NA	18	105	18 (3-53)	34 (4-151)
Kusano <i>et al</i> ^[67]	2011-2012	Japan	10	69.2	20	10	16.3	130.5
Kawamura <i>et al</i> ^[68]	NA	Japan	4	NA	25	4	24 (14-36)	50.5 (28-72)
Lee <i>et al</i> ^[69]	2003-2008	South Korea	461	62	30	487	NA	NA
Kim <i>et al</i> ^[70]	2003-2006	South Korea	337	NA	23	337	16	49
¹ Shin <i>et al</i> ^[71]	2003-2010	South Korea	1105	65 (27-87)	32	1105	NA	NA
Jang <i>et al</i> ^[72]	2004-2007	South Korea	402	60 (34-84)	37	402	NA	NA
Kim <i>et al</i> ^[73]	2004-2007	South Korea	142	62	34	142	NA	NA
Kang <i>et al</i> ^[74]	2005-2008	South Korea	456	62.4	23	456	20.6	NA
Goh <i>et al</i> ^[75]	2005-2009	South Korea	210	NA	NA	210	NA	NA
Ahn <i>et al</i> ^[76]	2005-2008	South Korea	889	62.8	23	916	21.5	37.5
Yoo <i>et al</i> ^[77]	2005-2010	South Korea	729	64 (55-70)	26	823	18 (12-25)	52 (33-84)
Lim <i>et al</i> ^[78]	2005-2011	South Korea	24	63 (56-75)	21	24	16 (4-52)	42 (16-103)
Park <i>et al</i> ^[79]	2005-2011	South Korea	916	62	73	931	NA	NA
Chung <i>et al</i> ^[80]	2005-2010	South Korea	76	61.1	42	76	NA	NA
Kim <i>et al</i> ^[81]	2007-2012	South Korea	126	55 (28-85)	44	126	12 (1-50)	NA
Min <i>et al</i> ^[82]	2007-2011	South Korea	1527	63 (27-87)	21	1577	16 (1-110)	NA
Kim <i>et al</i> ^[83]	2008-2010	South Korea	440	64	29	450	19	48
Yoon <i>et al</i> ^[84]	2008-2010	South Korea	1319	63	34	1443	15.7	61.8
Choi <i>et al</i> ^[85]	2008-2012	South Korea	616	NA	26	616	12.9	27.7
Chun <i>et al</i> ^[86]	2009-2012	South Korea	35	54.15	NA	35	18	32.3 (7-84)

¹ Chung <i>et al</i> ^[87]	2010-2012	South Korea	76	64	36	76	NA	44
Kim <i>et al</i> ^[88]	2012-2013	South Korea	446	NA	34	446	NA	NA
Bialek <i>et al</i> ^[89]	2007-2010	Poland	37	63 (24-86)	62	37	25 (10-60)	NA
Dinis-Ribeiro <i>et al</i> ^[90]	2005-2008	Portugal	19	74	NA	19	NA	90 (40-300)
Lee <i>et al</i> ^[91]	2004-2006	Taiwan	25	69 (36-82)	44	25	19	NA
¹ Chang <i>et al</i> ^[92]	2004-2007	Taiwan	70	66.5 (35-84)	36	70	18.5 (8-40)	92.4 (25-210)
Chu <i>et al</i> ^[93]	2009-2011	Taiwan	16	51.9 (35-65)	63	16	26.1 (20-42)	52 (30-120)
González <i>et al</i> ^[94]	NA	Uruguay	5	NA	NA	5	25.2	85 (30-180)

¹Multicenter studies. NA: Not available.

Table 3 Rates of adverse outcomes in patients undergoing gastric endoscopic submucosal dissection between 1998 and 2014

Adverse outcomes	Studies, <i>n</i>	Patients, <i>n</i>	Tumor, <i>n</i>	Rate (95%CI), % ¹
Immediate ²				
Perforation ³	66	24855	27118	2.7 (2.1, 3.3)
Major bleeding ⁴	19	3815	3943	2.9 (1.3, 6.6)
Delayed ⁵				
Perforation	13	2570	2852	0.39 (0.06, 2.4)
Major bleeding ⁶	63	21612	23338	3.6 (3.1, 4.3)
Recurrence ⁷				
Among tumors with R0	17	-	2027	0.02 (0.001, 1.4)
Among tumors without R0	13	-	203	7.7 (3.6, 16)
Irrespective of R0 status ⁸	33	11256	12398	0.75 (0.42, 1.3)

¹The rates are calculated as a percentage of the total number of tumors operated; ²Immediate refers to adverse outcomes occurring within 24 h of the procedure; ³The rate (95%CI) of immediate perforation was significantly lower with epithelial [2.7% (2.2%-3.6%)] compared with subepithelial tumors [8.9% (2.7%-15%)] ($P = 0.02$) and declined by 0.29% (0.05%-0.54%) per year over the duration of study ($P = 0.02$); ⁴The rate (95%CI) of major immediate bleeding declined by 2.3% (0.72%-3.9%) per year over the duration of study ($P = 0.007$); ⁵Delayed refers to adverse outcome occurring 24 h after the procedure; ⁶The rate (95%CI) of delayed bleeding increases by 1.3% (0.07%-2.5%) for every 10 year increase in age; ⁷Average follow-up was 26, 28 and 32 mo for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively; ⁸The rate (95%CI) of recurrence decreases by 0.4% (0.1%-0.7%) for every 10 year increase in age ($P = 0.01$) and there was a trend towards higher rate in Western countries [5.1% (0.5%-11%)] compared with Asia [0.5% (0.3%-0.6%)] ($P = 0.06$). R0: Histologically-confirmed *en bloc* resection.

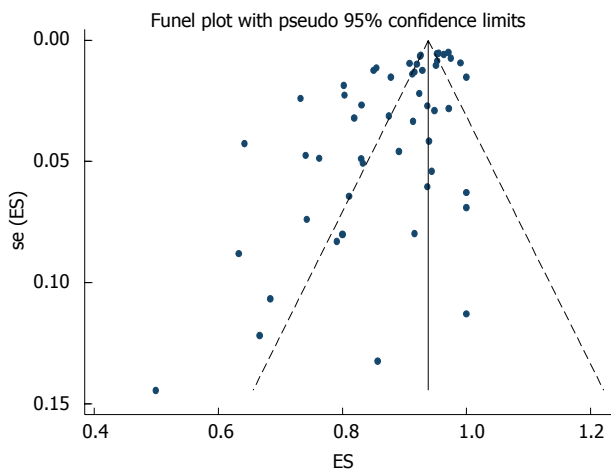


Figure 4 Funnel plot of histologically confirmed *en bloc* (R0) resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection. Each dot represents the R0 resection rate. Asymmetry in the distribution of study estimates around the center of the funnel suggests a potential publication bias. P value for egger's test < 0.001. ES: Estimate; se (ES): Standard error of estimate.

Our estimates were generally comparable to those of subgroup analysis restricting to studies reporting outcomes exclusively among patients with cancer although with slightly higher risk of recurrence (Table 4).

DISCUSSION

Our meta-analysis showed that, across multiple studies in 11 countries, ESD demonstrated an excellent treatment success in patients with gastric tumors. Perioperatively, perforation and major bleeding were the most commonly reported serious adverse outcomes but their risk is modest. In addition, the risk of tumor recurrence in patients with treatment success after a moderate duration of follow-up is very low. These findings provide evidence that ESD is effective and offers a reasonable safety profile across a wide range of patients.

Treatment success was assessed in three ways: R0, endoscopic *en bloc* and curative resection rates. In this study, we considered R0 resection as primary endpoint. Across studies, there were excellent results based on this endpoint. However, there was significant heterogeneity in study estimates that was partly explained by two main factors: First, the estimates vary by region, with higher rates of clinical success being reported by studies from Asia compared to the western world. This, in a way, was expected since the procedure was developed in Asia and has been used for a long time in this part of the world allowing for the development of expert skill needed for the procedure

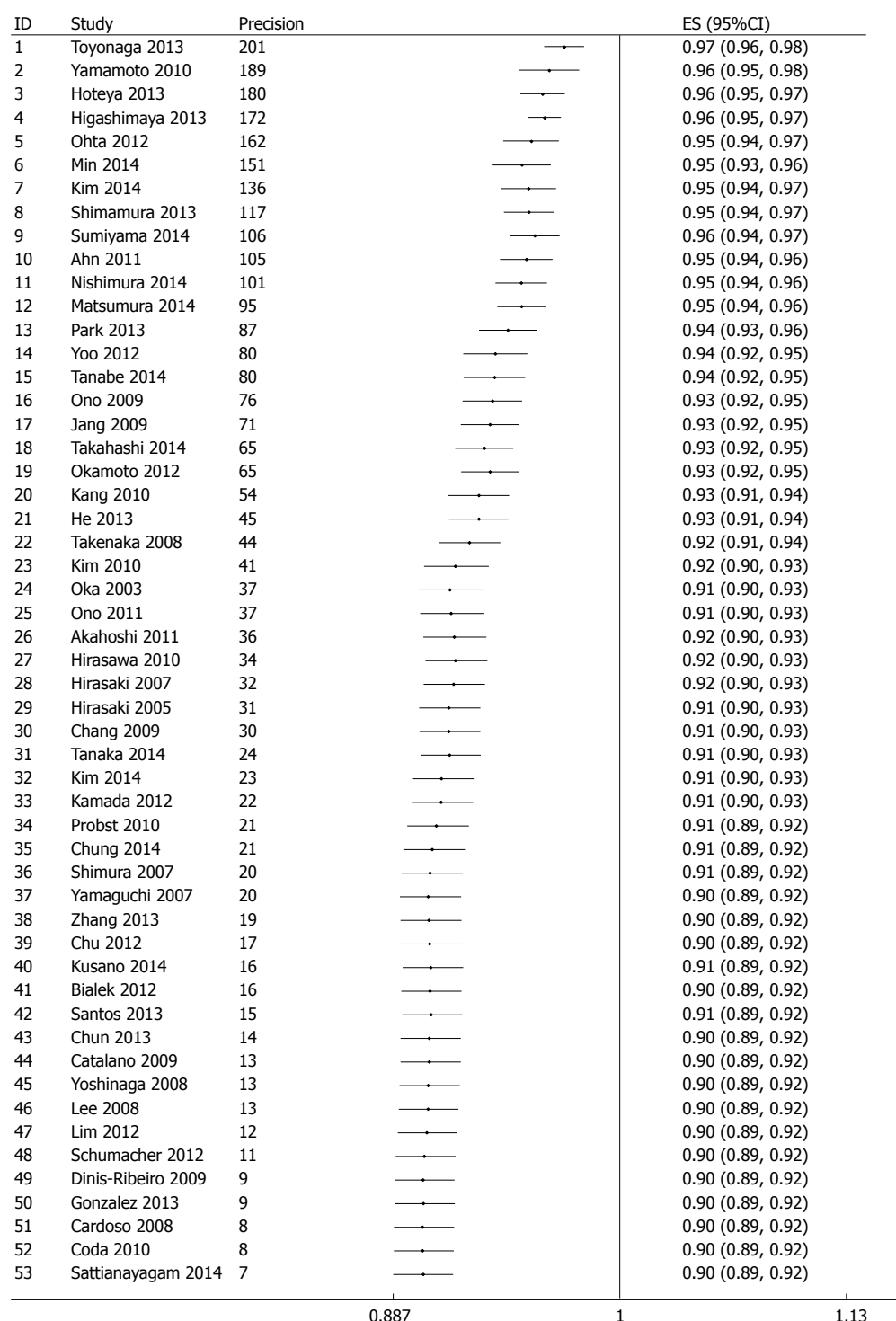


Figure 5 Evaluation of potential publication bias via a cumulative meta-analysis plotted as a function of study precision. The dots and the error bars correspond to the cumulative estimates and associated 95%CI respectively. After sorting by precision (calculated as inverse of standard error) from most precise to least precise study, a variance - weighted method was used to obtain cumulative meta-analysis estimates by adding one study at a time. Analysis begins with the most precise study; thereafter, effect estimate from the next study in order of decreasing precision are added at each step in the analysis and cumulative estimate and 95%CI is recalculated until the least precise study is added.

as well as development of better techniques. On the other hand, experience in the procedure had been low in other parts of the world. Second, lower rates of treatment success were reported in the smaller studies compared to the large ones. Since the number of tumor operated is expected to correlate with level of expertise,

we presume this is an indicator of better outcome with increasing level of expertise or experience.

Perioperatively, major bleeding and perforation were the most common serious adverse events. However, most of these adverse events were successfully managed endoscopically with only very few ones requiring surgical

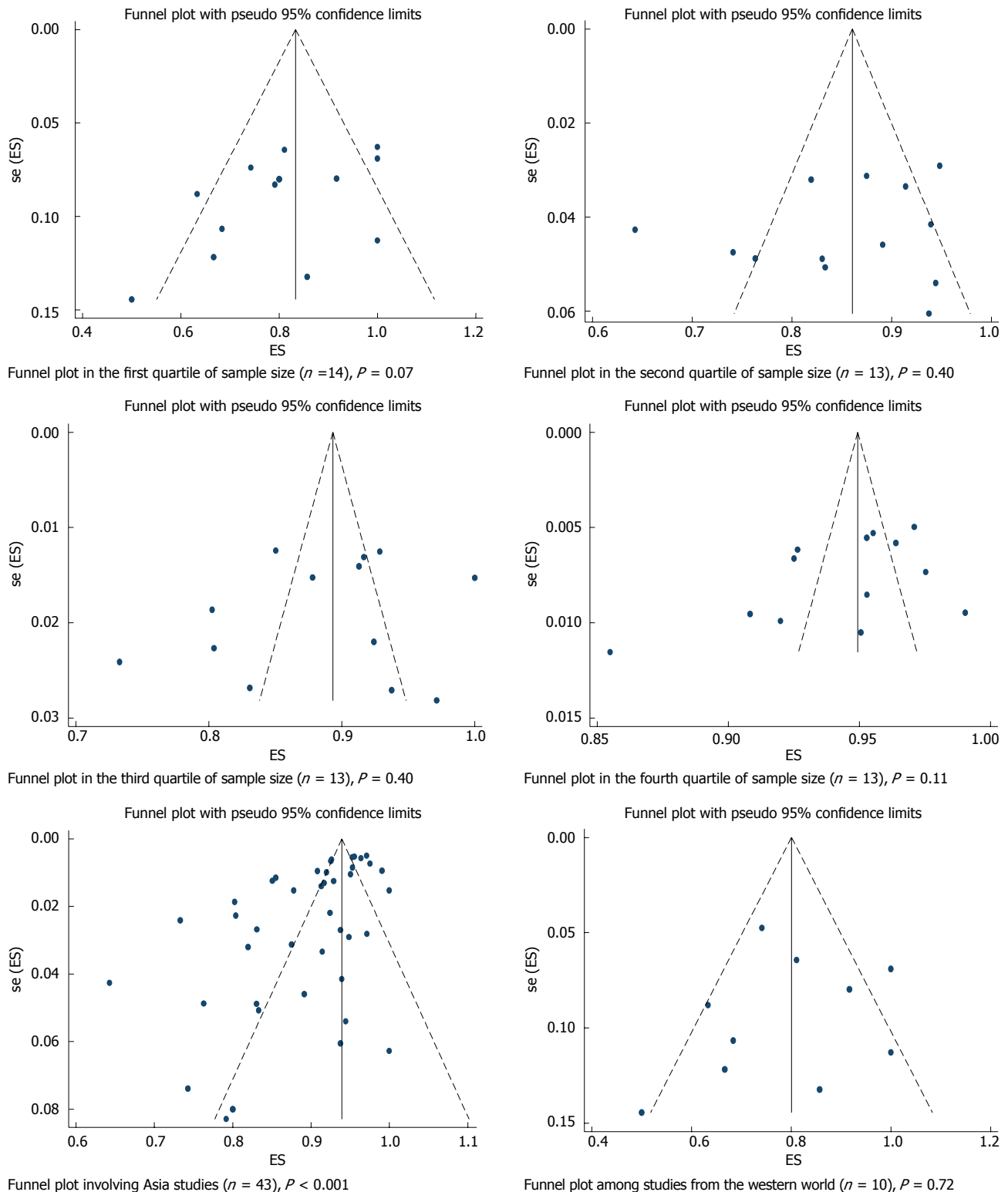


Figure 6 Funnel plot of histologically confirmed *en bloc* (R0) resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection, stratified based on sources of heterogeneity. Each dot represents the R0 resection rate. Lack of asymmetry in the funnel plot within quartile of study precision (calculated as inverse of standard error) indicates that the asymmetry in the overall plot (Figure 4) is most likely due to true heterogeneity by sample size rather than a publication bias. P values were calculated based on Egger's test. ES: Estimate; se (ES): Standard error of estimate.

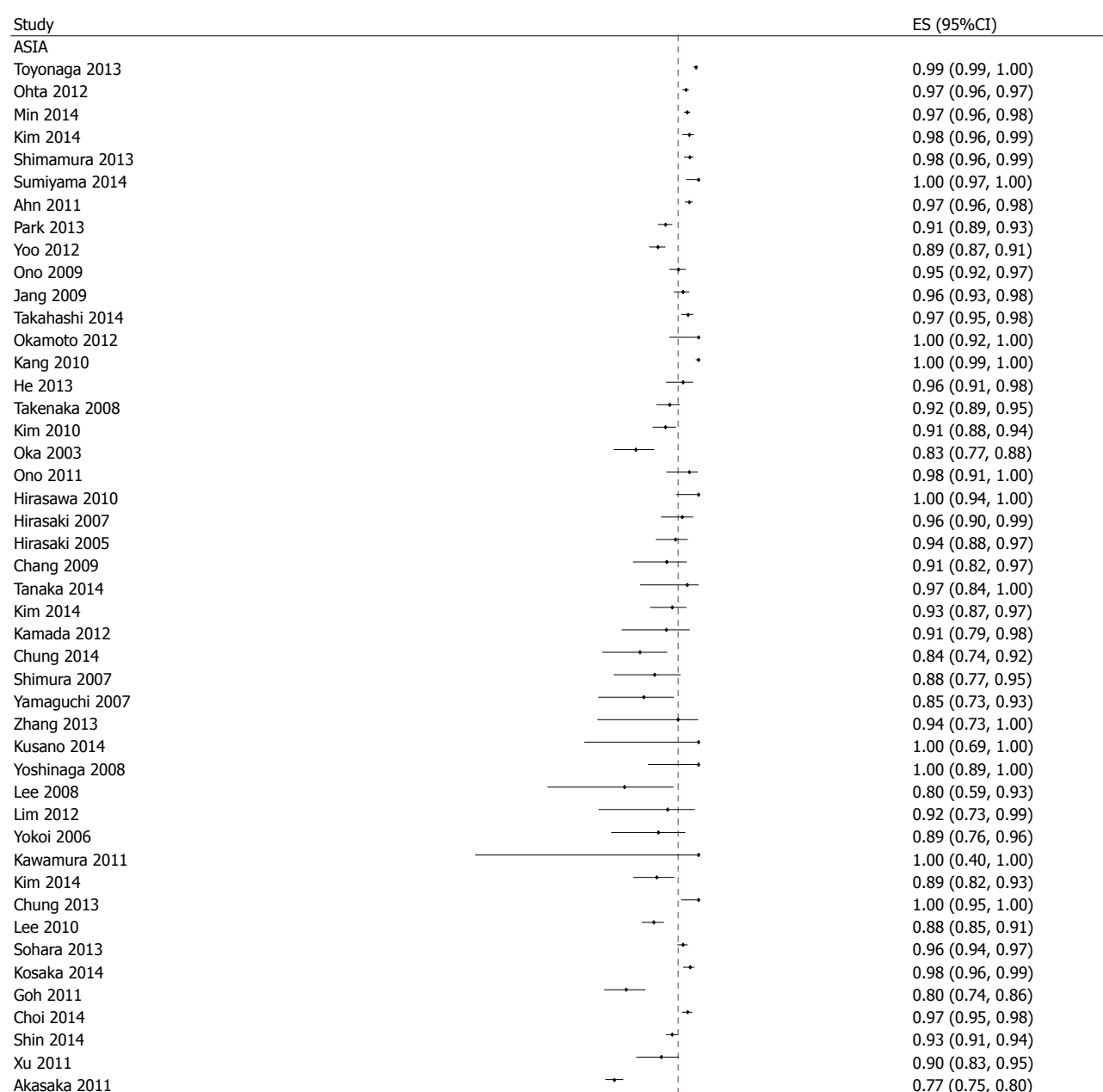
intervention. The relatively low risk of recurrence has been the attractive feature of ESD. After a moderate follow up, tumor recurrence was present in only 8 in 1000 tumors after the procedure, and this rate was

majorly influenced by those without R0 resection, *i.e.*, patients with positive lateral or vertical tumor margins. In patients with R0 resection, the risk of recurrence is negligible: 2 in 10000 tumors. Overall, our estimates

Table 4 Clinical outcomes among patients with gastric cancers who underwent endoscopic submucosal dissection

Outcomes	Studies, <i>n</i>	Tumor, <i>n</i>	Rate (95%CI) ¹
Efficacy measures			
R0 resection	24	8520	87 (84-90)
Endoscopic <i>en bloc</i> resection	29	9652	94 (91-96)
Curative resection	10	5234	83 (80-86)
Safety measures			
Immediate perforation ²	31	12076	3.1 (2.4-3.9)
Immediate major bleeding ²	6	303	2.9 (0.24-27)
Delayed perforation ³	6	1486	0.15 (0.01-3.8)
Delayed bleeding ³	29	11925	3.8 (3.0-4.7)
Recurrence (if R0) ⁴	8	724	0.14 (0.004-4.6)
Recurrence (if not R0) ⁴	7	152	8.5 (3.6-19)
Recurrence (irrespective of R0 status) ⁴	18	7681	0.77 (0.39-1.5)

¹The rates are calculated as a percentage of the total number of tumors operated; ²Immediate refers to adverse outcomes occurring within 24 h of the procedure; ³Delayed refers to adverse outcome occurring 24 h after the procedure; ⁴Average follow-up was about 26, 24 and 37 mo for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively. R0: Histologically-confirmed *en bloc* resection.



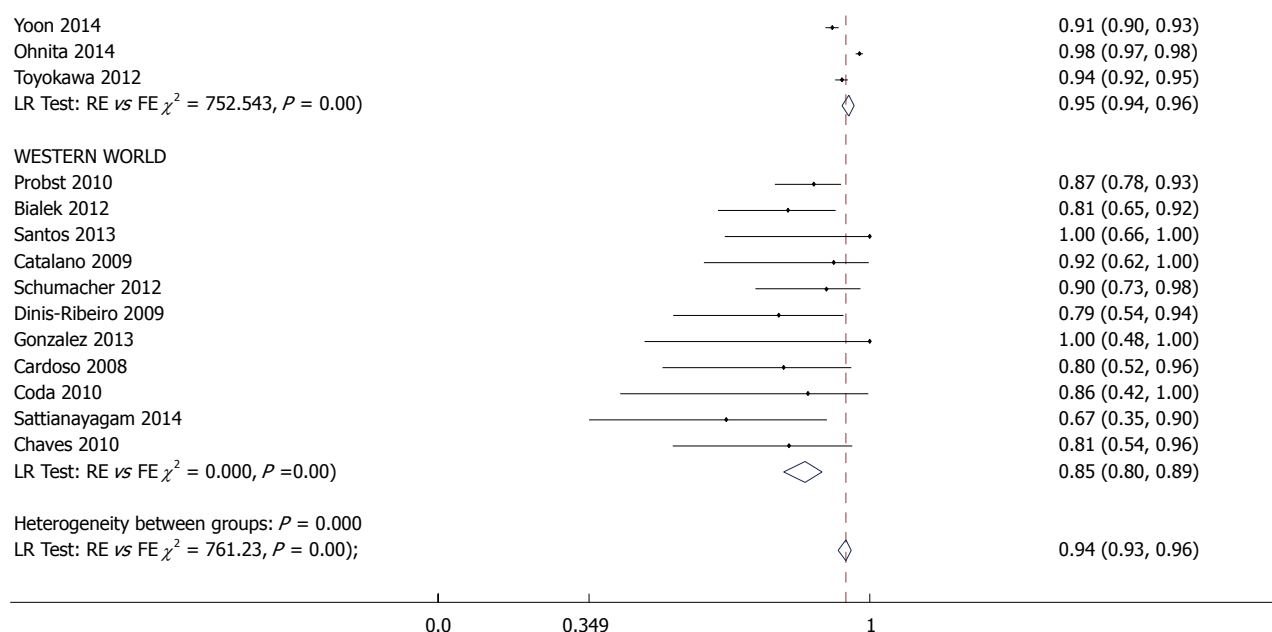


Figure 7 Meta-analysis of endoscopic *en bloc* resection rate in 60 studies involving 21511 tumors in 19935 patients that underwent gastric endoscopic submucosal dissection, stratified by region. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. ES: Estimate.

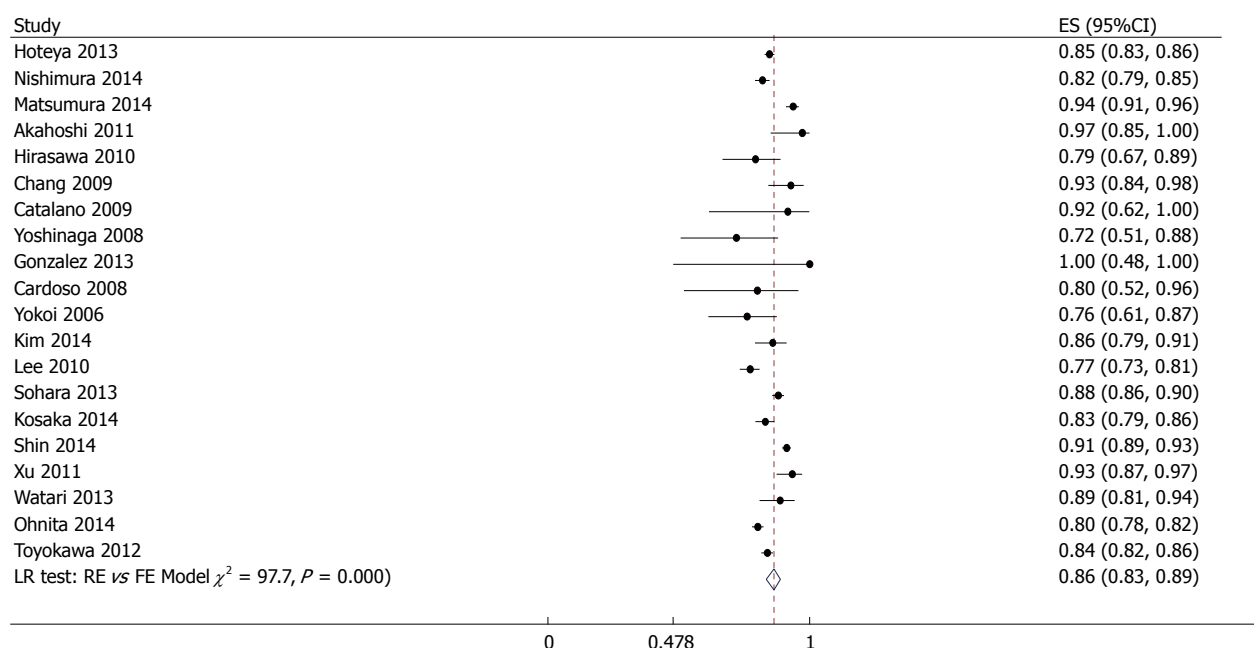


Figure 8 Meta-analysis of curative resection rate in 20 studies involving 8589 tumors in 7785 patients that underwent gastric endoscopic submucosal dissection. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. All studies except one (Emura 2014, Colombia) were from Asia. ES: Estimate.

were comparable to those of subgroup analysis involving studies exclusively among patients with cancer, although with slightly higher risk of recurrence in this subgroup.

Before the invention of ESD in the late 1990s in Japan, EMR was the most widely used minimally invasive option for non-invasive gastric tumors in the world; and it's still the most widely used in many Western countries.

However, the superior benefit of ESD in terms of complete resection and tumor recurrence as compared to EMR had been demonstrated in a few meta-analysis^[13-15]. Although the risk of bleeding and perforation tends to be higher with ESD, most cases of such adverse event were amenable to endoscopic management; thus, making the benefit to outweigh the risk^[16]. Absolute indications for

endoscopic resection had included moderately or well-differentiated elevated cancers ≤ 20 mm in diameter; and small (≤ 10 mm), flat and depressed lesions without ulceration or scarring. In addition, these lesions must be intra-mucosal and with no lymphovascular involvement. However, the success of ESD has led to the extension of this criteria to include intra-mucosal cancer without ulceration > 20 mm or with ulcerations ≤ 30 mm, and upper submucosal cancer ≤ 30 mm. Overall, ESD remains the best endoscopic option for cancers ≥ 20 mm while EMR is an option for those < 20 mm. Endoscopic resection is however not indicated in tumors with poorly differentiated component or signet ring cell^[17]. Furthermore, the proficiency of the ESD procedure takes some time to acquire as prior studies have suggested that it takes at least 30 procedures for a beginner to overcome the learning curve^[18,19].

Our study has several strengths. Notably, a guideline-driven approach ensures that our analysis was systematic and comprehensive. In addition, we made attempt to gather all available data by placing no restriction on language, date of publication, location, *etc.* Our moderately large number of studies enabled us to shed more light on potential sources of heterogeneity in clinical outcomes after ESD.

Limitations of this study should also be considered. First, due to rapidly evolving techniques in ESD procedures, the rates of each outcome may vary slightly by technique and our rates of adverse outcomes might have been over-estimated compared to new technique. This is particularly apparent with the finding of declining rates of immediate perforation and bleeding over the study period. Second, the recurrence rates were assessed after variable follow-up between and within study, and since the rate of recurrence is time-dependent, cautious interpretation of average follow-up reported is warranted when applied to individual cases. Third, there was significant asymmetry in the funnel plot of histologic *en bloc* resection rate indicating potential selective reporting of outcomes by authors. However, further exploration with cumulative meta-analysis indicates that this asymmetry is not likely due to publication bias since lower estimates were reported in the low precision studies^[20]. Rather, we presume that the asymmetry is probably due to chance or better expertise among the high precision studies since precision is proportional to the number of tumors operated, which in turn is expected to correlate with level of expertise. In addition, we mitigated against publication bias in our methodology by placing no restriction on publication language and excluding all overlapping studies^[20].

In conclusion, gastric ESD is a safe and effective technique based on the large and broad body of current medical literature. It compares favorably with EMR and warrants consideration as first-line therapy when an expert operator is available.

submucosal dissection (ESD) for *en-bloc* resection of gastrointestinal tumors. The authors systematically reviewed the medical literature to evaluate the safety and efficacy of gastric ESD.

Research frontiers

Accumulating evidence from Asia suggests that ESD is safe and more effective than other minimally invasive alternative such as endoscopic mucosal resection. However, the procedure is still not popular in the West and the available results (even from Asia) are mixed. The authors therefore performed a systematic review and meta-analysis to analyze available evidence and explore for potential sources of heterogeneity.

Innovations and breakthroughs

This meta-analysis represents the largest assessment of gastric ESD to date. The authors were able to show that gastric ESD is safe and effective when an expert operator is available. More importantly, they were also able to explore for sources of heterogeneity among the available results in the literature.

Applications

The authors believe that with proper training in the techniques of gastric ESD, this procedure can become the first line therapy for gastric tumor in Western countries.

Terminology

ESD is an advanced endoscopic technique used to remove gastrointestinal tumors. The procedure involves passage of endoscopic tube through the throat in order to assess the tumor in the stomach. Thereafter, the tumor dissection is performed by injecting fluid below the lesion at the submucosal layer in order to elevate the tumor. The procedure is completed by dissecting through the surrounding mucosa to the submucosal layer beneath the tumor. Meta-analysis is a statistical method used to combine results from multiple similar studies in order to achieve a greater statistical power and evaluate for potential sources of heterogeneity.

Peer-review

The article is very interesting and well written. The number of studies and patients included is also very satisfactory.

REFERENCES

- 1 **Watanabe K**, Ogata S, Kawazoe S, Watanabe K, Koyama T, Kajiura T, Shimoda Y, Takase Y, Irie K, Mizuguchi M, Tsunada S, Iwakiri R, Fujimoto K. Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest Endosc* 2006; **63**: 776-782 [PMID: 16650537 DOI: 10.1016/j.gie.2005.08.049]
- 2 **Barbieri LA**, Hassan C, Rosati R, Romario UF, Correale L, Repici A. Systematic review and meta-analysis: Efficacy and safety of POEM for achalasia. *United European Gastroenterol J* 2015; **3**: 325-334 [PMID: 26279840 DOI: 10.1177/2050640615581732]
- 3 **Lazarou J**, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200-1205 [PMID: 9555760]
- 4 **Puli SR**, Kakugawa Y, Saito Y, Antillon D, Gotoda T, Antillon MR. Successful complete cure *en-bloc* resection of large nonpedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. *Ann Surg Oncol* 2009; **16**: 2147-2151 [PMID: 19479308 DOI: 10.1245/s10434-009-0520-7]
- 5 **Kim JS**, Kim BW, Shin IS. Efficacy and safety of endoscopic submucosal dissection for superficial squamous esophageal neoplasia: a meta-analysis. *Dig Dis Sci* 2014; **59**: 1862-1869 [PMID: 24619279 DOI: 10.1007/s10620-014-3098-2]
- 6 **Park CH**, Kim EH, Kim HY, Roh YH, Lee YC. Clinical outcomes of endoscopic submucosal dissection for early stage esophagogastric junction cancer: a systematic review and meta-analysis. *Dig Liver Dis* 2015; **47**: 37-44 [PMID: 25454708 DOI: 10.1016/j.dld.2014.10.011]
- 7 **Tanimoto MA**, Guerrero ML, Morita Y, Aguirre-Valadez J, Gomez E, Moctezuma-Velazquez C, Estradas-Trujillo JA, Valdovinos MA,

COMMENTS

Background

Advances in endoscopic techniques have led to the development of endoscopic

- Uscanga LF, Fujita R. Impact of formal training in endoscopic submucosal dissection for early gastrointestinal cancer: A systematic review and a meta-analysis. *World J Gastrointest Endosc* 2015; **7**: 417-428 [PMID: 25901222 DOI: 10.4253/wjge.v7.i4.417]
- 8 **Bang CS**, Baik GH, Shin IS, Kim JB, Suk KT, Yoon JH, Kim YS, Kim DJ, Shin WG, Kim KH, Kim HY, Lim H, Kang HS, Kim JH, Kim JB, Jung SW, Kae SH, Jang HJ, Choi MH. Endoscopic submucosal dissection for early gastric cancer with undifferentiated-type histology: A meta-analysis. *World J Gastroenterol* 2015; **21**: 6032-6043 [PMID: 26019470 DOI: 10.3748/wjg.v21.i19.6032]
 - 9 **Nyaga VN**, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; **72**: 39 [PMID: 25810908 DOI: 10.1186/2049-3258-72-39]
 - 10 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670]
 - 11 **Leimu R**, Koricheva J. Cumulative meta-analysis: a new tool for detection of temporal trends and publication bias in ecology. *Proc Biol Sci* 2004; **271**: 1961-1966 [PMID: 15347521 DOI: 10.1098/rspb.2004.2828]
 - 12 **Sterne JA**, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; **343**: d4002 [PMID: 21784880 DOI: 10.1136/bmj.d4002]
 - 13 **Cao Y**, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; **41**: 751-757 [PMID: 19693750 DOI: 10.1055/s-0029-1215053]
 - 14 **Lian J**, Chen S, Zhang Y, Qiu F. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. *Gastrointest Endosc* 2012; **76**: 763-770 [PMID: 22884100 DOI: 10.1016/j.gie.2012.06.014]
 - 15 **Facciorusso A**, Antonino M, Di Maso M, Muscatello N. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. *World J Gastrointest Endosc* 2014; **6**: 555-563 [PMID: 25400870 DOI: 10.4253/wjge.v6.i11.555]
 - 16 **Park YM**, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. *Surg Endosc* 2011; **25**: 2666-2677 [PMID: 21424201 DOI: 10.1007/s00464-011-1627-z]
 - 17 **Hoppo T**, Jobe BA. Endoscopy and role of endoscopic resection in gastric cancer. *J Surg Oncol* 2013; **107**: 243-249 [PMID: 22532029 DOI: 10.1002/jso.23126]
 - 18 **Gotoda T**, Friedland S, Hamanaka H, Soetikno R. A learning curve for advanced endoscopic resection. *Gastrointest Endosc* 2005; **62**: 866-867 [PMID: 16301027 DOI: 10.1016/j.gie.2005.07.055]
 - 19 **Yamamoto S**, Uedo N, Ishihara R, Kajimoto N, Ogiyama H, Fukushima Y, Yamamoto S, Takeuchi Y, Higashino K, Iishi H, Tatsuta M. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* 2009; **41**: 923-928 [PMID: 19802773 DOI: 10.1055/s-0029-1215129]
 - 20 **van Enst WA**, Ochodo E, Scholten RJ, Hooft L, Leeftang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. *BMC Med Res Methodol* 2014; **14**: 70 [PMID: 24884381 DOI: 10.1186/1471-2288-14-70]
 - 21 **Sattianayagam PT**, Desmond PV, Jayasekera C, Chen RY. Endoscopic submucosal dissection: experience in an Australian tertiary center. *Ann Gastroenterol* 2014; **27**: 212-218 [PMID: 24976337]
 - 22 **Cardoso DM**, Campoli PM, Yokoi C, Ejima FH, Barreto PA, de Brito AM, Mota ED, de Fraga Junior AC, da Mota OM. Initial experience in Brazil with endoscopic submucosal dissection for early gastric cancer using insulation-tipped knife: a safety and feasibility study. *Gastric Cancer* 2008; **11**: 226-232 [PMID: 19132485 DOI: 10.1007/s10120-008-0489-0]
 - 23 **Chaves DM**, Maluf Filho F, de Moura EG, Santos ME, Arrais LR, Kawaguti F, Sakai P. Endoscopic submucosal dissection for the treatment of early esophageal and gastric cancer--initial experience of a western center. *Clinics (Sao Paulo)* 2010; **65**: 377-382 [PMID: 20454494 DOI: 10.1590/s1807-59322010000400005]
 - 24 **Santos JO**, Miyajima N, Carvalho R, Leal RF, Ayrisom Mde L, Coy CS. Feasibility of endoscopic submucosal dissection for gastric and colorectal lesions: Initial experience from the Gastrocentro--UNICAMP. *Clinics (Sao Paulo)* 2013; **68**: 141-146 [PMID: 23525307]
 - 25 **Xu LH**, Jun Bo Q, Liu Gen G, Fei L, Ya Min W, Yu Ming L, Hua Sheng L. Treatment of gastric epithelial tumours by endoscopic submucosal dissection using an insulated-tip diathermic knife. *Can J Gastroenterol* 2011; **25**: 97-101 [PMID: 21321682]
 - 26 **He Z**, Sun C, Wang J, Zheng Z, Yu Q, Wang T, Chen X, Liu W, Wang B. Efficacy and safety of endoscopic submucosal dissection in treating gastric subepithelial tumors originating in the muscularis propria layer: a single-center study of 144 cases. *Scand J Gastroenterol* 2013; **48**: 1466-1473 [PMID: 24131359 DOI: 10.3109/00365521.2013.845796]
 - 27 **Zhang S**, Chao GQ, Li M, Ni GB, Lv B. Endoscopic submucosal dissection for treatment of gastric submucosal tumors originating from the muscularis propria layer. *Dig Dis Sci* 2013; **58**: 1710-1716 [PMID: 23381103 DOI: 10.1007/s10620-013-2559-3]
 - 28 **Probst A**, Pommer B, Golger D, Anthuber M, Arnholdt H, Messmann H. Endoscopic submucosal dissection in gastric neoplasia - experience from a European center. *Endoscopy* 2010; **42**: 1037-1044 [PMID: 20972955 DOI: 10.1055/s-0030-1255668]
 - 29 **Schumacher B**, Charton JP, Nordmann T, Vieth M, Enderle M, Neuhaus H. Endoscopic submucosal dissection of early gastric neoplasia with a water jet-assisted knife: a Western, single-center experience. *Gastrointest Endosc* 2012; **75**: 1166-1174 [PMID: 22482915 DOI: 10.1016/j.gie.2012.02.027]
 - 30 **Catalano F**, Trecca A, Rodella L, Lombardo F, Tomezzoli A, Battista S, Silano M, Gaj F, de Manzoni G. The modern treatment of early gastric cancer: our experience in an Italian cohort. *Surg Endosc* 2009; **23**: 1581-1586 [PMID: 19263148 DOI: 10.1007/s00464-009-0350-5]
 - 31 **Coda S**, Trentino P, Antonellis F, Porowska B, Gossetti F, Ruberto F, Pugliese F, D'Amati G, Negro P, Gotoda T. A Western single-center experience with endoscopic submucosal dissection for early gastrointestinal cancers. *Gastric Cancer* 2010; **13**: 258-263 [PMID: 21128062 DOI: 10.1007/s10120-010-0544-5]
 - 32 **Hirasaki S**, Tanimizu M, Nasu J, Shinji T, Koide N. Treatment of elderly patients with early gastric cancer by endoscopic submucosal dissection using an insulated-tip diathermic knife. *Intern Med* 2005; **44**: 1033-1038 [PMID: 16293912]
 - 33 **Yokoi C**, Gotoda T, Hamanaka H, Oda I. Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006; **64**: 212-218 [PMID: 16860071]
 - 34 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or anti-platelet agents. *Dig Liver Dis* 2009; **41**: 725-728 [PMID: 19230799 DOI: 10.1016/j.dld.2009.01.007]
 - 35 **Hirasawa K**, Kokawa A, Oka H, Yahara S, Sasaki T, Nozawa A, Tanaka K. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. *Gastrointest Endosc* 2010; **72**: 960-966 [PMID: 21034897 DOI: 10.1016/j.gie.2010.07.030]
 - 36 **Yoshinaga S**, Gotoda T, Kusano C, Oda I, Nakamura K, Takayanagi R. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. *Gastrointest Endosc* 2008; **67**: 202-209 [PMID: 18226681]
 - 37 **Takenaka R**, Kawahara Y, Okada H, Hori K, Inoue M, Kawano S, Tanioka D, Tsuzuki T, Yagi S, Kato J, Uemura M, Ohara N, Yoshino T, Imagawa A, Fujiki S, Takata R, Yamamoto K. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. *Gastrointest Endosc* 2008; **68**:

- 887-894 [PMID: 18565523]
- 38 **Miyahara K**, Iwakiri R, Shimoda R, Sakata Y, Fujise T, Shiraishi R, Yamaguchi K, Watanabe A, Yamaguchi D, Higuchi T, Tominaga N, Ogata S, Tsuruoka N, Noda T, Hidaka H, Mannen K, Endo H, Yamanouchi K, Yamazato T, Sakata H, Fujimoto K. Perforation and postoperative bleeding of endoscopic submucosal dissection in gastric tumors: analysis of 1190 lesions in low- and high-volume centers in Saga, Japan. *Digestion* 2012; **86**: 273-280 [PMID: 22986899 DOI: 10.1159/000341422]
 - 39 **Ohnita K**, Isomoto H, Shikuwa S, Yajima H, Minami H, Matsushima K, Akazawa Y, Yamaguchi N, Fukuda E, Nishiyama H, Takeshima F, Nakao K. Early and long-term outcomes of endoscopic submucosal dissection for early gastric cancer in a large patient series. *Exp Ther Med* 2014; **7**: 594-598 [PMID: 24520251 DOI: 10.3892/etm.2014.1488]
 - 40 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890]
 - 41 **Shimura T**, Sasaki M, Kataoka H, Tanida S, Oshima T, Ogasawara N, Wada T, Kubota E, Yamada T, Mori Y, Fujita F, Nakao H, Ohara H, Inukai M, Kasugai K, Joh T. Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. *J Gastroenterol Hepatol* 2007; **22**: 821-826 [PMID: 17565635 DOI: 10.1111/j.1440-1746.2006.04505.x]
 - 42 **Hirasaki S**, Kanzaki H, Matsubara M, Fujita K, Ikeda F, Taniguchi H, Yumoto E, Suzuki S. Treatment of over 20 mm gastric cancer by endoscopic submucosal dissection using an insulation-tipped diathermic knife. *World J Gastroenterol* 2007; **13**: 3981-3984 [PMID: 17663514]
 - 43 **Ohta T**, Ishihara R, Uedo N, Takeuchi Y, Nagai K, Matsui F, Kawada N, Yamashina T, Kanzaki H, Hanafusa M, Yamamoto S, Hanaoka N, Higashino K, Iishi H. Factors predicting perforation during endoscopic submucosal dissection for gastric cancer. *Gastrointest Endosc* 2012; **75**: 1159-1165 [PMID: 22482916 DOI: 10.1016/j.gie.2012.02.015]
 - 44 **Kamada K**, Tomatsuri N, Yoshida N. Endoscopic submucosal dissection for undifferentiated early gastric cancer as the expanded indication lesion. *Digestion* 2012; **85**: 111-115 [PMID: 22269290 DOI: 10.1159/000334681]
 - 45 **Toyonaga T**, Man-i M, East JE, Nishino E, Ono W, Hirooka T, Ueda C, Iwata Y, Sugiyama T, Dozaiku T, Hirooka T, Fujita T, Inokuchi H, Azuma T. 1,635 Endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. *Surg Endosc* 2013; **27**: 1000-1008 [PMID: 23052530 DOI: 10.1007/s00464-012-2555-2]
 - 46 **Kosaka T**, Endo M, Toya Y, Abiko Y, Kudara N, Inomata M, Chiba T, Takikawa Y, Suzuki K, Sugai T. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a single-center retrospective study. *Dig Endosc* 2014; **26**: 183-191 [PMID: 23560494 DOI: 10.1111/den.12099]
 - 47 **Yamaguchi Y**, Katusmi N, Aoki K, Toki M, Nakamura K, Abe N, Morozumi K, Sugiyama M, Ishida H, Takahashi S. Resection area of 15 mm as dividing line for choosing strip biopsy or endoscopic submucosal dissection for mucosal gastric neoplasm. *J Clin Gastroenterol* 2007; **41**: 472-476 [PMID: 17450029 DOI: 10.1097/01.mcg.0000247987.02677.b3]
 - 48 **Akasaka T**, Nishida T, Tsutsui S, Michida T, Yamada T, Ogiyama H, Kitamura S, Ichiba M, Komori M, Nishiyama O, Nakanishi F, Zushi S, Nishihara A, Iijima H, Tsujii M, Hayashi N. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by Osaka university ESD study group. *Dig Endosc* 2011; **23**: 73-77 [PMID: 21198921 DOI: 10.1111/j.1443-1661.2010.01062.x]
 - 49 **Ono S**, Kato M, Nakagawa M, Imai A, Yamamoto K, Shimizu Y. Outcomes and predictive factors of "not self-completion" in gastric endoscopic submucosal dissection for novice operators. *Surg Endosc* 2013; **27**: 3577-3583 [PMID: 23549768 DOI: 10.1007/s00464-013-2929-0]
 - 50 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]
 - 51 **Tanabe S**, Ishido K, Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, Koizumi W. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. *Gastric Cancer* 2014; **17**: 130-136 [PMID: 23576197 DOI: 10.1007/s10120-013-0241-2]
 - 52 **Shimamura Y**, Ishii N, Nakano K, Ikeya T, Nakamura K, Takagi K, Fukuda K, Suzuki K, Fujita Y. Repeat endoscopic submucosal dissection for recurrent gastric cancers after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; **5**: 600-604 [PMID: 24368936 DOI: 10.4253/wjge.v5.i12.600]
 - 53 **Takahashi F**, Yoshitake N, Akima T, Kino H, Nakano M, Tsuchida C, Tsuchida K, Tominaga K, Sasai T, Masuyama H, Hiraishi H. A second-look endoscopy may not reduce the bleeding after endoscopic submucosal dissection for gastric epithelial neoplasm. *BMC Gastroenterol* 2014; **14**: 152 [PMID: 25148855 DOI: 10.1186/1471-230x-14-152]
 - 54 **Yamamoto Y**, Fujisaki J, Ishiyama A, Hirasawa T, Igarashi M. Current status of training for endoscopic submucosal dissection for gastric epithelial neoplasm at Cancer Institute Hospital, Japanese Foundation for Cancer Research, a famous Japanese hospital. *Dig Endosc* 2012; **24** Suppl 1: 148-153 [PMID: 22533772 DOI: 10.1111/j.1443-1661.2012.01278.x]
 - 55 **Higashimaya M**, Oka S, Tanaka S, Sanomura Y, Yoshida S, Hiyama T, Arihiro K, Shimamoto F, Chayama K. Outcome of endoscopic submucosal dissection for gastric neoplasm in relationship to endoscopic classification of submucosal fibrosis. *Gastric Cancer* 2013; **16**: 404-410 [PMID: 23053827 DOI: 10.1007/s10120-012-0203-0]
 - 56 **Hoteya S**, Matsui A, Iizuka T, Kikuchi D, Yamada A, Yamashita S, Furuhashi T, Domon K, Nakamura M, Mitani T, Ogawa O, Kasie M. Comparison of the clinicopathological characteristics and results of endoscopic submucosal dissection for esophagogastric junction and non-junctional cancers. *Digestion* 2013; **87**: 29-33 [PMID: 23343966 DOI: 10.1159/000343934]
 - 57 **Matsumura T**, Arai M, Maruoka D, Okimoto K, Minemura S, Ishigami H, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. *BMC Gastroenterol* 2014; **14**: 172 [PMID: 25280756 DOI: 10.1186/1471-230x-14-172]
 - 58 **Sohara N**, Hagiwara S, Arai R, Iizuka H, Onozato Y, Kakizaki S. Can endoscopic submucosal dissection be safely performed in a smaller specialized clinic? *World J Gastroenterol* 2013; **19**: 528-535 [PMID: 23382632 DOI: 10.3748/wjg.v19.i4.528]
 - 59 **Nishimura J**, Nishikawa J, Hamabe K, Nakamura M, Goto A, Okamoto T, Miura O, Sakaida I. Efficacy of endoscopic submucosal dissection for cancer of the operated stomach. *J Gastrointest Cancer* 2014; **45**: 27-33 [PMID: 23999820 DOI: 10.1007/s12029-013-9544-0]
 - 60 **Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838 DOI: 10.3748/wjg.v16.i23.2913]
 - 61 **Akahoshi K**, Honda K, Motomura Y, Kubokawa M, Okamoto R, Osoegawa T, Nakama N, Kashiwabara Y, Higuchi N, Tanaka Y, Oya M, Nakamura K. Endoscopic submucosal dissection using a grasping-type scissors forceps for early gastric cancers and adenomas. *Dig Endosc* 2011; **23**: 24-29 [PMID: 21198913 DOI: 10.1111/j.1443-1661.2010.01037.x]
 - 62 **Mukai S**, Cho S, Kotachi T, Shimizu A, Matuura G, Nonaka M, Hamada T, Hirata K, Nakanishi T. Analysis of delayed bleeding after endoscopic submucosal dissection for gastric epithelial neoplasms. *Gastroenterol Res Pract* 2012; **2012**: 875323 [PMID: 22533772 DOI: 10.1155/2012/875323]

- 22536221 DOI: 10.1155/2012/875323]
- 63 **Tanaka S**, Toyonaga T, Morita Y, Fujita T, Yoshizaki T, Kawara F, Wakahara C, Obata D, Sakai A, Ishida T, Ikehara N, Azuma T. Endoscopic submucosal dissection for early gastric cancer in anastomosis site after distal gastrectomy. *Gastric Cancer* 2014; **17**: 371-376 [PMID: 23868403 DOI: 10.1007/s10120-013-0283-5]
 - 64 **Okamoto K**, Okamura S, Muguruma N, Kitamura S, Kimura T, Imoto Y, Miyamoto H, Okahisa T, Takayama T. Endoscopic submucosal dissection for early gastric cancer using a cross-counter technique. *Surg Endosc* 2012; **26**: 3676-3681 [PMID: 22692462 DOI: 10.1007/s00464-012-2364-7]
 - 65 **Watari J**, Tomita T, Toyoshima F, Sakurai J, Kondo T, Asano H, Yamasaki T, Okugawa T, Ikehara H, Oshima T, Fukui H, Miwa H. Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study. *World J Gastrointest Endosc* 2013; **5**: 281-287 [PMID: 23772265 DOI: 10.4253/wjge.v5.i6.281]
 - 66 **Sumiyama K**, Toyozumi H, Ohya TR, Dobashi A, Hino S, Kobayashi M, Goda K, Imazu H, Kawakita Y, Kato T, Tajiri H. A double-blind, block-randomized, placebo-controlled trial to identify the chemical assistance effect of mesna submucosal injection for gastric endoscopic submucosal dissection. *Gastrointest Endosc* 2014; **79**: 756-764 [PMID: 24238308 DOI: 10.1016/j.gie.2013.09.027]
 - 67 **Kusano T**, Etoh T, Akagi T, Ueda Y, Shiroshita H, Yasuda K, Satoh M, Inomata M, Shiraishi N, Kitano S. Evaluation of 0.6% sodium alginate as a submucosal injection material in endoscopic submucosal dissection for early gastric cancer. *Dig Endosc* 2014; **26**: 638-645 [PMID: 24655031 DOI: 10.1111/den.12268]
 - 68 **Kawamura M**, Sekine H, Kikuchi T, Sakai Y, Nagasaki F, Naganuma H, Shibuya R, Ando M. Endoscopic submucosal dissection for gastric neoplasms by using a novel attachment device-a one-sided, expandable balloon. *Gastrointest Endosc* 2011; **74**: 415-418 [PMID: 21663906 DOI: 10.1016/j.gie.2011.03.1247]
 - 69 **Lee TH**, Cho JY, Chang YW, Kim JO, Lee JS, Cho WY, Kim HG, Kim WJ, Park YS, Jin SY. Appropriate indications for endoscopic submucosal dissection of early gastric cancer according to tumor size and histologic type. *Gastrointest Endosc* 2010; **71**: 920-926 [PMID: 20338564 DOI: 10.1016/j.gie.2009.12.005]
 - 70 **Kim BJ**, Chang TH, Kim JJ, Min BH, Lee JH, Son HJ, Rhee PL, Rhee JC, Kim KM, Park CK. Efficacy and safety of endoscopic submucosal dissection for early gastric cancer in patients with comorbid diseases. *Gut Liver* 2010; **4**: 186-191 [PMID: 20559520 DOI: 10.5009/gnl.2010.4.2.186]
 - 71 **Shin KY**, Jeon SW, Cho KB, Park KS, Kim ES, Park CK, Chung YJ, Kwon JG, Jung JT, Kim EY, Kim KO, Jang BI, Lee SH, Park JB, Yang CH. Clinical outcomes of the endoscopic submucosal dissection of early gastric cancer are comparable between absolute and new expanded criteria. *Gut Liver* 2015; **9**: 181-187 [PMID: 25167797 DOI: 10.5009/gnl13417]
 - 72 **Jang JS**, Choi SR, Qureshi W, Kim MC, Kim SJ, Jeung JS, Han SY, Noh MH, Lee JH, Lee SW, Baek YH, Kim SH, Choi PJ. Long-term outcomes of endoscopic submucosal dissection in gastric neoplastic lesions at a single institution in South Korea. *Scand J Gastroenterol* 2009; **44**: 1315-1322 [PMID: 19891582 DOI: 10.3109/0036520903254304]
 - 73 **Kim DY**, Hong SJ, Cho GS, Jeong GA, Kim HK, Han JP, Lee YN, Ko BM, Lee MS. Long-term efficacy of endoscopic submucosal dissection compared with surgery for early gastric cancer: a retrospective cohort study. *Gut Liver* 2014; **8**: 519-525 [PMID: 25228976 DOI: 10.5009/gnl13061]
 - 74 **Kang HY**, Kim SG, Kim JS, Jung HC, Song IS. Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. *Surg Endosc* 2010; **24**: 509-516 [PMID: 19585066 DOI: 10.1007/s00464-009-0614-0]
 - 75 **Goh PG**, Jeong HY, Kim MJ, Eun HS, Kim HJ, Kim ES, Kim YJ, Lee SY, Moon HS, Lee ES, Kim SH, Sung JK, Lee BS. Clinical outcomes of endoscopic submucosal dissection for undifferentiated or submucosal invasive early gastric cancer. *Clin Endosc* 2011; **44**: 116-122 [PMID: 22741122 DOI: 10.5946/ce.2011.44.2.116]
 - 76 **Ahn JY**, Choi KD, Choi JY, Kim MY, Lee JH, Choi KS, Kim DH, Song HJ, Lee GH, Jung HY, Kim JH. Procedure time of endoscopic submucosal dissection according to the size and location of early gastric cancers: analysis of 916 dissections performed by 4 experts. *Gastrointest Endosc* 2011; **73**: 911-916 [PMID: 21296348 DOI: 10.1016/j.gie.2010.11.046]
 - 77 **Yoo JH**, Shin SJ, Lee KM, Choi JM, Wi JO, Kim DH, Lim SG, Hwang JC, Cheong JY, Yoo BM, Lee KJ, Kim JH, Cho SW. Risk factors for perforations associated with endoscopic submucosal dissection in gastric lesions: emphasis on perforation type. *Surg Endosc* 2012; **26**: 2456-2464 [PMID: 22398962 DOI: 10.1007/s00464-012-2211-x]
 - 78 **Lim CH**, Park JM, Park CH, Cho YK, Lee IS, Kim SW, Choi MG, Chung IS. Endoscopic submucosal dissection of gastric neoplasia involving the pyloric channel by retroflexion in the duodenum. *Dig Dis Sci* 2012; **57**: 148-154 [PMID: 21842239 DOI: 10.1007/s10620-011-1863-z]
 - 79 **Park CH**, Shin S, Park JC, Shin SK, Lee SK, Lee YC, Lee H. Long-term outcome of early gastric cancer after endoscopic submucosal dissection: expanded indication is comparable to absolute indication. *Dig Liver Dis* 2013; **45**: 651-656 [PMID: 23422031 DOI: 10.1016/j.dld.2013.01.014]
 - 80 **Chung MW**, Jeong O, Park YK, Lee KH, Lee JH, Lee WS, Joo YE, Choi SK, Cho SB. [Comparison on the long term outcome between endoscopic submucosal dissection and surgical treatment for undifferentiated early gastric cancer]. *Korean J Gastroenterol* 2014; **63**: 90-98 [PMID: 24561695]
 - 81 **Kim MN**, Kim HK, Shim CN, Lee HJ, Lee H, Park JC, Shin SK, Lee SK, Lee YC. Tumour size is related to the curability of signet ring cell early gastric cancer with endoscopic submucosal dissection: a retrospective single centre study. *Dig Liver Dis* 2014; **46**: 898-902 [PMID: 24973115 DOI: 10.1016/j.dld.2014.05.019]
 - 82 **Min BH**, Kim KM, Park CK, Lee JH, Rhee PL, Rhee JC, Kim JJ. Outcomes of endoscopic submucosal dissection for differentiated-type early gastric cancer with histological heterogeneity. *Gastric Cancer* 2015; **18**: 618-626 [PMID: 24801199 DOI: 10.1007/s10120-014-0378-7]
 - 83 **Kim HH**, Park SJ, Park MI, Moon W. Clinical impact of second-look endoscopy after endoscopic submucosal dissection of gastric neoplasms. *Gut Liver* 2012; **6**: 316-320 [PMID: 22844558 DOI: 10.5009/gnl.2012.6.3.316]
 - 84 **Yoon JY**, Shim CN, Chung SH, Park W, Chung H, Lee H, Shin SK, Lee SK, Lee YC, Park JC. Impact of tumor location on clinical outcomes of gastric endoscopic submucosal dissection. *World J Gastroenterol* 2014; **20**: 8631-8637 [PMID: 25024619 DOI: 10.3748/wjg.v20.i26.8631]
 - 85 **Choi CW**, Kim HW, Kang DH, Hong YM, Kim SJ, Park SB, Cho M, Kim DJ, Hong JB. Clinical outcomes of second-look endoscopy after gastric endoscopic submucosal dissection: predictive factors with high risks of bleeding. *Surg Endosc* 2014; **28**: 2213-2220 [PMID: 24570014 DOI: 10.1007/s00464-014-3457-2]
 - 86 **Chun SY**, Kim KO, Park DS, Lee IJ, Park JW, Moon SH, Baek IH, Kim JH, Park CK, Kwon MJ. Endoscopic submucosal dissection as a treatment for gastric subepithelial tumors that originate from the muscularis propria layer: a preliminary analysis of appropriate indications. *Surg Endosc* 2013; **27**: 3271-3279 [PMID: 23519491 DOI: 10.1007/s00464-013-2904-9]
 - 87 **Chung WC**, Kim BW, Lim CH, Kim TH, Park JM, Kim JS. Grasper type scissors for endoscopic submucosal dissection of gastric epithelial neoplasia. *World J Gastroenterol* 2013; **19**: 6221-6227 [PMID: 24115820 DOI: 10.3748/wjg.v19.i37.6221]
 - 88 **Kim JS**, Chung MW, Chung CY, Park H, Rhyang DY, Myung DS, Cho SB, Lee WS, Joo YE. The need for second-look endoscopy to prevent delayed bleeding after endoscopic submucosal dissection for gastric neoplasms: a prospective randomized trial. *Gut Liver* 2014; **8**: 480-486 [PMID: 25228971 DOI: 10.5009/gnl13226]
 - 89 **Bialek A**, Wiechowska-Kozłowska A, Pertkiewicz J, Polkowski M, Milkiewicz P, Karpińska K, Lawniczak M, Starzyńska T. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). *Gastrointest Endosc* 2012; **75**: 276-286 [PMID: 22032850 DOI: 10.1016/j.gie.2011.08.029]

- 90 **Dinis-Ribeiro M**, Pimentel-Nunes P, Afonso M, Costa N, Lopes C, Moreira-Dias L. A European case series of endoscopic submucosal dissection for gastric superficial lesions. *Gastrointest Endosc* 2009; **69**: 350-355 [PMID: 19185696 DOI: 10.1016/j.gie.2008.08.035]
- 91 **Lee IL**, Wu CS, Tung SY, Lin PY, Shen CH, Wei KL, Chang TS. Endoscopic submucosal dissection for early gastric cancers: experience from a new endoscopic center in Taiwan. *J Clin Gastroenterol* 2008; **42**: 42-47 [PMID: 18097288 DOI: 10.1097/01.mcg.0000225696.54498.ff]
- 92 **Chang CC**, Lee IL, Chen PJ, Wang HP, Hou MC, Lee CT, Chen YY, Cho YP, Lin JT. Endoscopic submucosal dissection for gastric epithelial tumors: a multicenter study in Taiwan. *J Formos Med Assoc* 2009; **108**: 38-44 [PMID: 19181606 DOI: 10.1016/s0929-6646(09)60030-9]
- 93 **Chu YY**, Lien JM, Tsai MH, Chiu CT, Chen TC, Yang KC, Ng SC. Modified endoscopic submucosal dissection with enucleation for treatment of gastric subepithelial tumors originating from the muscularis propria layer. *BMC Gastroenterol* 2012; **12**: 124 [PMID: 22978826 DOI: 10.1186/1471-230x-12-124]
- 94 **González N**, Parra-Blanco A, Villa-Gómez M, Gamba A, Taullard A, Silveira A, Sanguinetti A, Olano C, Cohen H. Gastric endoscopic submucosal dissection: from animal model to patient. *World J Gastroenterol* 2013; **19**: 8326-8334 [PMID: 24363524 DOI: 10.3748/wjg.v19.i45.8326]

P- Reviewer: Giannopoulos GA, Lee CL, Mentos O
S- Editor: Gong XM **L- Editor:** A **E- Editor:** Lu YJ



Endoscopic multiple metal stenting for the treatment of enteral leaks near the biliary orifice: A novel effective rescue procedure

Massimiliano Mutignani, Lorenzo Dioscoridi, Stefanos Dokas, Paolo Aseni, Pietro Carnevali, Edoardo Forti, Raffaele Manta, Mariano Sica, Alberto Tringali, Francesco Pugliese

Massimiliano Mutignani, Lorenzo Dioscoridi, Edoardo Forti, Raffaele Manta, Mariano Sica, Alberto Tringali, Francesco Pugliese, Digestive and Interventional Endoscopy Unit, Ospedale Ca'Granda Niguarda, 20162 Milano, Italy

Stefanos Dokas, Endoscopy Department, St Lukes Hospital, Thessaloniki, 552 Panorama, Greece

Paolo Aseni, Emergency Department, Ospedale Ca'Granda Niguarda, 20162 Milano, Italy

Pietro Carnevali, General Oncology and Mini-Invasive Surgical Unit, Ospedale Ca'Granda Niguarda, 20162 Milano, Italy

Author contributions: All authors contributed to this paper.

Institutional review board statement: Approved by Institutional Review Board of Niguarda-Ca'Granda Hospital.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Massimiliano Mutignani, Digestive and Interventional Endoscopy Unit, Ospedale Ca'Granda Niguarda, Piazza dell'Ospedale Maggiore 3, 20162 Milano,

Italy. massimiliano.mutignani@ospedaleniguarda.it
Fax: +39-2-64442911

Received: March 24, 2016

Peer-review started: March 24, 2016

First decision: May 17, 2016

Revised: May 23, 2016

Accepted: June 14, 2016

Article in press: June 16, 2016

Published online: August 10, 2016

Abstract

Between April 2013 and October 2015, 6 patients developed perianastomotic duodenal or jejunal/biliary leaks after major abdominal surgery. In all patients, percutaneous drainage of the collection or re-operation with primary surgical repair was attempted at first but failed. A fully covered enteral metal stent was placed in all patients to seal the leak. Subsequently, we cannulated the common bile duct and, in some cases, and the main pancreatic duct inserting hydrophilic guidewires through the stent after dilating the stent mesh with a dilatation balloon or breaking the meshes with Argon Plasma Beam. Finally, we inserted a fully covered biliary metal stent to drain the bile into the lumen of the enteral stent. In cases of normal proximal upper gastrointestinal anatomy, a pancreatic plastic stent was also inserted. Oral food intake was initiated when the abdominal drain outflow stopped completely. Stent removal was scheduled four to eight weeks later after a CT scan to confirm the complete healing of the fistula and the absence of any perilesional residual fluid collection. The leak resolved in five patients. One patient died two days after the procedure due to severe, pre-existing, sepsis. The stents were removed endoscopically in four weeks in four patients. In one patient we experienced

stent migration causing small bowel obstruction. In this case, the stents were removed surgically. Four patients are still alive today. They are still under follow-up and doing well. Bilio-enteral fully covered metal stenting with or without pancreatic stenting was feasible, safe and effective in treating postoperative enteral leaks near the biliopancreatic orifice in our small series. This minimally invasive procedure can be implemented in selected patients as a rescue procedure to repair these challenging leaks.

Key words: Endoscopic retrograde pancreatic duct; Fully covered metal stent; Duodenal leak; Postoperative complications; Enteral leak; Enteral stent; Biliary stent; Pancreatic stent

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Despite the small number of patients treated, the results of our experience seem promising. Early total fluid diversion with bilio-enteric fully covered metal stent, and plastic pancreatic stent when necessary, is a feasible, safe, effective and minimally invasive endoscopic procedure for postoperative duodenal leaks/fistulas. It is a reasonable option when primary surgical repair or other surgical treatment has failed. Moreover, our treatment could be offered as a first line treatment in patients with poor clinical status avoiding surgery altogether.

Mutignani M, Dioscoridi L, Dokas S, Aseni P, Carnevali P, Forti E, Manta R, Sica M, Tringali A, Pugliese F. Endoscopic multiple metal stenting for the treatment of enteral leaks near the biliary orifice: A novel effective rescue procedure. *World J Gastrointest Endosc* 2016; 8(15): 533-540 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i15/533.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i15.533>

INTRODUCTION

Traumatic, anastomotic and staple line leaks are serious complications after upper gastrointestinal surgery. In particular, the management of patients with duodenal leaks close to the papilla is demanding and complex. The same is true for biliary leaks resulting from biliary anastomotic dehiscence after duodenopancreatectomy. These patients rapidly become poor surgical candidates especially if specific treatment is delayed and sepsis is well established. Furthermore, direct surgical repair of leaks in septic patients commonly yields unsatisfactory results^[1].

Duodenal and biliary stenting with covered metal stents is a well established palliative treatment for malignant duodenal and biliary strictures^[2,3] and for post-operative gastrointestinal leaks^[4,5].

Combined enteral, biliary and pancreatic stenting for the closure of duodenal and bilio-enteric fistulas has

never been reported.

We describe herein our experience along with technical details of combined enteral, biliary and pancreatic stenting with fully covered metal stents in six patients with postoperative, high output enterocutaneous fistulas in close proximity to the papilla or the surgically created biliary orifice.

Endoscopic procedure

With the following endoscopic procedure we aim to heal the fistula by diverting all fluids away from the leak preserving normal biliopancreatic flow at the same time.

All procedures were performed under propofol sedation and appropriate patient monitoring in the endoscopic retrograde pancreatic duct suite. All patients agreed to the procedure after thorough explanation of the treatment plan.

All patients have either abdominal percutaneous or surgical drains placed. The first step is to perform a cholangiopancreatography. This helps us locate the bilio/pancreatic orifice at a later stage. When a native papilla is present we proceed with endoscopic biliary sphincterotomy to facilitate cannulation later. In patients with normal upper gastrointestinal anatomy we used therapeutic duodenoscopes (ED-3490TK, Pentax) and in post pancreaticoduodenectomy patients we opted for pediatric colonoscopes (EC38-i10F, Pentax).

After opacification of the ducts, we insert a fully covered enteral metal stent through the scope. We used the NITI-S (Taewong Medical, Seoul, South Korea) fully covered metal stents with diameter of 20 mm, and length enough to cover the perforation and extend at least 2 cm both proximally and distally. After the enteral stent was placed, we gently performed trans-stent duodenoscopy, trying to avoid stent displacement (Figure 1A). Once into the stent, under fluoroscopy, we re-cannulated both the common bile duct and the main pancreatic duct, using a hydrophilic straight guidewire (Delta, Cook) through a double-lumen sphincterotome (CCPT-25 CannulaTome, Cook). After successful cannulation we leave in place the two guidewires (one for each duct) passing through the covering membrane of the stent (Figure 1B). Before biliopancreatic stenting, we dilated the stent meshes with an 8 mm dilatation balloon (Hurricane, Boston Scientific), or enlarged the hole by melting a few stent struts with Argon Plasma Coagulation (APC).

Afterwards biliary and pancreatic stenting was performed. We used fully covered metal stent for the common bile duct (Wallflex, Boston Scientific), 4-6 cm long and 8-10 mm in diameter to accommodate with the width of the common bile duct (Figure 2A). The distal end of the biliary stent was positioned protruding at least 1 cm inside the enteral stent lumen to guarantee stability and complete biliary drainage into the enteral stent (Figure 2B).

Pancreatic stents were plastic 7 Fr × 7 cm stents

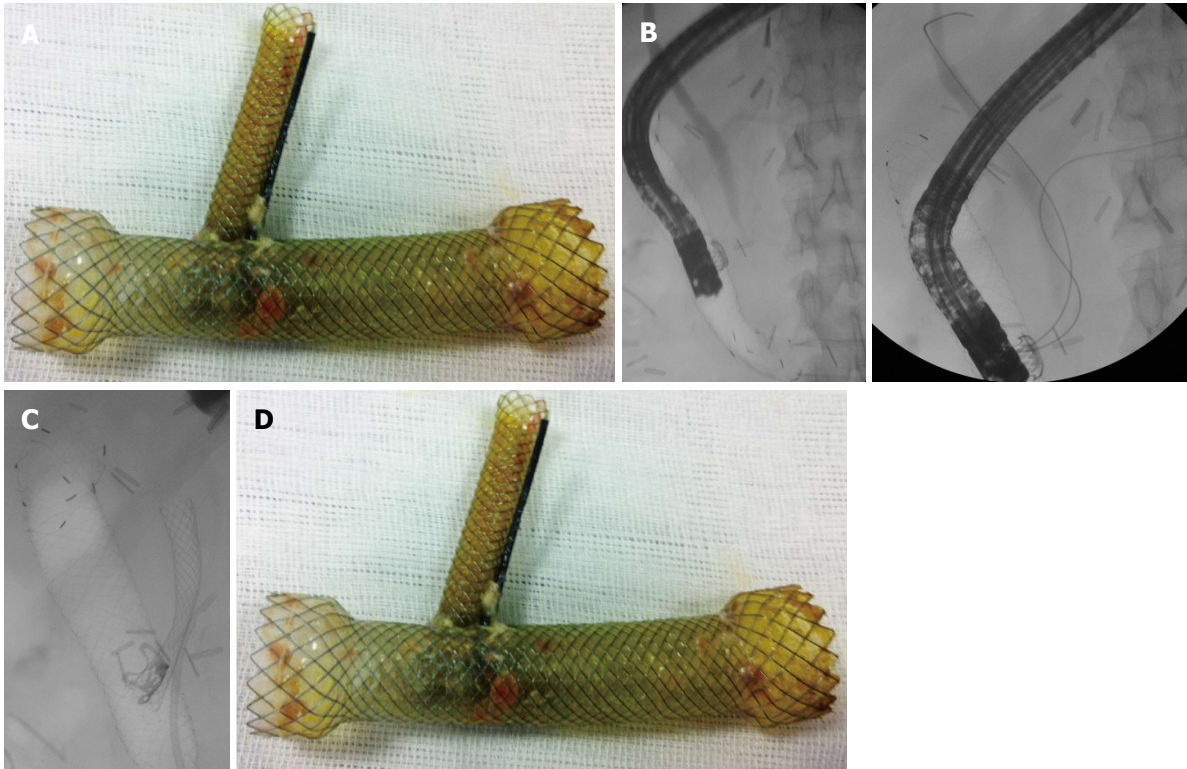


Figure 1 Fluoroscopy. A: Trans-stent duodenoscopy. Cholangiopancreatography already performed prior to enteral stenting; B: Two guidewires (biliary and pancreatic) inside the biliary and the pancreatic ducts; C: Final fluoroscopic image of a 6 cm × 10 mm biliary SEMS and a 7 Fr × 7 cm plastic pancreatic stent draining inside the enteral stent; D: After 4 wk, the multistent complex was removed endoscopically.

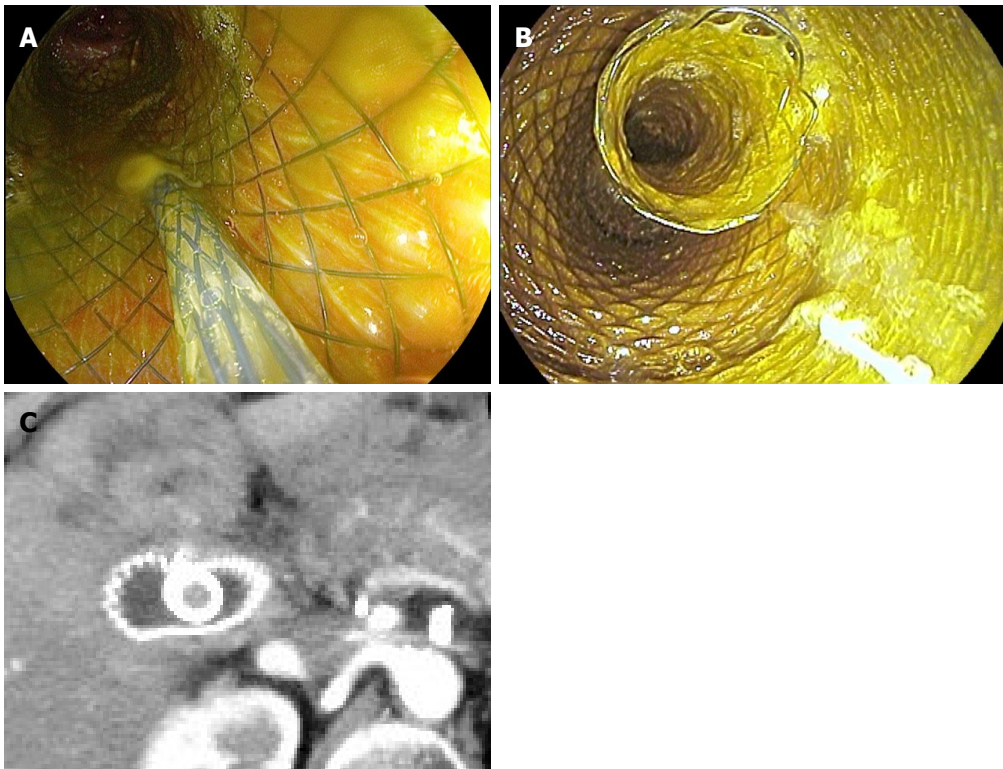


Figure 2 Bilio-enteric external fistula after pancreaticoduodenectomy. A: An 8 mm × 4 cm biliary SEMS was inserted into the common bile duct through the meshes of the enteral SEMS; B: Final stent complex at the end of the procedure; C: Detail of CT scan performed two days after the intervention showing the relationship between the two SEMS (biliary stent protruding inside the enteral).

with antimigration flanges (Figure 1C). These stents were also placed well protruding distally into the enteric

stent lumen for the same reasons.

The stents were left in place for a period of four to

eight weeks. The abdominal drain output was regularly checked after the procedure. The day after complete outflow stop, patients underwent a CT scan (Figure 2C) to confirm the absence of any residual fluid collection. If imaging confirmed our clinical data, patients were started on a semiliquid diet. Three days later we removed the abdominal drains. During the postprocedural period, non-operated patients continued a semiliquid diet to reduce the risk of stent's migration. At the scheduled time to remove the stents, we performed a new CT scan. If there was no contraindication, stents were removed *en-bloc* by grasping and pulling the enteral stent. The study has been approved by our (Niguarda-Ca' Granda Hospital) Institutional Review Board and our Ethical Committee. All the patients signed the informed consent about the procedure. The entire procedure lasts from 15 to 40 min.

CASE REPORT

Case 1

A 66-year-old female patient was admitted to our department due to bilio-enteric anastomotic leak. She had undergone Whipple's procedure for pancreatic cancer. At first endoscopy a complete dehiscence of the bilio-enteric anastomosis was diagnosed. We inserted a fully covered biliary metal stent (10 mm × 4 cm). A large subphrenic collection rapidly developed because of a complete duodenal wall necrosis around the bilio-enteral anastomosis; so, we removed the biliary stent. In order to fully divert fluids away from the leak we placed a fully covered enteral stent (20 mm × 8 cm) to cover the dehiscence, after draining the collection percutaneously. After bile duct cannulation through the stent mesh, we created a hole at the stent membrane and dilated the stent mesh with a 6 mm balloon. Finally we inserted a fully covered biliary stent (10 mm × 4 cm) through the fenestrated membrane of the enteral stent. The abdominal drain's output stopped in 3 d and was removed on the fourth day after the procedure. The two stents were removed *en bloc* 8 wk later. The fistula healed completely and the patient is in good condition 28 mo after the procedure (Table 1).

Case 2

A 57-year-old male patient was admitted to our hospital, for septic fever, three weeks after a Whipple's procedure for IPMN of the main pancreatic duct. Intra-operatively, a nelaton tube was inserted at the dilated pancreatic duct to facilitate pancreatic flow. A large supra-mesocolic collection was diagnosed at abdominal CT, along with partial complex dehiscence of the bilio-digestive anastomosis associated with duodenal wall necrosis of the surrounding area. We inserted a fully covered enteric stent (20 mm × 8 cm) at the site of the bilio-jejunal anastomosis. Subsequently we punctured the stent membrane and cannulated the common bile duct. We dilated the stent mesh with a 6 mm balloon

and finally we inserted a fully covered biliary stent (8 mm × 4 cm) with the distal end of the stent protruding inside the enteric stent. The pancreatic nelaton tube was left in place and drawn well into the lumen of the enteric stent. Four days after the procedure, bile appeared at the abdominal drain. This was due to enteral perforation induced by pressure necrosis from the distal end of the stent. So, we inserted a second fully-covered enteric stent (20 mm × 8 cm) to cover and overpass the enteral perforation. Six weeks later all stents were removed successfully. The leak healed completely and the patient is doing well 24 mo after the procedure (Table 1).

Case 3

A 72-year-old male patient was admitted to our hospital for the treatment of a refractory duodenal fistula. This fistula developed as a complication of an infected perirenal hematoma after partial nephrectomy for renal cell carcinoma. His past history was remarkable for liver transplantation five years before. At first, surgical drains were placed to drain the hematoma along with total parenteral nutrition and antibiotics. Following fistula persistence, 5 d later, primary surgical repair was attempted but ultimately failed. A new surgical attempt to repair the leak was performed with pyloric exclusion and gastrojejunostomy. Unfortunately this procedure was also ineffective. The patient was already in critical condition when we inserted a fully covered duodenal stent through the scope (20 mm × 10 cm). Subsequently, we punctured the duodenal stent membrane and cannulated the pancreatic and the biliary ducts. Finally we dilated the stent mesh with a 6 mm balloon and inserted a fully covered biliary stent (10 mm × 6 cm) and a plastic (7 Fr × 7 cm) stent into the pancreatic duct both protruding well into the duodenal stent. No contrast leak was evident after the procedure. Unfortunately the patient passed away 2 d later due to severe pre-existing sepsis (Table 1).

Case 4

A 68-year-old male patient underwent right nephroureterectomy, right adrenalectomy, right colectomy and wedge resection of the duodenal wall for a large retroperitoneal liposarcoma involving the above sites. The postoperative course was complicated by high-output duodenal fistula. At first we attempted endoscopic repair with the Ovesco clip but without success. Subsequently we inserted a fully covered TTS duodenal stent (20 mm × 12 cm). After fenestrating the duodenal stent membrane with APC, we inserted a pancreatic plastic stent (7 Fr × 7 cm) and a biliary fully covered stent (8 mm × 6 cm). After 4 wk, we removed the prosthetic complex but the fistula did not heal because of necrosis of the peripapillary duodenal wall. Thus, we decided to perform surgical necrosectomy of a retroperitoneal collection through a lapotomy, we re-inserted enteral (20 mm × 12

Table 1 Case series

Patient (yr/gender)	Original procedure	Indication to treat	Treatment protocol	Success (days to obtain fistula closure)	Removal	F/u (mo)
1 (66/F)	Whipple's procedure for pancreatic adenocarcinoma	Dehiscence of the bilio-enteric anastomosis	FCESEMS (8 cm × 20 mm) + FCBSEMS (4 cm × 10 mm)	Yes (3)	<i>En bloc</i> endoscopic removal 8 wk later	28
2 (57/M)	Whipple's procedure with pancreatic nelon tube for main duct IPMN	Dehiscence of the bilioenteric and the pancreatico-jejunal anastomosis	FCESEMS (8 cm × 20 mm) + FCBSEMS (4 cm × 8 mm) + positioning of nelon tube into enteral stent + FCESEMS (8 cm × 20 mm)	Yes after second stenting (1)	First enteral stenting induced a jejunal perforation A 2 nd enteral stenting was performed All stents removed endoscopically 6 wk later	24
3 (72/M)	Nephrectomy Liver transplantation 5 yr ago	Duodenal leak after rupture of infected perirenal hematoma	FCESEMS (10 cm × 20 mm) + FCBSEMS (6 cm × 10 mm) + Pancreatic plastic stent (7 cm × 7 Fr)	Pre-existing sepsis Patient died 48 h after procedure	N/A	N/A
4 (68/M)	Right nephrectomy, adrenalectomy and right colectomy for retroperitoneal liposarcoma	Duodenal fistula	FCESEMS (12 cm × 20 mm) (12 cm × 20 mm) + FCBSEMS (6 cm × 8 mm) (4 cm × 10 mm) + Pancreatic plastic stent (7 Fr × 7 cm)	Yes after removal of second set of stents (1)	Stents removed surgically due to migration causing enteral obstruction New stents re-inserted a few days later which were removed endoscopically 4 wk later	18
5 (51/M)	Distal duodenal wedge resection for duodenal adenoma with focal adenocarcinoma	Dehiscence of duodenal suture + Biliary fistula at previous T tube placement site	FCESEMS (10 cm × 20 mm) + FCBSEMS (6 cm × 10 mm) + Pancreatic plastic stent (7 cm × 7 Fr)	Yes (1)	All stents removed endoscopically 4 wk later	36
6 (56/F)	Cholecystectomy	Duodenal fistula-Duodenal wall erosion from surgical drain	FCESEMS (10 cm × 24 mm) + FCBSEMS (6 cm × 10 mm) + Pancreatic plastic stent (7 cm × 7 Fr)	Yes (1)	All stents removed endoscopically 8 wk later	6

cm), biliary (8 mm × 6 cm) and pancreatic stents (7 Fr × 7 cm). Unfortunately, at that time we only had partially covered enteral stent available. The duodenal fistula resolved completely. At a first attempt of stents removal after 4 wk, the prostheses complex was found to be embedded at the pylorus and could not be pulled out. Before a second removal attempt, the stents had migrated distally, causing small bowel obstruction and were extracted surgically. At surgery, we confirmed the complete healing of the duodenal fistula. Postsurgical course was uneventful. The tumour relapsed 18 mo later. The patient underwent pancreaticoduodenectomy and eventually died of postsurgical septic complications (Table 1).

Case 5

A 51-year-old male patient underwent distal duodenal wedge resection for duodenal adenoma with focal adenocarcinoma. The postoperative course was complicated by duodenal wall dehiscence and biliary leak at the level of a previously placed T-tube. A periduodenal, retroperitoneal infected collection formed rapidly. The

collection was drained percutaneously, but the fistula persisted. A first attempt to seal the leaks was performed with an Ovesco clip and a covered biliary stent, but without success. Subsequently we removed the biliary stent, we inserted a fully covered duodenal stent (20 mm × 10 cm) and fenestrated its membrane with APC. Through the aperture we inserted a plastic pancreatic stent (7 Fr × 7 cm) and a fully covered biliary SEMS (10 mm × 6 cm). The leak resolved and the stents were extracted successfully 1 mo later. The patient is doing well 36 mo after the intervention (Table 1).

Case 6

A 56-year-old female patient was admitted due to post-cholecystectomy duodenal fistula. The surgical drain placed approximately 12 mo ago was found eroding the duodenal wall. The drain was pulled back and an attempt to seal the perforation was undertaken with the Ovesco clip, but without success. Subsequently we placed a fully covered colonic stent (24 mm × 10 cm) with the over the scope modified technique because the

duodenum was quite enlarged. The stent membrane was perforated and the mesh was dilated with a 6mm balloon. Finally, a pancreatic plastic stent (7 Fr × 7 cm) and a fully covered biliary stent (10 mm × 6 cm) were inserted. The stents were removed one month later. The fistula healed and the patient is doing well 6 mo after the procedure (Table 1).

DISCUSSION

The treatment of postoperative bilio-enteric leaks is complex and challenging. Their optimal management remains controversial. The presence of bile and pancreatic secretions interfere with the healing process. Several treatment strategies are available for these patients. Immediate, primary surgical repair is a reasonable tactic for patients in good clinical condition^[6]. Pyloric exclusion has been utilized extensively for traumatic and post-operative duodenal lesions with reportedly mixed results^[7-9]. Other less invasive options include cessation of oral intake, total parenteral nutrition, percutaneous collection drainage, nasogastric drain and suction along with antibiotic treatment; but this rarely is enough. Additionally, late surgical re-intervention is often associated with high mortality, especially in patients with advanced sepsis. Overall, the low success rate and the long duration of available treatments maintain and support the research for improved and less invasive alternatives.

Recently, the development of removable fully covered enteric metal stents has expanded our treatment options in several fields. These stents combine two very important attributes. They can be removed endoscopically several weeks after implantation and provide full contact with the underlying mucosa allowing for fluid to flow through the lumen insulating the enteric mucosa at the same time. Indeed, fully covered metal stents have demonstrated advantages and cost-effectiveness over traditional management^[1].

Combined bilio-enteric stenting has been reported before, but for other indications. Previous published studies reported on feasibility and effectiveness of combined bilio-enteric metal stenting for the treatment of malignant bilioduodenal strictures in a single or double step procedure^[3]. In the field of postoperative duodenal or bilio-enteric anastomotic leaks no reports regarding combined endoscopic bilio-enteric stenting have been published before. In our opinion, in these situations, over-the-scope clipping cannot be used because it creates, especially on duodenal wall, an ischemic damage that, if it is not associated with adequate repair reaction (by granulation tissue), results in leak's worsening. In case 4, the presence of necrotic tissue around the duodenal leak does not let the Ovesco to work properly.

The rationale for the proposed treatment is simple. For the leak/fistula to heal we must divert all fluids away from the leak. Fully covered stents can insulate the underlying mucosa. For a random enteral fistula to heal, placing a fully covered metal stent to cover the leak

would, in theory, suffice. In the case of duodenal leaks, bile and pancreatic secretions must be taken into account. In order to maintain a dry fistula we need to divert enteric, biliary and pancreatic secretions away from the leak. Fully covered biliary stents and plastic pancreatic stents can effectively accomplish such fluid diversion. A good alternative method is the percutaneous biliary drainage but it could be difficult without intrahepatic ducts dilation, it represents an important discomfort for the patient and comorbidities of this procedure must be considered.

Hitherto, we found no reports on treating bilio-enteric leaks with complete fluid diversion based on endoscopic fully covered metal stenting. Most patients with post-surgical periampullary leaks are treated either surgically with primary repair or with complex, major abdominal procedures often with poor results. Timing is of the essence in these cases. Taking into account that most leaks are usually accompanied by severe sepsis, one can easily explain the disappointing results especially for the case of late surgical intervention. We believe that in selected patients with established sepsis and poor general condition endoscopic total fluid diversion could be offered as a first line of treatment, avoiding surgery. Our good results along with the minimally invasive manipulations and low tissue damage during this intervention support our claim.

Four (cases 1, 3, 4 and 5) out of 6 patients were in septic condition at the time of the endoscopic intervention. Total fluid diversion along with abdominal drainage, antibiotics and general support rapidly improved the clinical condition in most (5/6) of our patients. All five patients quickly resumed oral intake. They demonstrated swift clinical improvement and resolution of the septic collection. Only the three patients with normal upper gastrointestinal anatomy were maintained on semi-liquid diet during stenting period in order to minimize the risk of stent migration (due to the food impaction into the duodenal stent).

One of our patients unfortunately died of pre-existing severe sepsis 48 h after the intervention. He was operated, with no success, twice for the leak, he had a liver transplantation five years ago and was already in extreme sepsis at the time of the endoscopic intervention. We believe that previous unsuccessful interventions along with immunosuppression may have deteriorated his condition to a point of no return.

One known issue with duodenal stents is post stenting acute pancreatitis^[10,11]. Direct papillary pressure from the stent resulting in pancreatic juice flow impairment is believed to be the cause of this complication. We encountered no such complication. Pancreatic stenting anyway maintains the pancreatic flow, so in theory pancreatitis is not an expected event. Obstructive jaundice is another theoretical complication after duodenal stenting. Although stenting the common bile duct is not prerequisite for duodenal stenting^[12], covered biliary stents maintain biliary flow and ductal patency.

Making holes at the covering membrane of an enteral stent, or enlarging stent interstices with APC is described

in the current literature^[10,13,14]. After enteral stent placement, we re-cannulate the ducts under fluoroscopy through the stent covering membrane, leaving in place two guidewires. After that, we dilate the stent mesh with a balloon or enlarge the hole with APC and finally we insert biliary fully covered metal stents and pancreatic plastic stents when necessary. This multi-stent complex, besides creating the desirable fluid diversion network, also provides stability for the whole stent complex itself, acting as an antimigration arrangement/mechanism. Indeed, fully covered biliary and enteral stents, especially in the absence of stricture, are prone to migration^[15]. Stent migration occurred in one of our patients causing small bowel obstruction. The stents had to be removed surgically.

Our study is a small prospective cohort with no randomization. It is actually a pilot study to assess the feasibility and effectiveness of the proposed treatment in postoperative duodenal leaks/fistulas. All interventions were performed by a single, expert operator. It is a complex and technically demanding procedure and this is an important limitation.

In conclusion, despite the small number of patients treated, the results of our experience seem promising. Early total fluid diversion with bilio-enteric fully covered metal stent, and plastic pancreatic stent when necessary, is a feasible, safe, effective and minimally invasive endoscopic procedure for postoperative duodenal leaks/fistulas. It is a reasonable option when primary surgical repair or other surgical treatment has failed. Moreover, our treatment could be offered as a first line treatment in patients with poor clinical status avoiding surgery altogether. Further studies are needed in order to determine the safety and effectiveness of this novel treatment.

COMMENTS

Case characteristics

The patients present with enteral leaks near the biliary orifice after abdominal surgery.

Clinical diagnosis

Enteral leaks near the bilio-pancreatic orifice.

Differential diagnosis

The site of enteral leak is determined by endoscopic retrograde pancreatic duct (ERCP).

Laboratory diagnosis

White blood cell and polymerase chain reaction monitoring are helpful for diagnosis and reveal if sepsis is present.

Imaging diagnosis

Fluid collections at abdominal computed tomography scan and enteral leaks/fistulas at endoscopic retrograde cholangiopancreatography are found.

Pathological diagnosis

Enteral leaks involving the bilio-pancreatic orifice.

Treatment

Triple endoscopic stenting inserting an enteral, a biliary and a pancreatic stent.

Related reports

This is the first case series about triple endoscopic stenting in these pathological conditions. However, enteral stenting with or without making holes through the stent meshes were previously described.

Experiences and lessons

Biliopancreatic fluid diversion is the key of the present treatment. Timing is important too: if sepsis is present, the prognosis is worse.

Peer-review

This technique is safe and effective as first-line endoscopic treatment in case of enteral leaks near the biliary orifice.

REFERENCES

- 1 **Babor R**, Talbot M, Tyndal A. Treatment of upper gastrointestinal leaks with a removable, covered, self-expanding metallic stent. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: e1-e4 [PMID: 19238047 DOI: 10.1097/SLE.0b013e318196c706]
- 2 **Jeurnink SM**, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, Kuipers EJ, Siersema PD. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc* 2010; **71**: 490-499 [PMID: 20003966 DOI: 10.1016/j.gie.2009.09.042]
- 3 **Mutignani M**, Tringali A, Shah SG, Perri V, Familiari P, Iacopini F, Spada C, Costamagna G. Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. *Endoscopy* 2007; **39**: 440-447 [PMID: 17516351 DOI: 10.1055/s-2007-966327]
- 4 **Raimondo D**, Sinagra E, Facella T, Rossi F, Messina M, Spada M, Martorana G, Marchesa PE, Squatrito R, Tomasello G, Lo Monte AI, Pompei G, La Rocca E. Self-expandable metal stent placement for closure of a leak after total gastrectomy for gastric cancer: report on three cases and review of the literature. *Case Rep Gastrointest Med* 2014; **2014**: 409283 [PMID: 25371833 DOI: 10.1155/2014/409283]
- 5 **Walsh C**, Karmali S. Endoscopic management of bariatric complications: A review and update. *World J Gastrointest Endosc* 2015; **7**: 518-523 [PMID: 25992190 DOI: 10.4253/wjge.v7.i5.518]
- 6 **Girgin S**, Gedik E, Yağmur Y, Uysal E, Baç B. Management of duodenal injury: our experience and the value of tube duodenostomy. *Ulus Travma Acil Cerrahi Derg* 2009; **15**: 467-472 [PMID: 19779988]
- 7 **DuBose JJ**, Inaba K, Teixeira PG, Shiflett A, Putty B, Green DJ, Plurad D, Demetriades D. Pyloric exclusion in the treatment of severe duodenal injuries: results from the National Trauma Data Bank. *Am Surg* 2008; **74**: 925-929 [PMID: 18942615]
- 8 **Fang JF**, Chen RJ, Lin BC. Surgical treatment and outcome after delayed diagnosis of blunt duodenal injury. *Eur J Surg* 1999; **165**: 133-139 [PMID: 10192570 DOI: 10.1080/110241599750007315]
- 9 **Seamon MJ**, Pieri PG, Fisher CA, Gaughan J, Santora TA, Pathak AS, Bradley KM, Goldberg AJ. A ten-year retrospective review: does pyloric exclusion improve clinical outcome after penetrating duodenal and combined pancreaticoduodenal injuries? *J Trauma* 2007; **62**: 829-833 [PMID: 17426536 DOI: 10.1097/TA.0b013e318033a790]
- 10 **Liu SY**, Mao AW, Jia YP, Wang ZL, Jiang HS, Li YD, Yin X. Placement of a duodenal stents bridge the duodenal papilla may predispose to acute pancreatitis. *Hepatogastroenterology* 2014; **61**: 475-479 [PMID: 24901165]
- 11 **Shi-Yi L**, Ai-Wu M, Yi-Ping J, Zhen-Lei W, Hao-Sheng J, Yong-Dong L, Xiang Y. Placement of duodenal stents across the duodenal papilla may predispose to acute pancreatitis: a retrospective analysis. *Diagn Interv Radiol* 2012; **18**: 360-364 [PMID: 22399365 DOI: 10.4261/1305-3825.dir.5045-11.1]
- 12 **Poincloux L**, Goutorbe F, Rouquette O, Mulliez A, Goutte M,

- Bommelaer G, Abergel A. Biliary stenting is not a prerequisite to endoscopic placement of duodenal covered self-expandable metal stents. *Surg Endosc* 2016; **30**: 437-445 [PMID: 25894447]
- 13 **Ogura T**, Takagi W, Onda S, Sano T, Masuda D, Fukunishi S, Higuchi K. Hole-making technique for the treatment for acute pancreatitis due to placement of a fully covered duodenal metallic stent. *Endoscopy* 2015; **47** Suppl 1: E486-487 [PMID: 26479298 DOI: 10.1055/s-0034-1393146]
- 14 **Vanbiervliet G**, Piche T, Caroli-Bosc FX, Dumas R, Peten EP, Huet PM, Tran A, Demarquay JF. Endoscopic argon plasma trimming of biliary and gastrointestinal metallic stents. *Endoscopy* 2005; **37**: 434-438 [PMID: 15844021 DOI: 10.1055/s-2005-860989]
- 15 **Kullman E**, Frozanpor F, Söderlund C, Linder S, Sandström P, Lindhoff-Larsson A, Toth E, Lindell G, Jonas E, Freedman J, Ljungman M, Rudberg C, Ohlin B, Zacharias R, Leijonmarck CE, Teder K, Ringman A, Persson G, Gözen M, Eriksson O. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. *Gastrointest Endosc* 2010; **72**: 915-923 [PMID: 21034892 DOI: 10.1016/j.gie.2010.07.036]

P- Reviewer: Lorenzo-Zuniga V **S- Editor:** Qi Y **L- Editor:** A
E- Editor: Lu YJ



Standardized technique for single-incision laparoscopic-assisted stoma creation

Norikatsu Miyoshi, Shiki Fujino, Masayuki Ohue, Masayoshi Yasui, Shingo Noura, Yuma Wada, Ryuichiro Kimura, Keijiro Sugimura, Akira Tomokuni, Hirofumi Akita, Shogo Kobayashi, Hidenori Takahashi, Takeshi Omori, Yoshiyuki Fujiwara, Masahiko Yano

Norikatsu Miyoshi, Shiki Fujino, Masayuki Ohue, Masayoshi Yasui, Yuma Wada, Ryuichiro Kimura, Keijiro Sugimura, Akira Tomokuni, Hirofumi Akita, Shogo Kobayashi, Hidenori Takahashi, Takeshi Omori, Yoshiyuki Fujiwara, Masahiko Yano, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan

Shingo Noura, Department of Surgery, Osaka Rosai Hospital, Osaka 591-8025, Japan

Author contributions: All the authors contribute to the paper.

Institutional review board statement: The institutional review board is satated by Osaka Medical Center for Cancer and Cardiovascular Diseases.

Informed consent statement: The informed consent is satated by Osaka Medical Center for Cancer and Cardiovascular Diseases.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Norikatsu Miyoshi, MD, PhD, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan. miyosi-no@mc.pref.osaka.jp
Telephone: +81-06-69721181
Fax: +81-06-69818005

Received: February 21, 2016
Peer-review started: February 23, 2016
First decision: March 25, 2016
Revised: April 11, 2016
Accepted: June 1, 2016
Article in press: June 3, 2016
Published online: August 10, 2016

Abstract

To describe the procedure, efficacy, and utility of single-incision laparoscopic-assisted stoma creation (SILStoma) for transverse colostomy. Using single-incision laparoscopic surgery, we developed a standardized technique for SILStoma. Twelve consecutive patients underwent SILStoma for transverse colostomy at Osaka Medical Center for Cancer and Cardiovascular Diseases from April 2013 to March 2016. A single, intended stoma site was created with a 2.5-3.5 cm skin incision for primary access to the intra-abdominal space, and it functioned as the main port through which multi-trocars were placed. Clinical and operative factors and postoperative outcomes were evaluated. Patient demographics, including age, gender, body mass index, and surgical indications for intestinal diversion were evaluated. SILStoma was performed in nine cases without the requirement of additional ports. In the remaining three cases, 1-2 additional 5-mm ports were required for mobilization of the transverse colon and safe dissection of abdominal adhesions. No cases required conversion to open surgery. In all cases, SILStoma was completed at the initial stoma site marked preoperatively. No intraoperative or postoperative complications greater than Grade II (the Clavien-Dindo classification) were reported in the complication survey. Surgical site infection at stoma sites was observed in four cases; however, surgical interventions were not required and all infections

were cured completely. In all cases, the resumption of bowel movements was observed between postoperative days 1 and 2. SILStoma for transverse loop colostomy represents a feasible surgical procedure that allows the creation of a stoma at the preoperatively marked site without any additional large skin incisions.

Key words: Laparoscopic surgery; Colostomy; Stoma; Postoperative complications; Cosmetic outcomes

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We described the procedure, efficacy, and utility of single-incision laparoscopic-assisted stoma creation (SILStoma) for transverse colostomy. Using single-incision laparoscopic surgery, we developed a standardized technique for SILStoma. Twelve consecutive patients underwent SILStoma for transverse colostomy. In all cases, SILStoma was completed at the initial stoma site marked preoperatively. No complications were reported in the complication survey. SILStoma for transverse loop colostomy represents a feasible surgical procedure allowing stoma creation at ideal stoma sites marked preoperatively. Reductions in the number of port sites and the avoidance of additional skin incisions may result in improved cosmetic outcomes and patient quality of life.

Miyoshi N, Fujino S, Ohue M, Yasui M, Noura S, Wada Y, Kimura R, Sugimura K, Tomokuni A, Akita H, Kobayashi S, Takahashi H, Omori T, Fujiwara Y, Yano M. Standardized technique for single-incision laparoscopic-assisted stoma creation. *World J Gastrointest Endosc* 2016; 8(15): 541-545 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i15/541.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i15.541>

INTRODUCTION

In the last decade, laparoscopy has been effectively utilized for colorectal surgery in many institutions and is associated with decreased blood loss, shorter hospital stays, decreased postoperative pain, faster postoperative recovery, and improved quality of life^[1-4]. Conventional multiport laparoscopic colorectal surgery, such as for colorectal cancer, is generally performed using 4-5 trocar: 1 trocar for a laparoscopist, 2 trocars for an operator, and 1-2 trocars for an assistant. To reduce patient stress (*i.e.*, wound pain and cosmetic outcome), efforts have been made to decrease the number of port sites and shorten the length of skin incisions. Therefore, reduced port surgery (RPS), including single-incision laparoscopic surgery, has been developed for colorectal surgery^[5-8].

In general, RPS utilizes an umbilical incision as the main port for multi-trocar (generally, 2-4 trocars) access to remove specimens and perform anastomosis at bowel ends during colorectal surgery. The skin incision length of the main port depends on the surgical

procedure performed. Although shorter skin incisions and decreased numbers of port sites limit the work space for laparoscopic handling, they have been shown to reduce wound pain and improve cosmetic outcome.

Stoma creation for intestinal diversion is a common surgical procedure. Compared with ileostomy, the stoma site of colostomy is limited by the length and mobilization of the target section of the colon such as transverse colon. Utilizing single-incision laparoscopic surgery, we developed a standardized technique for single-incision laparoscopic-assisted stoma creation (SILStoma). Herein, we describe the procedure, technical details, efficacy, and utility of SILStoma for transverse colostomy.

CASE REPORT

Twelve consecutive patients with bowel obstruction at a left-sided colon or rectum underwent SILStoma for transverse colostomy at Osaka Medical Center for Cancer and Cardiovascular Diseases from April 2013 to March 2016. A surgeon and an experienced enterostomal therapy nurse preoperatively marked an appropriate stoma site. A single, intended stoma site was created with a 2.5-3.5 cm skin incision for primary access to the intra-abdominal space, and it functioned as the main port through which multi-trocars were placed. SILStoma was performed as follows: An initial skin incision was made at the stoma site marked preoperatively and Lap-Protector (Hakko Co. Ltd., Nagano, Japan) and EZ Access (Hakko Co. Ltd., Nagano, Japan) were placed into the incision site. Three devices were introduced through the EZ Access and were adjusted to fit the Lap-Protector, including a flexible laparoscope (Olympus, Tokyo, Japan) and two operating forceps (Figure 1). An operator used two trocars and an assistant handled the laparoscope. In cases where the completion of the surgical procedure using a single port proved technically challenging, an additional port was introduced *via* the lateral abdomen.

The entire abdominal cavity was inspected laparoscopically. In the head-up tilt position with right side up, the transverse colon was detected and the target section of the intestinal tract was identified. Using forceps laparoscopically, dissection of greater omentum and mobilization were performed to construct a loop colostomy at the initial stoma site, and the mobilized transverse colon was extracted through the Lap-Protector, which was placed at the stoma site (Figure 2). Depending on the size of the transverse colon, the fascia was closed with Vicryl (size 1; Johnson and Johnson, New Brunswick, NJ, United States) to prevent stoma site hernia. The skin and intestine were sutured and fixed with vicryl.

Clinical and operative factors and postoperative outcomes were evaluated. Surgical complications were assessed according to the Clavien-Dindo classification system^[9], in which all complications were graded from I to IV. The present study was approved by the institutional review board of Osaka Medical Center for Cancer and

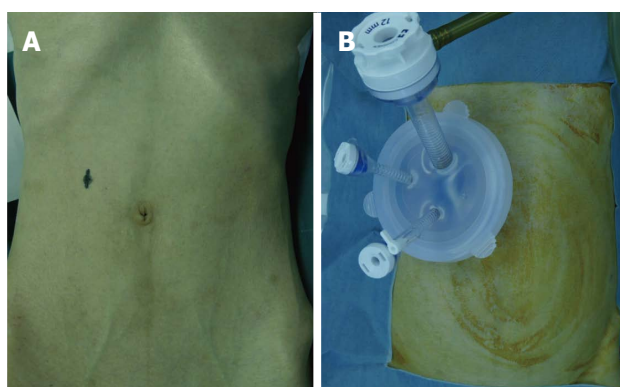


Figure 1 Image of the single-incision laparoscopic-assisted stoma creation technique. At the preoperatively-marked ideal stoma site (A), three trocars were placed in the EZ Access device (B).

Cardiovascular Diseases.

Patient demographics, including age, gender, body mass index, and surgical indications for intestinal diversion are shown in Table 1. Previous history related to surgical interventions, such as previous abdominal surgeries, operation time, intraoperative bleeding, number of additional port sites, conversion to laparotomy, postoperative complications, and median days until stoma functioned were investigated (Table 2).

SILStoma was performed in nine cases without the requirement of additional ports. In two cases, one additional port (5 mm at the left-side lateral abdomen) was required, and in another case, two additional ports (5 mm trocars at left- and right-side lateral abdomen) were required. In the remaining three cases, additional ports allowed mobilization of the transverse colon and the safe dissection of abdominal adhesions. No cases required conversion to open surgery. In all cases, SILStoma was completed at the initial stoma sites marked preoperatively with a success rate of 100%.

No intra- or postoperative complications greater than or equal to Grade II were reported in the postoperative complication survey. Surgical site infection at the stoma sites was observed in four cases; however, surgical interventions were not required and all infections were completely cured within 30 d after the operation.

In all cases, the resumption of bowel movements was observed between postoperative days 1 and 2. Postoperative diets were provided after confirmation of the resumption of bowel movements.

DISCUSSION

Laparoscopic surgery was introduced to improve patient quality of life by reducing wound length and pain, leading to quicker postoperative recovery. Results from several randomized studies have demonstrated the non-inferiority of laparoscopic surgery in terms of short-term oncological outcomes compared with conventional open surgery^[1,10,11]. Laparoscopic surgery has been applied in the treatment of colorectal cancer, where radical resection is the overall goal of treatment to reduce disease

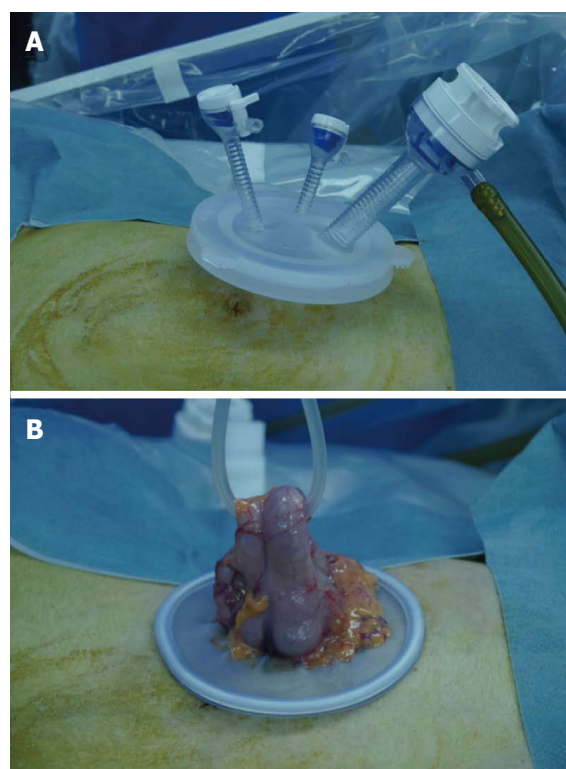


Figure 2 Image of single-incision laparoscopic-assisted stoma creation utilizing multi-trocar access via EZ Access at the stoma site. SILStoma was performed using a total of 3 trocars: 2 trocars for an operator and 1 trocar for a laparoscopist (A). After the mobilization to construct a loop colostomy the transverse colon was extracted through the Lap-Protector at the stoma site (B).

recurrence and improve patient survival^[1,10-12].

The introduction of RPS, including single-incision laparoscopic surgery, has been shown to improve cosmetic outcomes; however, reducing the number of port sites limits laparoscopic handling space. In recent years, a small number of reports have compared the clinicopathological factors and outcomes between single-incision laparoscopic surgery and conventional laparoscopic surgery for colectomy^[13-15]. These studies reported no differences in operative duration, conversion rate to open surgery, number of lymph nodes harvested, length of hospital stay, postoperative complications, or mortality^[13-15]. Among the 12 cases included in the present study, no intra- or postoperative complications greater than or equal to Grade II were reported. No cases required conversion to open surgery.

In the present study, we performed colostomy at the transverse colon because the obstructive effect such as colitis and edema at the sigmoid colon. The stoma site was a major concern as the surgical procedure was performed *via* a single port site; however, we were able to mobilize the transverse colon by laparoscopic surgery and create the stoma at the site initially marked preoperatively. Resultant stoma sites were those marked preoperatively in all cases, indicating the substantial benefit of this rational approach to stoma creation. Another concern was the reduction in the number of port sites that may have increased the technical difficulty of

Table 1 Patient demographics

Age (yr)	61.5 (54-76)
Sex (male/female)	5/7
Body mass index	21.85 (13.7-24.5)
Previous surgical history	1
Indications	
Unresectable obstructive descending colon cancer	1
Unresectable obstructive rectal cancer	10
Recurrence of uterine corpus cancer with rectal obstruction	1
Preoperative decompression of intestine	7

All continuous variables are expressed as medians (range).

Table 2 Perioperative factors associated with single-incision laparoscopic-assisted stoma creation

All continuous variables are expressed as medians (range)	
Operative duration (min)	58.5 (28-140)
Blood loss (mL)	0 (0-5)
Additional port (except single incision)	0 (0-2)
Conversion to open	0
Complications (Grade \geq II ¹)	0
Median days until stoma functioning	1 (1-2)
All continuous variables are expressed as average and standard deviation	
Operative duration (min)	76.9 \pm 38.3
Blood loss (mL)	0.4 \pm 1.4
Additional port (except single incision)	0 (0-2)
Conversion to open	0
Complications (Grade \geq II ¹)	0

¹Postoperative complications \geq Grade II are listed.

operative handling during the surgical procedure. In order to reduce the difficulty caused by the limited work space at the main port for multi-trocar access, we placed three trocars in the EZ Access device and make differences of the trocar length. In the first five cases, the surgical procedure took long time (supplementary table S1); however, the relatively short operation time observed in the succeeding cases indicates that SILStoma is no more time-consuming than comparable techniques, and indirectly demonstrated that technical challenges encountered during the surgical procedure may be less than anticipated. Although we included consecutive cases in the present study, we did not perform a comparison of open vs single-incision laparoscopic surgery using patient randomization. Therefore, selection bias may have been introduced to the results of the present study. There have been several previous studies of single-incision laparoscopic surgery for ileostomy and sigmoid colostomy, however small number of cases was evaluated for transverse colostomy^[16-18]. Although further studies are required to fully determine the potential benefit of the presented technique, SILStoma did not impede stoma creation, indicating its utility in transverse loop colostomy.

SILStoma for transverse loop colostomy represents

a feasible surgical procedure allowing stoma creation at ideal stoma sites marked preoperatively. Reductions in the number of port sites and the avoidance of additional skin incisions may result in improved cosmetic outcomes and patient quality of life.

COMMENTS

Case characteristics

The procedure, efficacy, and utility of single-incision laparoscopic-assisted stoma creation (SILStoma) for transverse colostomy.

Clinical diagnosis

A single, intended stoma site was created with a 2.5-3.5 cm skin incision for primary access to the intra-abdominal space, and it functioned as the main port through which multi-trocar were placed.

Differential diagnosis

SILStoma was performed as follows: An initial skin incision was made at the stoma site marked preoperatively and Lap-Protector (Hakko Co. Ltd., Nagano, Japan) and EZ Access (Hakko Co. Ltd., Nagano, Japan) were placed into the incision site.

Treatment

The skin and intestine were sutured and fixed with vicryl.

Related reports

Laparoscopic surgery was introduced to improve patient quality of life by reducing wound length and pain, leading to quicker postoperative recovery. Results from several randomized studies have demonstrated the non-inferiority of laparoscopic surgery in terms of short-term oncological outcomes compared with conventional open surgery.

Experiences and lessons

SILStoma for transverse loop colostomy represents a feasible surgical procedure allowing stoma creation at ideal stoma sites marked preoperatively. Reductions in the number of port sites and the avoidance of additional skin incisions may result in improved cosmetic outcomes and patient quality of life.

Peer-review

The paper is interesting, and well-presented and developed and consequently.

REFERENCES

- Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA* 2002; **287**: 321-328 [PMID: 11790211 DOI: 10.1001/jama.287.3.321]
- Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; **350**: 2050-2059 [PMID: 15141043 DOI: 10.1056/NEJMoa032651]
- Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; **25**: 3061-3068 [PMID: 17634484 DOI: 10.1200/JCO.2006.09.7758]
- Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, Sugihara K, Watanabe M, Moriya Y, Kitano S. Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. *Ann Surg* 2014; **260**: 23-30 [PMID: 24509190 DOI: 10.1097/SLA.0000000000000499]
- Makino T, Milsom JW, Lee SW. Feasibility and safety of single-incision laparoscopic colectomy: a systematic review. *Ann*

- Surg* 2012; **255**: 667-676 [PMID: 22258065 DOI: 10.1097/SLA.0b013e31823fbae7]
- 6 **Champagne BJ**, Papaconstantinou HT, Parmar SS, Nagle DA, Young-Fadok TM, Lee EC, Delaney CP. Single-incision versus standard multiport laparoscopic colectomy: a multicenter, case-controlled comparison. *Ann Surg* 2012; **255**: 66-69 [PMID: 22104563 DOI: 10.1097/SLA.0b013e3182378442]
 - 7 **Yang TX**, Chua TC. Single-incision laparoscopic colectomy versus conventional multiport laparoscopic colectomy: a meta-analysis of comparative studies. *Int J Colorectal Dis* 2013; **28**: 89-101 [PMID: 22828958 DOI: 10.1007/s00384-012-1537-0]
 - 8 **Vestweber B**, Galetin T, Lammerting K, Paul C, Giehl J, Straub E, Kaldowski B, Alfes A, Vestweber KH. Single-incision laparoscopic surgery: outcomes from 224 colonic resections performed at a single center using SILS. *Surg Endosc* 2013; **27**: 434-442 [PMID: 22806519 DOI: 10.1007/s00464-012-2454-6]
 - 9 **Clavien PA**, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187-196 [PMID: 19638912 DOI: 10.1097/SLA.0b013e3181b13ca2]
 - 10 **Veldkamp R**, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477-484 [PMID: 15992696 DOI: 10.1016/S1470-2045(05)70221-7]
 - 11 **Guillou PJ**, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 1718-1726 [PMID: 15894098 DOI: 10.1016/S0140-6736(05)66545-2]
 - 12 **Fleshman J**, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, Hellinger M, Flanagan R, Peters W, Nelson H. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007; **246**: 655-662; discussion 662-664 [PMID: 17893502 DOI: 10.1097/SLA.0b013e318155a762]
 - 13 **Kim SJ**, Ryu GO, Choi BJ, Kim JG, Lee KJ, Lee SC, Oh ST. The short-term outcomes of conventional and single-port laparoscopic surgery for colorectal cancer. *Ann Surg* 2011; **254**: 933-940 [PMID: 22107740 DOI: 10.1097/SLA.0b013e318237826b]
 - 14 **Fujii S**, Watanabe K, Ota M, Watanabe J, Ichikawa Y, Yamagishi S, Tatsumi K, Suwa H, Kunisaki C, Taguri M, Morita S, Endo I. Single-incision laparoscopic surgery using colon-lifting technique for colorectal cancer: a matched case-control comparison with standard multiport laparoscopic surgery in terms of short-term results and access instrument cost. *Surg Endosc* 2012; **26**: 1403-1411 [PMID: 22101420 DOI: 10.1007/s00464-011-2047-9]
 - 15 **Huscher CG**, Mingoli A, Sgarzini G, Mereu A, Binda B, Brachini G, Trombetta S. Standard laparoscopic versus single-incision laparoscopic colectomy for cancer: early results of a randomized prospective study. *Am J Surg* 2012; **204**: 115-120 [PMID: 22178484 DOI: 10.1016/j.amjsurg.2011.09.005]
 - 16 **Nguyen HM**, Causey MW, Steele SR, Maykel JA. Single-port laparoscopic diverting sigmoid colectomy. *Dis Colon Rectum* 2011; **54**: 1585-1588 [PMID: 22067189 DOI: 10.1097/DCR.0b013e3182315556]
 - 17 **Zaghiyan KN**, Murrell Z, Fleshner PR. Scarless single-incision laparoscopic loop ileostomy: a novel technique. *Dis Colon Rectum* 2011; **54**: 1542-1546 [PMID: 22067183 DOI: 10.1097/DCR.0b013e31822b71eb]
 - 18 **Hasegawa J**, Hirota M, Kim HM, Mikata S, Shimizu J, Soma Y, Nezu R. Single-incision laparoscopic stoma creation: experience with 31 consecutive cases. *Asian J Endosc Surg* 2013; **6**: 181-185 [PMID: 23683320 DOI: 10.1111/ases.12034]

P- Reviewer: Garcia-Vallejo L, Hiraki M, Nakayama Y, Neri V
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 August 25; 8(16): 546-571





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

GUEST EDITORIAL BOARD

MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Demitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Chisato Hamashima, *Tokyo*

Naoki Hotta, *Nagoya*
Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroyuki Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurihonjo*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Izuru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satoshi Matsumoto, *Saitama*
Hiroyuki Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Noshio, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwa*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*

**Poland**

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*

**Portugal**

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*

**Romania**

Lucian Negreanu, *Bucharest*

**Singapore**

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*

**Slovenia**

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*

**South Korea**

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *Uijeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*

**Spain**

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*

**Thailand**

Somchai Amornytin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*

**Turkey**

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentese, *Ankara*
 Orhan V Ozkan, *Sakarya*

**United Arab Emirates**

Maher A Abbas, *Abu Dhabi*

**United Kingdom**

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*

**United States**

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*



MINIREVIEWS

- 546 Endoscopic applications of cryospray ablation therapy-from Barrett's esophagus and beyond
Sreenarasimhaiah J

ORIGINAL ARTICLE

Retrospective Study

- 553 Bleeding risk with clopidogrel and percutaneous endoscopic gastrostomy
Sohail U, Harleen C, Mahdi AO, Arif M, Nguyen DL, Bechtold ML
- 558 What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?
Watari J, Ueyama S, Tomita T, Ikehara H, Hori K, Hara K, Yamasaki T, Okugawa T, Kondo T, Kono T, Tozawa K, Oshima T, Fukui H, Miwa H

CASE REPORT

- 568 Small bowel Dieulafoy lesions: An uncommon cause of obscure bleeding in cirrhosis
Holleran G, Hussey M, McNamara D

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 16 August 25, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Kenjiro Yasuda, MD, PhD, N/A, Department of Gastroenterology, Kyoto Second Red Cross Hospital, Kyoto 602-8026, Japan

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Shui Qiu*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

EDITORS-IN-CHIEF
Juan Manuel Herrerías Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL OFFICE
Jin-Lei Wang, Director

Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
August 25, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/geninfo/204>

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Endoscopic applications of cryospray ablation therapy-from Barrett's esophagus and beyond

Jayaprakash Sreenarasimhaiah

Jayaprakash Sreenarasimhaiah, Department of Medicine, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX 75390, United States

Author contributions: Sreenarasimhaiah J designed, composed, and edited the entire manuscript; all pictures were also from the direct work of Sreenarasimhaiah J; the manuscript was written completely by this author alone.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Jayaprakash Sreenarasimhaiah, MD, Department of Internal Medicine, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, MC 9083, Dallas, TX 75390, United States. jayaprakash.sree@yahoo.com
Telephone: +1-214-6450595

Received: March 26, 2016

Peer-review started: March 27, 2016

First decision: May 17, 2016

Revised: June 1, 2016

Accepted: June 27, 2016

Article in press: June 29, 2016

Published online: August 25, 2016

Abstract

In the last decade, the treatment of dysplastic Barrett's esophagus has evolved into primarily endoscopic

therapy. Many techniques have become well-established to destroy or remove the mucosal lining of Barrett's esophagus. One of the newest therapies, cryospray ablation, has become a modality to treat both dysplastic Barrett's esophagus as well as esophageal carcinoma. In endoscopic applications, the cryogen used is either liquid nitrogen or carbon dioxide which causes tissue destruction through rapid freeze-thaw cycles. Unlike other endoscopic ablation techniques, its unique mechanism of action and depth of tissue injury allow cryoablation to be used effectively in flat or nodular disease. It can be combined with other modalities such as endoscopic mucosal resection or radiofrequency ablation. Its esophageal applications stem well-beyond Barrett's into ablation of early carcinoma, palliative debulking of advanced carcinoma and reduction of tumor ingrowth into stents placed for dysphagia. Although there are fewer reported studies of endoscopic cryoablation in the literature compared to other endoscopic ablation methods, emerging research continues to demonstrate its efficacy as a durable ablation technology with a variety of applications. The aim of this review is to examine the pathophysiology of endoscopic cryospray ablation, describe its outcomes in Barrett's with dysplasia and esophageal carcinoma, and examine its role in other gastrointestinal applications such as hemostasis in the stomach and rectum.

Key words: Barrett's esophagus; Dysplasia; Esophageal carcinoma; Endoscopic cryoablation; Cryotherapy

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The current standard of care in treatment of dysplastic Barrett's esophagus is endoscopic ablation. Cryospray ablation, the newest modality can achieve complete eradication of dysplasia and intestinal metaplasia in over 90% of patients. Unlike other endoscopic methods, its unique mechanisms and depth of injury enable successful ablation of early esophageal

carcinoma, palliative debulking of advanced carcinoma and reduction of tumor ingrowth into stents. The applications of cryospray ablation beyond the esophagus include control of bleeding from gastric antral vascular ectasia, portal hypertensive gastropathy, and radiation proctitis. This modality continues to evolve as an important tool of therapeutic endoscopy.

Sreenarasimhaiah J. Endoscopic applications of cryospray ablation therapy-from Barrett's esophagus and beyond. *World J Gastrointest Endosc* 2016; 8(16): 546-552 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i16/546.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i16.546>

INTRODUCTION

The treatment of Barrett's esophagus with dysplasia or intramucosal cancer has evolved in the past decade from a primarily surgical management into endoscopic therapy as the initial modality. Many endoscopic techniques have become well established to destroy or remove the mucosal lining of Barrett's esophagus. One of the newest therapies, cryospray ablation, continues to evolve as a method for treatment of dysplastic Barrett's esophagus as well as esophageal carcinoma. This technology was first introduced commercially to gastroenterologists in 2007 but has been based on methods used for over thirty years in fields such as dermatology, gynecology and urology to apply liquid nitrogen in the destruction of superficial lesions. In endoscopic applications, the cryogen used is either liquid nitrogen or carbon dioxide that are applied to cause rapid freezing and thawing of a target area with resulting tissue sloughing and subsequent growth of normal mucosa in its place. As one of the newest modalities for endoscopic ablation of Barrett's, several studies have been reported and more are still underway to demonstrate its efficacy.

After its introduction in treatment of esophageal disease, endoscopic applications of cryospray ablation have continued into other areas of the gastrointestinal tract. FDA approval of the technology has been granted for a broad range indication of "cryosurgical tool for destruction of unwanted tissue in the field of general surgery, specifically for endoscopic applications". With this charge, cryospray ablation has been applied in treatment of a variety of conditions such as palliation of obstructive esophageal cancer, gastric antral vascular ectasia and radiation proctitis. This review will describe the pathophysiology as well as the clinical applications of cryospray ablation in mainly the esophagus but also other areas of gastrointestinal endoscopy.

PATHOPHYSIOLOGY OF CRYOSPRAY ABLATION

Introduced first in the 1960's, liquid nitrogen cryosurgery

was used to destroy lesions with applications of -20°C . Since then, it has been shown that cellular apoptosis is achieved after reaching temperatures less than -50°C ^[1]. Carbon dioxide cryospray ablation has been shown to reach temperatures of -78°C while liquid nitrogen cryospray can reach temperatures of -196°C . Freezing is usually performed at two to three cycles with applications ranging between 10 to 30 s each. The mechanism of action of thermal injury has two modalities. Flash freezing and thawing cycles that are repeatedly applied to a tissue causes immediate effects of slowing cellular metabolism and freezing intracellular water. Subsequently, ice formation results in disruption of cellular membranes and organelle dysfunction. Repeat freeze-thaw cycles add to the injury and cellular apoptosis ensues. The stromal intracellular collagen matrix remains intact and so the injury is not seen by endoscopic view during the immediate phase except for hyperemia of the mucosal surface. There is an immediate vasoconstriction followed later by vasodilation of the microcirculation and thus bleeding is not a major component of the early cellular injury. Delayed effects of the freeze-thaw cycles begin within hours to days with mucosal edema, anoxia, microthrombi formation, and apoptosis of the remaining surrounding tissue. This inflammatory response results in a cytokine mediated response involving Th1 cells following cellular apoptosis^[2]. As the cellular scaffolding remains intact, healthy tissue regeneration follows over several weeks.

DEVICES FOR CRYOSPRAY ABLATION

There are two main devices available commercially for the endoscopic application of cryospray ablation. First is liquid nitrogen cryospray known as Trufreeze (CSA Medical, Baltimore, MD) and the other is carbon dioxide cryospray known as Polar Wand (GI Supply, Camphill, PA). Another device that is currently undergoing clinical testing is the Coldplay Focal Cryoballoon Ablation System (C2 Therapeutics, Redwood City, CA).

Liquid nitrogen cryospray ablation

The Trufreeze liquid nitrogen system has become the most widely used of the endoscopic cryospray ablation systems with over 11000 treatments performed. This technology uses a generator that delivers cold liquid nitrogen at -196°C through a flexible spray catheter with a low-flow (2-4 psi) continuous delivery in a noncontact method. Due to the potential for rapid expansion of the liquid nitrogen into 4 to 6 L of gas during a 20 s treatment, a multiport orogastric decompression catheter is placed with constant suction during the delivery of liquid nitrogen (Figure 1). The new generation flexible catheter permits retroflexion applications in the stomach or rectum up to 180° .

The treatment is performed with direct visualization of the mucosa to spray large areas of up to 4 cm length at a time. The depth of injury is dependent on

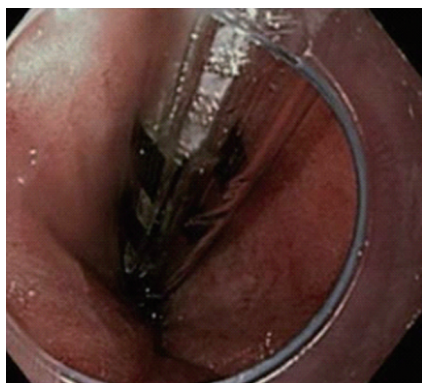


Figure 1 Decompression catheter placement for liquid nitrogen cryospray.

the dosimetry of liquid nitrogen spray time. Traditional applications use 20 s cycles performed twice at each site for dysplastic Barrett's mucosa. In the setting of intramucosal carcinoma, treatment may be performed for longer cycles of 30 s.

The depth of treatment is not limited to the mucosal surface. In contrast, radiofrequency ablation (RFA) has a set dosimetry and ablation depth of 500 microns which will not penetrate below the mucosal surface. Studies into the depth of penetration have been performed with cryospray liquid nitrogen application in the esophagus. Ribeiro prospectively studied a group of patients who were to undergo esophagectomy and applied liquid nitrogen cryospray preoperatively. Using 20 s cycles twice in the same area showed that 93% of patients had cell necrosis into the submucosal layer^[3]. If applied in the same area long-enough, esophageal perforation can result as a combination of deep ablation as well as increased esophageal wall tension from rapid gas expansion^[4].

Polar wand ablation

This technology uses a through-the-scope spray catheter to deliver compressed liquid carbon dioxide that rapidly expands during spray and reaches -78°C as it exits the catheter. This temperature has been shown to be effective for inducing cellular apoptosis. It has been given FDA clearance for use throughout the GI tract for focal mucosal ablation. Due to the lower flow volume compared to the liquid nitrogen cryospray, a separate decompression catheter is not required. However, a suction channel is directly connected to the spray catheter as it requires a flow of 6 to 8 L/min CO_2 to achieve a temperature of less than -70°C . Rapid expansion from a high pressure liquid to a low pressure gas results in a significant drop in temperature as explained by the Joule-Thomson effect.

Focal cryoballoon ablation

While the vast majority of endoscopic ablation of Barrett's mucosa is performed by either RFA or spray cryotherapy, both have their limitations such as the need for sizing, multiple deployment steps, large

consoles, and decompression catheter placement. The new Coldplay Focal Cryoballoon Ablation System aims to overcome some of these restrictions. It uses a combination of an inflatable balloon passed through the accessory channel of the endoscope and applies liquid carbon dioxide. The balloon is highly compliant and conforms to the esophageal lumen without excessive tension of the esophageal wall and does not require special decompression catheters. Unlike the inflatable balloon device of RFA, pretreatment sizing is not required with this system. The device has received United States FDA 510 (k) clearance and is undergoing clinical study.

APPLICATIONS IN BARRETT'S ESOPHAGUS

Endoscopic ablation of dysplastic Barrett's has become well established and validated by many studies within the past decade. As per AGA guidelines, endoscopic ablation of Barrett's esophagus is indicated in high-grade dysplasia (HGD) and possibly persistent low-grade dysplasia (LGD) but not in nondysplastic Barrett's epithelium^[5]. The ACG practice guidelines of 2015 confirm these same recommendations and also recommend endoscopic mucosal resection (EMR) initially for nodules followed later by endoscopic ablation therapy^[6]. The vast majority of recent studies have examined a different modality, RFA. In a meta-analysis of 18 studies in 3802 patients examining RFA for Barrett's, the results show a complete response in eradication of intestinal metaplasia of 78% and overall dysplasia of 91%^[7]. However, there are several important studies examining the efficacy of cryospray therapy. Most of these are in regard to liquid nitrogen therapy and show results that are equal to the outcomes of RFA (Figure 2).

Most patients undergoing esophageal cryoablation will require treatment in multiple sessions that are usually separated by 6 to 8 wk intervals to allow for healing of the mucosa. Contraindications to treatment include mucosal breaks such as active esophagitis, erosions, and ulcerations seen at the time of endoscopy due to potential perforation. A tight stricture of the esophagus through which a decompression catheter as well as endoscopic spray catheter cannot both be placed together will also preclude safe treatment. Altered anatomy such as bariatric surgery is a contraindication for therapy due to difficulty in ventilating gas safely from the gastrointestinal tract. The safety of this procedure has been shown in several studies below.

Shaheen *et al*^[6] examined 98 patients with HGD with a mean age of 65.4 years and mean Barrett's length of 5.3 cm. In this group of 87% males, an average of 3.4 treatments per patient was performed with liquid nitrogen cryospray to achieve complete ablation. HGD was eradicated in 97% of all patients while 87% had complete eradication of all dysplasia. No perforations occurred and a stricture rate of 3% was identified

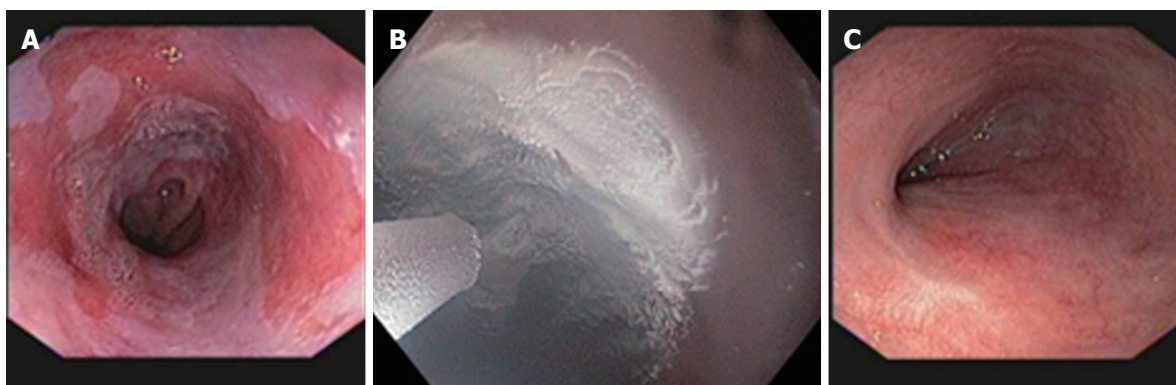


Figure 2 Results that are equal to the outcomes of radiofrequency ablation. A: Barrett's esophagus with high grade dysplasia; B: Liquid nitrogen cryospray ablation; C: Complete eradication of dysplasia and intestinal metaplasia.

and treated easily with endoscopic balloon dilation in all cases^[8]. Additionally, this study showed a 1%-2% incidence of chest discomfort that required outpatient narcotic use. This is in contrast to RFA therapy which has been shown to have a significantly higher incidence of chest discomfort sometimes requiring hospitalization up to day 8 following the procedure compared to a sham treatment group and an overall esophageal stricture rate of 6%^[9].

Greenwald *et al*^[10] further demonstrated in a group of 7 patients with stage I esophageal adenocarcinoma that complete response was achieved in 100% with liquid nitrogen cryospray ablation alone. The same group demonstrated recently in a cohort of 33 patients followed long-term for at least 24 mo that a durable response can be achieved. Complete response for HGD was 97% and complete response for intestinal metaplasia was 87% at 24 mo^[11].

Recurrence of disease after cryoablation for HGD achieved a complete response has also been evaluated. Halsey *et al*^[12] prospectively examined a group of 36 patients who had HGD and underwent liquid nitrogen cryospray therapy. In 11 (30%) patients, recurrent disease was identified at a median of 6.5 mo. In 70% of these patients, recurrences occurred below the neosquamocolumnar junction including a variety of histology such as HGD, LGD, and intestinal metaplasia. In one patient, recurrent disease was esophageal carcinoma within the previously treated esophagus. This patient as well as a total of 33 patients (92%) ultimately achieved complete response to retreatment with cryotherapy^[12]. This demonstrates the importance of follow-up surveillance biopsies after completion of cryoablation therapy not only within the previously treated esophagus but also at the gastric cardia immediately below the squamocolumnar junction.

While the cryoballoon focal ablation system is not commercially available, it has been studied for feasibility and efficacy in ablation of Barrett's mucosa. In a prospective, non-randomized trial of 39 patients, 62 ablations were performed between 6-10 s. No adverse events occurred and no strictures resulted from the treatment. Mild pain was noted in 27% of patients. Full

squamous regeneration was noted in 47 treated areas (60 % of 6-s cycles, 82% of 8-s cycles, and 100% of 10-s areas). Long-term follow-up of these patients as well as durable responses for HGD or LGD is being examined in ongoing studies^[13].

APPLICATIONS IN ESOPHAGEAL NEOPLASIA

The presentation of esophageal neoplasia can range from a small nodule or flat area of intramucosal carcinoma to a large bulky obstructing tumor with ulceration, bleeding and metastases. The standard of care in management of nodular mucosa within Barrett's esophagus is endoscopic mucosal resection. However, larger flat areas of intramucosal cancer may be difficult to treat with EMR alone as well as difficulty with overlapping areas for complete treatment^[14]. The combination of cryoablation therapy with EMR has been reported to be effective.

Liquid nitrogen cryoablation has been performed safely prior to and following EMR, as well as during the same session^[15]. As described above, cryoablation causes destruction of cellular contents but maintains the intracellular collagen matrix. The structural injury is delayed and enables further therapy to the treated tissue. This may explain how this treatment can be easily combined with endoscopic mucosal resection which alone may be challenging if there is scarring or adherence of esophageal wall layers (Figure 3).

While the data for liquid nitrogen as the cryogen for ablation of esophageal neoplasia seems promising, the use of carbon dioxide has not been shown to achieve similar results. In a recent study of 30 patients with Barrett's and early neoplasia, CO₂ cryoablation therapy was performed. In 9 patients, nodular areas were first treated with EMR. With a mean of 2.5 cryoablation sessions and a six-month follow up of 10 patients, early termination of the study occurred due to the disappointing results with eradication of dysplasia in only 44% and persistence of neoplasia in a large portion. This study suggests that CO₂ cryoablation combined with EMR may not be an effective modality for treatment of

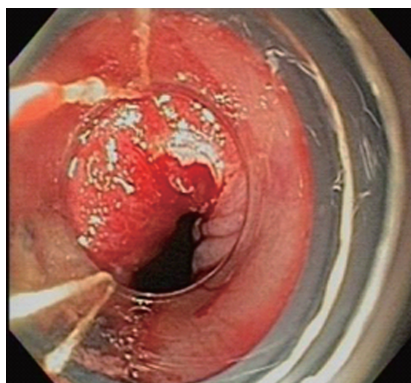


Figure 3 Endoscopic mucosal resection following liquid nitrogen cryoablation.

Barrett's associated neoplasia^[16].

Debulking of esophageal cancer for palliation of swallowing has been shown to be feasible (Figure 4). Tumor ingrowth into a palliative metal esophageal stent can also be treated^[17]. No outcome studies of cryoablation for palliation of dysphagia have been published. In a recent report, a 63-year-old patient with esophageal squamous cell carcinoma who had recurrence of disease had tumor ingrowth at the ends of a previously placed metal stent resulting in dysphagia. Liquid nitrogen cryotherapy was used to recanalize the lumen of the metal stent successfully^[18]. Cash *et al*^[19] reported the first application of liquid nitrogen cryotherapy for recurrent esophageal squamous cell cancer that occurred 3 years after definitive chemotherapy. This patient was disease-free at two year follow-up. In another study, 7 patients with superficial esophageal adenocarcinoma had complete response to cryoablation therapy in all patients at a range of follow-up between 3 to 18 mo^[10]. Greenwald *et al*^[20] reported liquid nitrogen cryoablation treatment of 79 patients with adenocarcinoma (tumor stage included T1-60, T2-16, and T3/4-3). Complete response of intraluminal disease was achieved in 61% and in 75% of patients with intramucosal (T1) disease. Mean follow up was 10.6 mo overall and 11.5 mo for T1 disease.

Hemostasis of bleeding from advanced esophageal carcinoma has been shown to be feasible with endoscopic cryoablation. Shah *et al*^[21] reported a case of a 62-year-old male with locally advanced unresectable adenocarcinoma of the esophagus with bleeding that did not respond to chemotherapy, radiation therapy, brachytherapy, or photodynamic therapy. Liquid nitrogen cryospray ablation was used with three 20 s applications and resulted in reduction of blood transfusions from 30 units over the preceding two weeks to one unit over the following two weeks. Immediate post-procedural hemostasis as well as a durable response was noted.

TREATMENT OF GASTRIC ANTRAL VASCULAR ECTASIA

Gastric antral vascular ectasia (GAVE) is a well-

recognized entity that causes chronic blood loss from the upper gastrointestinal tract. It is often associated with connective tissue disease, liver cirrhosis, and renal failure but may also be of idiopathic origin^[22]. The most common type is also known as "water-melon stomach" due to its classic endoscopic appearance of striped mucosa radiating from the pylorus. The other type is characterized by diffuse punctate erythematous angiomias of the antrum that is often associated with portal hypertension and cirrhosis^[23].

Traditional endoscopic therapies of GAVE include the gold-standard of argon plasma coagulation (APC) which is a non-contact thermal method that can cause mucosal ablation and perhaps deeper injury as well. It often requires multiple sessions and has been shown to be very effective in mild to moderate disease but bleeding may be refractory in underlying cirrhosis or severe mucosal involvement^[24]. Other treatments that have been tried with some limited success include thermal heater probe therapy, YAG laser ablation, and band ligation. In small studies, RFA has recently been demonstrated to be effective in reducing the blood transfusion requirements within the 6 mo period following treatment for those patients with GAVE refractory to initial APC therapy^[25,26].

Cryospray ablation can be used as a secondary line of endoscopic therapy for refractory GAVE as it may be able to cover a larger area through spray therapy than other modalities. However, it is limited by gas flow and potential air entrapment in the small intestine. While it has been described, very few studies are available to show its efficacy. Kantsevov showed in a pilot study of 7 patients with GAVE and recurrent bleeding that nitrous oxide cryoablation was effective in 71% for cessation of bleeding^[27]. Carbon dioxide cryoablation was examined in a study of 12 patients with refractory GAVE and significant iron-deficiency anemia. All of these patients had undergone APC therapy with a median of 6 sessions. In this group, 50% achieved complete response with a mean of 3 sessions of cryoablation and 50% had a partial response manifest by incomplete ablation but stable hemoglobin. The entire group had a mean increase in hemoglobin from 9.9 to 11.3 g/dL. No adverse events were noted in any patient^[28]. Liquid nitrogen spray cryotherapy has also been examined in treatment of GAVE and portal hypertensive gastropathy with refractory bleeding. It was shown to be very effective in cessation of bleeding from portal hypertensive gastropathy that did not respond to either APC or transjugular intrahepatic portosystemic shunt placement^[29].

TREATMENT OF RADIATION PROCTITIS

Chronic radiation proctitis occurs in up to 15% of patients within months to even decades following radiation therapy for pelvic malignancies. Most patients will present with recurrent rectal bleeding and often have rectal pain and tenesmus. Traditional medical therapies

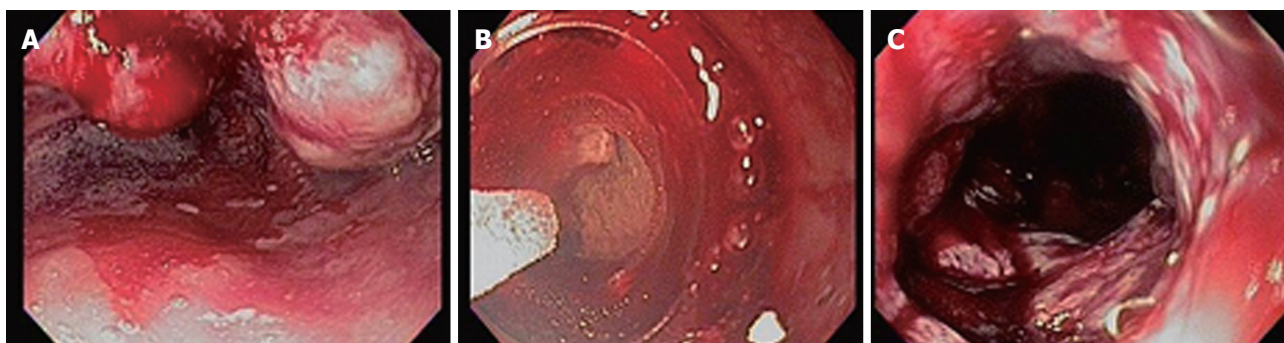


Figure 4 Debulking of esophageal cancer for palliation of swallowing. A: Bulky friable esophageal adenocarcinoma causing dysphagia and bleeding; B: Liquid nitrogen cryospray ablation of tumor for palliation; C: Post-ablation appearance of tumor at 8 wk.

for radiation proctitis include enemas with salicylates, sucralfate, and corticosteroids which may help short-term symptoms but have not been shown to have long-term effects^[30]. Endoscopic therapy has traditionally included APC which is very effective in mild to moderate radiation proctitis requiring several sessions to achieve ablation. In more severe mucosal damage, refractory proctitis is present in up to 50% of patients^[31]. Recent reports demonstrate RFA with the Halo90 system to be effective in moderate radiation proctitis with 1 to 2 sessions and effective control of lower gastrointestinal bleeding^[32].

While both APC and RFA require a contact method of treatment and may be limited by blood or tissue adherence, cryoablation has been used as noncontact application for treatment of chronic radiation proctitis. In a recent study, treatment was applied for 5 s applications to reduce the risk of proximal gas entrapment and perforation. Patients required between 1 and 4 sessions. In all patients, significant response was seen in endoscopic score of proctitis, and improvement in rectal pain and bleeding^[33].

CONCLUSION

Cryoablation therapy has become well-established as a modality for treatment of dysplastic Barrett's esophagus. Due to its potential for deeper tissue injury, it has evolved into successful applications of ablation of nodular Barrett's and early esophageal carcinoma with or without combined EMR therapy. This modality also serves as an alternative when other endoscopic ablation modalities such as RFA or APC are refractory or contraindicated in high risk settings such as chronic anticoagulation, implanted cardiac defibrillators, esophageal strictures, radiation therapy, or within esophageal stents. Other applications of cryoablation in the stomach or rectum to treat bleeding angiodysplasia have been shown to be feasible. As the newest modality of endoscopic mucosal ablation, more efficacy studies as well as novel applications within the gastrointestinal tract are continuing to emerge, ensuring that cryotherapy will remain an important tool for therapeutic endoscopy.

REFERENCES

- 1 **Gage AA**, Baust JM, Baust JG. Experimental cryosurgery investigations in vivo. *Cryobiology* 2009; **59**: 229-243 [PMID: 19833119 DOI: 10.1016/j.cryobiol.2009.10.001]
- 2 **Gage AA**, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology* 1998; **37**: 171-186 [PMID: 9787063 DOI: 10.1006/cryo.1998.2115]
- 3 **Ribeiro A**, Bejarano P, Livingstone A, Sparling L, Franceschi D, Ardan B. Depth of injury caused by liquid nitrogen cryospray: study of human patients undergoing planned esophagectomy. *Dig Dis Sci* 2014; **59**: 1296-1301 [PMID: 24395381 DOI: 10.1007/s10620-013-2991-4]
- 4 **Dumot JA**, Vargo JJ, Falk GW, Frey L, Lopez R, Rice TW. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. *Gastrointest Endosc* 2009; **70**: 635-644 [PMID: 19559428 DOI: 10.1016/j.gie.2009.02.006]
- 5 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: 1084-1091 [PMID: 21376940 DOI: 10.1053/j.gastro.2011.01.030]
- 6 **Shaheen NJ**, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *Am J Gastroenterol* 2016; **111**: 30-50; quiz 51 [PMID: 26526079 DOI: 10.1038/ajg.2015.322]
- 7 **Orman ES**, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 1245-1255 [PMID: 23644385 DOI: 10.1016/j.cgh.2013.03.039]
- 8 **Shaheen NJ**, Greenwald BD, Peery AF, Dumot JA, Nishioka NS, Wolfsen HC, Burdick JS, Abrams JA, Wang KK, Mallat D, Johnston MH, Zfass AM, Smith JO, Barthel JS, Lightdale CJ. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc* 2010; **71**: 680-685 [PMID: 20363409 DOI: 10.1016/j.gie.2010.01.018]
- 9 **Shaheen NJ**, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; **360**: 2277-2288 [PMID: 19474425 DOI: 10.1056/NEJMoa0808145]
- 10 **Greenwald BD**, Dumot JA, Horvath JD, Lightdale CJ, Abrams JA. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. *Dis Esophagus* 2010; **23**: 13-19 [PMID: 19515183 DOI: 10.1111/j.1442-2050.2009.00991.x]
- 11 **Gosain S**, Mercer K, Twaddell WS, Uradomo L, Greenwald BD. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. *Gastrointest Endosc* 2013; **78**:

- 260-265 [PMID: 23622979 DOI: 10.1016/j.gie.2013.03.002]
- 12 **Halsey KD**, Chang JW, Waldt A, Greenwald BD. Recurrent disease following endoscopic ablation of Barrett's high-grade dysplasia with spray cryotherapy. *Endoscopy* 2011; **43**: 844-848 [PMID: 21826629 DOI: 10.1055/s-0030-1256649]
- 13 **Schölvinck DW**, Künzli HT, Kestens C, Siersema PD, Vleggaar FP, Canto MI, Cosby H, Abrams JA, Lightdale CJ, Tejeda-Ramirez E, DeMeester SR, Greene CL, Jobe BA, Peters J, Bergman JJ, Weusten BL. Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. *Endoscopy* 2015; **47**: 1106-1112 [PMID: 26158241 DOI: 10.1055/s-0034-1392417]
- 14 **Mino-Kenudson M**, Brugge WR, Puricelli WP, Nakatsuka LN, Nishioka NS, Zukerberg LR, Misraji J, Lauwers GY. Management of superficial Barrett's epithelium-related neoplasms by endoscopic mucosal resection: clinicopathologic analysis of 27 cases. *Am J Surg Pathol* 2005; **29**: 680-686 [PMID: 15832094]
- 15 **Hussain Z**, Fukami N, Smith M, Sreenarasimhaiah J, Kaul V, Kothari S, Greenwald BD, Shaheen NJ. Safety and Efficacy of Same Session Spray Cryotherapy and Endoscopic Mucosal Resection for Barrett's Esophagus and Early Esophageal Neoplasia: a Multicenter Experience. *Gastrointest Endosc* 2015; **81** Suppl: AB508 [DOI: 10.1016/j.gie.2015.03.1746]
- 16 **Verbeek RE**, Vleggaar FP, Ten Kate FJ, van Baal JW, Siersema PD. Cryospray ablation using pressurized CO2 for ablation of Barrett's esophagus with early neoplasia: early termination of a prospective series. *Endosc Int Open* 2015; **3**: E107-E112 [PMID: 26135648 DOI: 10.1055/s-0034-1390759]
- 17 **Barthel JS**, Kucera S, Harris C, Canchi D, Hoffe S, Meredith K. Cryoablation of persistent Barrett's epithelium after definitive chemoradiation therapy for esophageal adenocarcinoma. *Gastrointest Endosc* 2011; **74**: 51-57 [PMID: 21549371 DOI: 10.1016/j.gie.2011.03.1121]
- 18 **Goetz M**, Malek NP, Kanz L, Hetzel J. Cryorecanalization for instant recanalization in the esophagus. *Gastroenterology* 2014; **146**: 1168-1170 [PMID: 24631576 DOI: 10.1053/j.gastro.2014.03.004]
- 19 **Cash BD**, Johnston LR, Johnston MH. Cryospray ablation (CSA) in the palliative treatment of squamous cell carcinoma of the esophagus. *World J Surg Oncol* 2007; **5**: 34 [PMID: 17367523 DOI: 10.1186/1477-7819-5-34]
- 20 **Greenwald BD**, Dumot JA, Abrams JA, Lightdale CJ, David DS, Nishioka NS, Yachimski P, Johnston MH, Shaheen NJ, Zfass AM, Smith JO, Gill KR, Burdick JS, Mallat D, Wolfsen HC. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. *Gastrointest Endosc* 2010; **71**: 686-693 [PMID: 20363410 DOI: 10.1016/j.gie.2010.01.042]
- 21 **Shah MB**, Schnoll-Sussman F. Novel use of cryotherapy to control bleeding in advanced esophageal cancer. *Endoscopy* 2010; **42** Suppl 2: E46 [PMID: 20157884 DOI: 10.1055/s-0029-1215370]
- 22 **Naidu H**, Huang Q, Mashimo H. Gastric antral vascular ectasia: the evolution of therapeutic modalities. *Endosc Int Open* 2014; **2**: E67-E73 [PMID: 26135263 DOI: 10.1055/s-0034-1365525]
- 23 **Stotzer PO**, Willén R, Kilander AF. Watermelon stomach: not only an antral disease. *Gastrointest Endosc* 2002; **55**: 897-900 [PMID: 12024147]
- 24 **Lecleire S**, Ben-Soussan E, Antonietti M, Gorla O, Riachi G, Lerebours E, Ducrotté P. Bleeding gastric vascular ectasia treated by argon plasma coagulation: a comparison between patients with and without cirrhosis. *Gastrointest Endosc* 2008; **67**: 219-225 [PMID: 18226684 DOI: 10.1016/j.gie.2007.10.016]
- 25 **McGorisk T**, Krishnan K, Keefer L, Komanduri S. Radiofrequency ablation for refractory gastric antral vascular ectasia (with video). *Gastrointest Endosc* 2013; **78**: 584-588 [PMID: 23660565 DOI: 10.1016/j.gie.2013.04.173]
- 26 **Dray X**, Repici A, Gonzalez P, Kantsevoy SV, Frstrup C, Wengrower D, Camus M, Carlino A, Pérez-Roldán F, Adar T, Rask P, Elbe P, Lecleire S, Marteau PR. 1040 Radiofrequency Ablation Treatment of Gastric Antral Vascular Ectasia: Results From an International Collaborative Study. *Gastrointest Endosc* 2013; **77**: AB180 [DOI: 10.1016/j.gie.2013.04.151]
- 27 **Kantsevoy SV**, Cruz-Correa MR, Vaughn CA, Jagannath SB, Pasricha PJ, Kalloo AN. Endoscopic cryotherapy for the treatment of bleeding mucosal vascular lesions of the GI tract: a pilot study. *Gastrointest Endosc* 2003; **57**: 403-406 [PMID: 12612530]
- 28 **Cho S**, Zanati S, Yong E, Cirocco M, Kandel G, Kortan P, May G, Marcon N. Endoscopic cryotherapy for the management of gastric antral vascular ectasia. *Gastrointest Endosc* 2008; **68**: 895-902 [PMID: 18640673 DOI: 10.1016/j.gie.2008.03.1109]
- 29 **Patel J**, Parra V, Kedia P, Sharaiha RZ, Kahaleh M. Salvage cryotherapy in portal hypertensive gastropathy. *Gastrointest Endosc* 2015; **81**: 1003 [PMID: 25028270 DOI: 10.1016/j.gie.2014.05.326]
- 30 **Talley NA**, Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Dis Colon Rectum* 1997; **40**: 1046-1050 [PMID: 9293933]
- 31 **Sebastian S**, O'Connor H, O'Morain C, Buckley M. Argon plasma coagulation as first-line treatment for chronic radiation proctopathy. *J Gastroenterol Hepatol* 2004; **19**: 1169-1173 [PMID: 15377295]
- 32 **Zhou C**, Adler DC, Becker L, Chen Y, Tsai TH, Figueiredo M, Schmitt JM, Fujimoto JG, Mashimo H. Effective treatment of chronic radiation proctitis using radiofrequency ablation. *Therap Adv Gastroenterol* 2009; **2**: 149-156 [PMID: 20593010]
- 33 **Hou JK**, Abudayyeh S, Shaib Y. Treatment of chronic radiation proctitis with cryoablation. *Gastrointest Endosc* 2011; **73**: 383-389 [PMID: 21295650 DOI: 10.1016/j.gie.2010.10.044]

P- Reviewer: Geraci G, Guo YM S- Editor: Qi Y

L- Editor: A E- Editor: Wu HL



Retrospective Study

Bleeding risk with clopidogrel and percutaneous endoscopic gastrostomy

Umair Sohail, Chela Harleen, Amin O Mahdi, Murtaza Arif, Douglas L Nguyen, Matthew L Bechtold

Umair Sohail, Chela Harleen, Amin O Mahdi, Murtaza Arif, Matthew L Bechtold, Division of Gastroenterology and Hepatology, Department of Medicine, University of Missouri, Columbia, MO 65212, United States

Douglas L Nguyen, Department of Medicine, University of California, Irvine, CA 92697, United States

Author contributions: Sohail U, Arif M and Bechtold ML contributed to conception and design; Sohail U, Harleen C and Mahdi AO contributed to acquisition of data and drafting of manuscript; Sohail U, Arif M, Nguyen DL and Bechtold ML contributed to analysis and interpretation of data; Arif M, Nguyen DL and Bechtold ML contributed to critical revision of manuscript; Nguyen DL and Bechtold ML contributed to statistical expertise; Bechtold ML contributed to overall supervision of project.

Institutional review board statement: IRB reviewed and approved this project as a record review.

Informed consent statement: Given the nature of the retrospective record review, no informed consent was mandated per IRB.

Conflict-of-interest statement: No conflicts of interest noted.

Data sharing statement: Dataset is available from the corresponding author, Matthew Bechtold at bechtoldm@health.missouri.edu. Given that is a retrospective study, informed consent was not obtained for data sharing but data was anonymized and project approved by the IRB.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Matthew L Bechtold, MD, FACP, FASGE, FACC, AGAF, Division of Gastroenterology and Hepatology, Department of Medicine, University of Missouri, CE405, DC043.00, Five Hospital Drive, Columbia, MO 65212, United States. bechtoldm@health.missouri.edu
Telephone: +1-573-8821013
Fax: +1-573-8844595

Received: April 28, 2016
Peer-review started: April 29, 2016
First decision: May 17, 2016
Revised: June 1, 2016
Accepted: June 27, 2016
Article in press: June 29, 2016
Published online: August 25, 2016

Abstract

AIM

To compare bleeding within 48 h in patients undergoing percutaneous endoscopic gastrostomy (PEG) with or without clopidogrel.

METHODS

After institutional review board approval, a retrospective study involving a single center was conducted on adult patients having PEG (1/08-1/14). Patients were divided into two groups: Clopidogrel group consisting of those patients taking clopidogrel within 5 d of PEG and the non-clopidogrel group including those patients not taking clopidogrel within 5 d of the PEG.

RESULTS

Three hundred and nineteen PEG patients were found. One hundred and sixty-eight males and 151 females with mean body mass index 28.47 ± 9.75 kg/m² and mean age 65.03 ± 16.11 years were identified. Thirty-three patients were on clopidogrel prior to PEG with 286 patients not on clopidogrel. No patients in either group developed hematochezia, melena, or hematemesis

within 48 h of percutaneous endoscopic gastrostomy (PEG). No statistical differences were observed between the two groups with 48 h for hemoglobin decrease of > 2 g/dL (2 *vs* 5 patients; $P = 0.16$), blood transfusions (2 *vs* 7 patients; $P = 0.24$), and repeat endoscopy for possible gastrointestinal bleeding (no patients in either group).

CONCLUSION

Based on the results, no significant post-procedure bleeding was observed in patients undergoing PEG with recent use of clopidogrel.

Key words: Percutaneous endoscopic gastrostomy; Clopidogrel; Bleeding; Complications; Antiplatelets

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Percutaneous endoscopic gastrostomy (PEG) is a common but invasive procedure. In the past, many medications were held prior to the procedure to reduce the risk of potential bleeding complication, such as clopidogrel. Much debate has been performed regarding the need for cessation of clopidogrel prior to PEG placement with little evidence found in the literature. This manuscript showed that clopidogrel use in patients undergoing PEG placement had no increased early post-procedure bleeding risk.

Sohail U, Harleen C, Mahdi AO, Arif M, Nguyen DL, Bechtold ML. Bleeding risk with clopidogrel and percutaneous endoscopic gastrostomy. *World J Gastrointest Endosc* 2016; 8(16): 553-557 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i16/553.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i16.553>

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is most commonly performed to provide nutritional support to patients who fail to swallow for a long time requiring tube feeding support^[1]. This procedure was first reported by Gauderer *et al*^[2] in 1980. Since then PEG has become an important technique for inserting feeding tubes in patients with swallowing difficulties who require long term nutritional support without undergoing laparotomy^[2,3]. The placement of PEG tube is classified among high-risk endoscopic procedure because of the risk of associated clinically significant bleeding. The enteric tube can be placed surgically, under radiological guidance or by endoscopic technique. When compared, the endoscopic technique has the least overall risk^[4]. Due to having the least overall risk, it is considered to be the technique of choice. However, endoscopic procedures may be low or high risk procedures. High risk endoscopic procedures are ones which are associated with the risk of bleeding being > 1%. PEG is considered a high risk procedure

and carries a 2.5% risk of complications^[3]. PEG tube is usually required in patients who are elderly and have multiple comorbidities. These patients are usually on antithrombotic agents or anticoagulants and hence are at increased risk of procedure-related bleeding. At the same time, holding the antiplatelet or anticoagulant agents could have potential thromboembolic complications from the underlying pro-thrombotic state. These medications for various cerebrovascular, cardiovascular, and hematological disorders has drastically increased^[3]. These agents significantly increase gastrointestinal (GI) bleeding risk. However, a recent study revealed that the incidence of bleeding after a PEG placement appears to be similar at 2.8%^[5]. Based on literature review, PEG post-procedure bleeding risk is estimated to be 2%-2.5%^[6,7]. According to current guidelines, clopidogrel discontinuation for 7-10 d prior to PEG in patients with underlying low thromboembolic risks is recommended^[6-8].

In case of high underlying thromboembolic risk, it is recommended to consider postponing the procedure until it is safe to hold the thienopyridines (clopidogrel, *etc.*). They should be held for 7-10 d when the underlying risk is low. In patients taking dual antiplatelet therapy, it is safe to continue aspirin while holding the clopidogrel. In cases where patients are on monotherapy with thienopyridines, these patients can be started on aspirin during peri-procedure period.

The patterns of clinical practice for the management of these medications differ from these recommendations. Differences also exist in the patterns of practice among gastroenterologists themselves in the use of these agents. An international survey that was conducted in 2008 revealed that differences exist between Western and Eastern countries with regards to management of these agents^[9].

To further evaluate the use of clopidogrel in PEG placement, we performed a retrospective study examining the potential post-procedure risks of bleeding.

MATERIALS AND METHODS

A retrospective study was conducted at a single tertiary-care center on all adult patients having PEG placement (January 2008-January 2014). Institutional review board approval was obtained. PEG was performed by using the standard push or pull technique^[2]. The procedure was performed by the attending gastroenterologist and the gastroenterology fellow at our tertiary-care center. All patients were nothing per mouth from midnight to the procedure and received a prophylactic antibiotic 30 min prior to the procedure (if not already receiving antibiotic treatment at the time of PEG insertion for any other reason).

The data pertaining to the several parameters was collected. These included patient demographics, indication for PEG placement, comorbid illnesses, and laboratory data, including hematology profile (hemoglobin, platelets, and coagulation values). The use of each

Table 1 General demographics of patients included in the study

All patients	
Patients (<i>n</i>)	320
Age (mean years \pm SD)	65.03 \pm 16.11
BMI (mean years \pm SD)	28.47 \pm 9.75
Gender	
Male (<i>n</i>)	169
Female (<i>n</i>)	151

BMI: Body mass index.

antiplatelet drug was noted and data regarding the timing of the last dose prior to PEG placement and the first dose following PEG was also recorded. Patients were divided into two groups: Clopidogrel group consisting of those patients taking clopidogrel within 5 d prior to the PEG and the non-clopidogrel group including those patients not taking clopidogrel within 5 d of the PEG.

Procedure-related complications, repeat endoscopy, and blood transfusions < 48 h of PEG was collected. The complications were classified as early (< 48 h of PEG placement) vs late (> 48 h). GI bleeding was defined as hemoglobin (hgb) drop > 2 g/dL from baseline, observation of GI bleeding (hematochezia, melena, hematemesis), required blood transfusion, and endoscopic hemostasis. The severity of bleeding was defined as mild (clinical evidence of bleeding, no transfusion required), moderate (transfusion required, less than 4 units, but no surgery required) and severe (transfusion of more than 5 units, radiological or surgical intervention).

Statistical analysis was conducted using the following: Descriptive statistics (demographics), two-tailed unpaired *t* test (continuous data), and Fisher's exact test (categorical data). Statistical significance was significant at *P* < 0.05. Statistics were reviewed by two biostatisticians (Matthew L Bechtold and Doug L Nguyen).

RESULTS

Three hundred and nineteen patients with PEG placement were identified, consisting of 168 males, 151 females, mean age 65.03 \pm 16.11 years, and mean BMI 28.47 \pm 9.75 kg/m² (Table 1). Thirty-three patients were using clopidogrel (mean age 71.21 \pm 11.43 years). Thirty patients out of these 33 patients received a dose of clopidogrel within 5 d prior to the actual day of the procedure, whereas three patients out of 33 received a dose of Plavix within 7 d prior to the procedure. Two hundred and eighty-six patients were not taking clopidogrel (mean age 64.37 \pm 16.44 years). Within 48 h of PEG, no patients in either group developed hematochezia, hematemesis, or melena (Table 2). Within 48 h of PEG, decrease in hgb of > 2 g/dL was identified in 2 patients (clopidogrel group) vs 5 patients (non-clopidogrel group) (*P* = 0.16). Blood transfusion

Table 2 Demographics and complications in patients taking clopidogrel vs patients not on clopidogrel

Outcome	No plavix	Plavix	<i>P</i> value
Patients (<i>n</i>)	286	33	-
Age (mean years \pm SD)	64.37 \pm 16.44	71.21 \pm 11.43	0.02
BMI (mean years \pm SD)	28.30 \pm 9.59	29.25 \pm 10.66	0.60
Hgb drop < 48 h	5	2	0.16
Local complications < 48 h	8	2	0.28
Transfusions < 48 h	7	2	0.24
Rescope < 48 h	1	1	0.20

BMI: Body mass index; Hgb: Hemoglobin.

within 48 h was necessary in 2 patients (clopidogrel group) vs 7 patients (non-clopidogrel group) (*P* = 0.24). No patients underwent repeat endoscopy for GI bleeding.

DISCUSSION

PEG over the years has emerged as a popular method to provide long-term enteral nutrition to patients. A PEG is required in those with inadequate intake of nutrition but have a normally functioning GI tract^[1].

Some of the common indications for placement of a PEG include: Neurological disorders that impair the normal physiology of swallowing, malignancies involving the oropharynx or the esophagus and facial trauma^[10-12]. There are several options available when considering placement of a gastrostomy tube. However, the endoscopic technique is preferred due lower incidence of complications and is more cost effective than open surgical gastrostomy^[13]. Even though the incidence is less, there are still several complications reported that are secondary to PEG placement^[14-17]. In a meta-analysis performed by Wollman *et al*^[18], the procedure-related mortality was noted as 0.5% and the 30-d all-cause mortality was 15%. Bleeding is one of the complicating factors contributing to mortality.

Our study focused on the risk of post-PEG placement early bleeding in patients that were already on clopidogrel as compared to those not taking clopidogrel. The study did not reveal any significant increase in the risk of early post-procedure bleeding (occurring within 48 h after the procedure) in patients who were taking clopidogrel. When the data was analyzed according to age (above and below the age of 60) and body mass index (BMI) (more than or less than BMI of 30), there was also no significant differences in the bleeding risks or need for blood transfusions. With this data, the use of clopidogrel should not be considered a contraindication to PEG placement. However, other parameters must be considered prior to PEG in this patient population.

First, prior to performing any endoscopic procedure, the risks and benefits should be thoroughly reviewed, including risk of bleeding^[6,7]. Second, careful consideration to the clinical impact of withholding an antithrombotic agent must be performed. Hence, each case

should be individually evaluated and the decision made after evaluating the pros and cons of proceeding with procedure and holding any antithrombotic agents.

As with any study, strengths and limitations were observed. The strengths include a large amount of patients undergoing PEG placement at a single tertiary-care center over 6 years. However, limitations are observed as well and should be considered when interpreting the results. First, this is retrospective study and not a randomized controlled trial. Certain biases may be involved in accordance to a retrospective study but efforts were done to try to minimize those biases. Second, given the small sample size of patients undergoing PEG while on clopidogrel ($n = 33$), a type II statistical error may be present which indicates the study lacked the power to detect a significant difference between the two groups. However, given that PEG placement has traditionally been withheld on patient who have been on recent clopidogrel, a limited number of patients underwent PEG with clopidogrel over the 6-year period and all of those patients were included in the study. Based on this possibility, results should be interpreted with caution and further larger studies are required to evaluate the overall effect of clopidogrel and PEG placement.

In conclusion, bleeding is a potential complication of PEG placement. Our retrospective study demonstrated no statistically significant increase in bleeding risk or requirement of blood transfusions in patients who were on clopidogrel for PEG placement. Therefore, clopidogrel did not increase bleeding risk despite cessation for a shorter time period as recommended by current guidelines.

COMMENTS

Background

Percutaneous endoscopic gastrostomy is a common procedure for patients who require enteral supplemental nutrition. In the past, any medications that could lead to increased bleeding risk were held prior to the percutaneous endoscopic gastrostomy (PEG) placement. However, recently, this practice has been challenged, especially with clopidogrel with little evidence in the literature.

Research frontiers

Little evidence is in the literature regarding the use of clopidogrel during PEG placement. This retrospective study evaluates the use of concomitant clopidogrel and PEG placement in a tertiary-care hospital in regards to post-procedure bleeding. Very few publications are available in the literature to evaluate this subject. Two publications that are related are below. Lucendo AJ, Sánchez-Casanueva T, Redondo O, Tenías JM, Arias Á. Risk of bleeding in patients undergoing PEG tube insertion under antiplatelet therapy: a systematic review with a meta-analysis. *Rev Esp Enferm Dig* 2015; 107: 128-136; Richter JA, Patrie JT, Richter RP, Henry ZH, Pop GH, Regan KA, Peura DA, Sawyer RG, Northup PG, Wang AY. Bleeding after percutaneous endoscopic gastrostomy is linked to serotonin reuptake inhibitors, not aspirin or clopidogrel. *Gastrointest Endosc* 2011; 74: 22-34.e1.

Innovations and breakthroughs

This is a rare study evaluating the use of clopidogrel with PEG placement. Very few studies have evaluated this subject. This study shows that clopidogrel may not require cessation prior to PEG placement which is a change in current and past practice.

Applications

For PEG placement, clopidogrel does not require cessation prior to procedure. This will allow patients to continue their much needed clopidogrel for PEG placement.

Terminology

PEG placement is a common procedure performed on patients who require supplemental enteral nutrition. Clopidogrel is also a common medication for antiplatelet properties.

Peer-review

The manuscript is provided useful information that clopidogrel discontinuation before PEG is not necessary in case of urgent need for such procedure.

REFERENCES

- 1 Kirby DF, Delege MH, Fleming CR. American Gastroenterological Association technical review on tube feeding for enteral nutrition. *Gastroenterology* 1995; 108: 1282-1301 [PMID: 7698596 DOI: 10.1016/0016-5085(95)90231-7]
- 2 Gauderer MW, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; 15: 872-875 [PMID: 6780678 DOI: 10.1016/S0022-3468(80)80296-X]
- 3 Schapiro GD, Edmundowicz SA. Complications of percutaneous endoscopic gastrostomy. *Gastrointest Endosc Clin N Am* 1996; 6: 409-422 [PMID: 8673334]
- 4 Lozoya-González D, Pelaez-Luna M, Farca-Belsaguy A, Salceda-Otero JC, Vazquez-Ballesteros E. Percutaneous endoscopic gastrostomy complication rates and compliance with the American Society for Gastrointestinal Endoscopy guidelines for the management of antithrombotic therapy. *JPEN J Parenter Enteral Nutr* 2012; 36: 226-230 [PMID: 21868718 DOI: 10.1177/0148607111413897]
- 5 Richter JA, Patrie JT, Richter RP, Henry ZH, Pop GH, Regan KA, Peura DA, Sawyer RG, Northup PG, Wang AY. Bleeding after percutaneous endoscopic gastrostomy is linked to serotonin reuptake inhibitors, not aspirin or clopidogrel. *Gastrointest Endosc* 2011; 74: 22-34.e1 [PMID: 21704806 DOI: 10.1016/j.gie.2011.03.1258]
- 6 Anderson MA, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Lichtenstein DR, Maple JT, Shen B, Strohmer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; 70: 1060-1070 [PMID: 19889407 DOI: 10.1016/j.gie.2009.09.040]
- 7 Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaikat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016; 83: 3-16 [PMID: 26621548 DOI: 10.1016/j.gie.2015.09.035]
- 8 Zuckerman MJ, Hirota WK, Adler DG, Davila RE, Jacobson BC, Leighton JA, Qureshi WA, Rajan E, Hambrick RD, Fanelli RD, Baron TH, Faigel DO. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. *Gastrointest Endosc* 2005; 61: 189-194 [PMID: 15729224 DOI: 10.1016/S0016-5107(04)02392-2]
- 9 Lee SY, Tang SJ, Rockey DC, Weinstein D, Lara L, Sreenarasimhaiah J, Choi KW. Managing anticoagulation and antiplatelet medications in GI endoscopy: a survey comparing the East and the West. *Gastrointest Endosc* 2008; 67: 1076-1081 [PMID: 18384789 DOI: 10.1016/j.gie.2007.11.037]
- 10 DiSario JA, Baskin WN, Brown RD, DeLegge MH, Fang JC, Ginsberg GG, McClave SA. Endoscopic approaches to enteral nutritional support. *Gastrointest Endosc* 2002; 55: 901-908 [PMID: 12024148 DOI: 10.1067/mge.2002.124209]
- 11 Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, Mallory JS, Raddawi HM, Vargo JJ, Waring JP, Fanelli RD, Wheeler-Harbaugh J. Role of endoscopy in enteral feeding.

- Gastrointest Endosc* 2002; **55**: 794-797 [PMID: 12024129]
- 12 **Luman W**, Kwek KR, Loi KL, Chiam MA, Cheung WK, Ng HS. Percutaneous endoscopic gastrostomy--indications and outcome of our experience at the Singapore General Hospital. *Singapore Med J* 2001; **42**: 460-465 [PMID: 11874149]
- 13 **Rosenberger LH**, Newhook T, Schirmer B, Sawyer RG. Late accidental dislodgement of a percutaneous endoscopic gastrostomy tube: an underestimated burden on patients and the health care system. *Surg Endosc* 2011; **25**: 3307-3311 [PMID: 21533968 DOI: 10.1007/s00464-011-1709-y]
- 14 **Singh D**, Laya AS, Vaidya OU, Ahmed SA, Bonham AJ, Clarkston WK. Risk of bleeding after percutaneous endoscopic gastrostomy (PEG). *Dig Dis Sci* 2012; **57**: 973-980 [PMID: 22138961 DOI: 10.1007/s10620-011-1965-7]
- 15 **McClave SA**, Chang WK. Complications of enteral access. *Gastrointest Endosc* 2003; **58**: 739-751 [PMID: 14595312 DOI: 10.1016/S0016-5107(03)02147-3]
- 16 **Tokunaga T**, Kubo T, Ryan S, Tomizawa M, Yoshida S, Takagi K, Furui K, Gotoh T. Long-term outcome after placement of a percutaneous endoscopic gastrostomy tube. *Geriatr Gerontol Int* 2008; **8**: 19-23 [PMID: 18713185 DOI: 10.1111/j.1447-0594.2008.00442]
- 17 **Jain R**, Maple JT, Anderson MA, Appalaneni V, Ben-Menachem T, Decker GA, Fanelli RD, Fisher L, Fukami N, Ikenberry SO, Jue T, Khan K, Krinsky ML, Malpas P, Sharaf RN, Dominitz JA. The role of endoscopy in enteral feeding. *Gastrointest Endosc* 2011; **74**: 7-12 [PMID: 21704804 DOI: 10.1016/j.gie.2010.10.021]
- 18 **Wollman B**, D'Agostino HB, Walus-Wigle JR, Easter DW, Beale A. Radiologic, endoscopic, and surgical gastrostomy: an institutional evaluation and meta-analysis of the literature. *Radiology* 1995; **197**: 699-704 [PMID: 7480742 DOI: 10.1148/radiology.197.3.7480742]

P- Reviewer: Kim CL, Kim S **S- Editor:** Ji FF **L- Editor:** A
E- Editor: Wu HL



Retrospective Study

What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?

Jiro Watari, Shigemitsu Ueyama, Toshihiko Tomita, Hisatomo Ikehara, Kazutoshi Hori, Ken Hara, Takahisa Yamasaki, Takuya Okugawa, Takashi Kondo, Tomoaki Kono, Katsuyuki Tozawa, Tadayuki Oshima, Hirokazu Fukui, Hiroto Miwa

Jiro Watari, Shigemitsu Ueyama, Toshihiko Tomita, Hisatomo Ikehara, Ken Hara, Takahisa Yamasaki, Takuya Okugawa, Takashi Kondo, Tomoaki Kono, Katsuyuki Tozawa, Tadayuki Oshima, Hirokazu Fukui, Hiroto Miwa, Division of Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo 663-8501, Japan

Kazutoshi Hori, Department of Inflammatory Bowel Disease, Hyogo College of Medicine, Nishinomiya, Hyogo 663-8501, Japan

Author contributions: Watari J and Ueyama S designed and performed the research study; Tomita T, Ikehara H, Hori K, Hara K, Yamasaki T, Okugawa T, Kondo T, Kono T, Tozawa K, Oshima T and Fukui H helped to collect the data; Watari J performed statistical analysis and wrote the paper; Miwa H approved the final version of the manuscript.

Institutional review board statement: This study was approved by Institutional Review Board at Hyogo College of Medicine, Nishinomiya, Japan.

Informed consent statement: All patients in the study gave informed consent prior to endoscopy.

Conflict-of-interest statement: None.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (watarij@hyo-med.ac.jp). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Jiro Watari, Division of Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. watarij@hyo-med.ac.jp
Telephone: +81-798-456662
Fax: +81-798-456661

Received: April 2, 2016
Peer-review started: April 6, 2016
First decision: May 17, 2016
Revised: June 7, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: August 25, 2016

Abstract

AIM

To clarify the diagnostic efficacy and limitations of endoscopic ultrasonography (EUS) and the characteristics of early gastric cancers (EGCs) that are indications for EUS-based assessment of cancer invasion depth.

METHODS

We retrospectively investigated the cases of 153 EGC patients who underwent conventional endoscopy (CE) and EUS (20 MHz) before treatment.

RESULTS

We found that 13.7% were "inconclusive" cases with low-quality EUS images, including all nine of the cases with protruded (0-I)-type EGCs. There was no significant difference in the diagnostic accuracy

between CE and EUS. Two significant independent risk factors for misdiagnosis by EUS were identified—ulcer scarring [UL(+); odds ratio (OR) = 4.49, $P = 0.003$] and non-indication criteria for endoscopic resection (ER) (OR = 3.02, $P = 0.03$). In the subgroup analysis, 23.1% of the differentiated-type cancers exhibiting SM massive invasion (SM2) invasion (submucosal invasion $\geq 500 \mu\text{m}$) by CE were correctly diagnosed by EUS, and 23.1% of the undifferentiated-type EGCs meeting the expanded-indication criteria for ER were correctly diagnosed by EUS.

CONCLUSION

There is no need to perform EUS for UL(+) EGCs or 0-I-type EGCs, but EUS may enhance the pretreatment staging of differentiated-type EGCs with SM2 invasion without UL or undifferentiated-type EGCs revealed by CE as meeting the expanded-indication criteria for ER.

Key words: Gastric cancer; Endoscopic ultrasonography; Invasion depth diagnosis; Conventional endoscopy; Endoscopic submucosal dissection

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: With the increasingly expanded indications of endoscopic resection for early gastric cancer (EGC), the accurate diagnosis of the invasion depth has become more important in the pretreatment strategy. Although there have been many investigations comparing the efficacy of endoscopic ultrasonography (EUS) and conventional endoscopy (CE) for invasion depth diagnosis of EGCs, much controversy remains. Our results revealed that there is no need to perform EUS for EGCs that are protruded type or those that have an ulcer scar, but EUS may have an add-on effect in the pretreatment staging of differentiated-type EGCs diagnosed as SM2 (submucosal invasion $\geq 500 \mu\text{m}$) and undifferentiated-type EGCs diagnosed by CE as meeting the expanded-indication criteria for endoscopic resection.

Watari J, Ueyama S, Tomita T, Ikehara H, Hori K, Hara K, Yamasaki T, Okugawa T, Kondo T, Kono T, Tozawa K, Oshima T, Fukui H, Miwa H. What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth? *World J Gastrointest Endosc* 2016; 8(16): 558-567 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i16/558.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i16.558>

INTRODUCTION

Until recently, the Japanese Gastric Cancer Treatment Guidelines^[1] stipulated that mucosal lesions < 2 cm in size and without ulceration are indicated for endoscopic resection (ER). However, in response to a report by Gotoda *et al.*^[2] on the low incidence of lymph node

metastasis from early gastric cancers (EGCs), the indications for ER described in those Guidelines have been expanded to include EGCs with a very low risk of lymph node metastasis. Another part of the rationale behind this decision was that endoscopic submucosal dissection (ESD), which was developed in Japan^[3-7], has made *en bloc* resection possible for lesions of all sizes. Along with the expanded indications for the ER of EGCs, therefore, the accurate diagnosis of invasion depth has become a very important component of pretreatment strategies.

Conventional endoscopy (CE) remains a useful modality for detecting EGCs and gauging their invasion depth. Although there have been many investigations, mostly in Japan, of the ability of CE to gauge the invasion depth of mucosal (M) and submucosal (SM) invasive cancers, collectively the rate of successful depth measurement has ranged from 62% to 80%^[8-10]. Thus it is sometimes difficult to establish diagnostic criteria for differentiating M from SM cancers by CE alone. Endoscopic ultrasonography (EUS) permits a more objective assessment by providing a tomographic image, and is thus sometimes used as an adjunct diagnostic tool for determining the depth of gastric cancer invasion.

Several studies have compared the accuracy of invasion depth measurement between CE and EUS, and some of these reports clearly demonstrated the superiority of EUS for diagnosing EGC invasion depth^[11-14] whereas others did not^[9,15]. Two recent meta-analyses showed that EUS has relatively low accuracy for staging the depth of EGC invasion, and thus EUS may not be indispensable in the staging of EGCs^[16,17]. It has also been reported that the accurate determination of invasion depth is difficult in cases with a large tumor size^[11,15,18-21], upper location^[15,18,20], depressed-type lesion^[11,20], undifferentiated histology^[15,21] or ulcerous finding (UL)^[15,19,21,22].

There are also a number of practical technical difficulties that impede the production of suitable EUS images, and the use of poor-quality EUS images to determine the depth of EGCs may lead to incorrect results^[23]. Unfortunately, most of the previous comparative studies (with the exception of the study by Tsujii *et al.*^[24]) analyzed only cases in which good-quality EUS images were obtained, and thus their findings may not show the true diagnostic capability of EUS in actual practice.

Along with the expanded indications for EGC dissection, it is expected that the number of ESDs of EGCs will increase, and the precise invasion depth staging of EGCs will therefore be important. Accordingly, the aims of the present study were to clarify: (1) the comparative diagnostic efficacies and limitations of EUS and CE for the pre-operative staging of EGC; and (2) the characteristic(s) of EGCs that are indications for the use of EUS as an adjunct diagnostic tool for measuring invasion depth.

MATERIALS AND METHODS

Patients

Between April 2012 and March 2015, 452 consecutive patients with a total of 510 neoplasias comprised of gastric adenomas and EGCs were treated with ESD (360 neoplasias) and surgery (150 neoplasias) at Hyogo College of Medicine Hospital in Nishinomiya, Japan. Among them, 153 EGCs in 140 patients were examined using both CE and EUS. Both the absolute-indication and the expanded-indication criteria for the ER of EGCs followed the Japanese Gastric Cancer Treatment Guidelines^[1]. The absolute-indication criteria for ER are: M cancer, differentiated-type adenocarcinoma, UL(-), and < 2 cm in dia. The proposed extended-indication criteria for ER are as follows: (1) M cancer, differentiated-type adenocarcinoma, UL(-) and any tumor size; (2) M cancer, differentiated-type adenocarcinoma, UL(+) and < 3 cm in size; (3) minute submucosal cancer (< 500 μ m invasion into the submucosa, SM1), differentiated-type adenocarcinoma and < 3 cm in size; and (4) M cancer, undifferentiated-type carcinoma, UL(-) and < 2 cm in size.

Written informed consent was obtained from all patients prior to the procedures and treatment, and the study design was approved by the Ethics Committee of Hyogo College of Medicine (No. 2109).

The CE and EUS diagnoses of the invasion depth of EGCs

When the invasion depth of an EGCs is being diagnosed, close endoscopic observation is necessary to adjust the air volume in the patient's stomach. The endoscopic criteria for cancer invasion in the present patient series were judged based on previous reports^[8-10,15,24-26]. Briefly, in the CE diagnosis, the presence or absence of the following CE findings of SM massive invasion was determined: (1) irregular surface including nodules in the depressed area; (2) submucosal tumor-like elevation without flexibility; (3) abnormal converging folds such as clubbing and fusion; and (4) deep ulceration with marked marginal elevation. All endoscopic observations were performed by chromoendoscopy using an endoscope (GIF-Q260, H260, H260Z, H290Z, H290 or HQ290; Olympus Medical Systems, Tokyo) followed by EUS.

EUS was performed with a 20-MHz miniature probe UM-3R (Olympus Medical Systems), which was connected to an endoscopic ultrasonic observation unit (EU-M2000; Olympus Medical Systems). Approximately 200-500 mL of deaerated water was instilled in the stomach to improve the transmission of the ultrasound beam. In the EUS diagnoses, lesions confined to the 1st and 2nd sonographic layers were considered mucosal cancer. Massive submucosal invasion was defined as obvious irregular narrowing or budding into the 3rd sonographic layer as shown in previous reports^[9-11,14,15,20,21,23-26].

In the UL(+) lesions, the previous criteria for EUS diagnosis were used^[13,27]; namely, if a fan-shaped hypoechoic area was demonstrated in the 3rd layer, the lesion was defined as M/SM1, and when an arch-shaped hypoechoic area was observed in the 3rd layer, the lesions were regarded as SM massive invasion (SM2). In the cases in which at least five layers of the gastric wall, including the lesion, were unclear and an assessment by EUS was difficult due to the low-quality image, the lesions were judged to be "inconclusive"^[24].

It is very difficult to discriminate SM1 from M cancer even by CE or EUS, and the therapeutic strategies for these lesions are also similar. We therefore clinically divided these lesions into two groups: The M/SM1 group, for which ER may be suitable, and the SM2 group, for which surgery was indicated.

In this retrospective study, two endoscopists (Jiro Watari and Shigemitsu Ueyama) with 29 and 17 years of endoscopic practice experience, respectively and board certification from the Japan Gastroenterological Endoscopy Society independently reviewed the CE and EUS images without any pathologic information. The results were used for the calculation of interobserver agreement (κ value).

Histological evaluation

Resected specimens were sectioned at 2-mm intervals for ESD and 5-mm intervals for surgical resection. The histology, tumor location, gross morphologic type, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer^[28]. We histologically classified the specimens into two groups based on their depth of submucosal invasion: Invasion into the SM1 (invasion < 500 μ m) or SM2 (invasion \geq 500 μ m) layer. The largest measured tumor size of the resected specimen was recorded histologically as the tumor dia.

Statistical analysis

We assessed the data by performing the Mann-Whitney *U* test for comparisons between two independent groups, and the χ^2 test or Fisher's exact test was used to examine differences between two proportions. Statistical significance was defined as a *P* value < 0.05. Risk factors for the misdiagnosis of the depth of cancer invasion by EUS that were found to be significant with a *P* value of < 0.05 in a univariate analysis were entered into a multiple logistic regression model and analyzed using a backward approach. Odds ratios (ORs) and 95%CIs were calculated for each risk factor.

The interobserver agreement for the CE imaging and the EUS imaging evaluations was calculated by κ statistics, which were interpreted as follows: Poor (\leq 0.2), mild (0.2-0.4), moderate (0.4-0.6), good (0.6-0.8), and excellent (0.8-1.0). Differences at *P* < 0.05 were considered significant. All statistical analyses were performed using the StatView software program, ver. 5.0 (SAS Institute, Cary, NC).

Table 1 Patient characteristics

Total no. of lesions (patients)	153 (140)
Mean (\pm SD) age, years	68.7 \pm 10.4
Sex, male/female	102/38
Macroscopic type	
0-I / 0-IIa/0-IIb / 0-IIc	9/51/1/92
Location	
Upper/middle/lower	45/69/39
Mean (\pm SD) tumor size, mm	20.5 \pm 14.4
Depth of invasion	
M/SM1/SM2	93/17/43
Histology	
Differentiated/undifferentiated	118/35
Ulcer scar	
Positive/negative	29/124
Criteria for endoscopic resection	
Absolute/expanded/non-indication	51/38/64

M: Mucosal cancer; SM1: Submucosal invasive cancer invaded into the submucosal layer < 500 μ m from the muscularis mucosa; SM2: Submucosal invasive cancer with invasion of \geq 500 μ m into the submucosal layer.

RESULTS

Patient characteristics and clinicopathological data of EGCs

Table 1 shows the characteristics of the 140 patients and a summary of the 153 studied EGCs. The mean age of the patients was 68.7 \pm 10.4 years (range 23-87 years), and women accounted for 27.1% of the patients. The mean tumor size was 20.5 \pm 14.4 mm in dia. The numbers of lesions that met the absolute- and expanded-indication criteria for ER were 51 and 38 lesions, respectively. The lesions were located mainly in the middle portion of the stomach.

Clinical characteristics of the "inconclusive" cases

Twenty-one (13.7%) of the 153 EGCs were judged as "inconclusive". As shown in Table 2, all nine of the protruded-type (0-I) cancers yielded low-quality images. The inconclusive rate was significantly higher in the lower portion of the stomach than in other portions ($P = 0.03$). There was no significant difference in the inconclusive rate between the lesions with and without UL.

Comparison of EGC invasion-depth diagnoses between EUS and CE

The κ -values for the interobserver agreement for the invasion depth diagnosis between the two endoscopists were 0.78 (95%CI: 0.68-0.89) for EUS and 0.82 (95%CI: 0.72-0.92) for CE. Thus the interobserver agreement for invasion depth diagnosis by EUS and CE was good to excellent. When the results of the diagnostic accuracy by one endoscopist whose accuracy rate was higher than that of the other endoscopist were used in both modalities, the accuracy rate of EUS was 71.2% (109 of 153 lesions) (Table 3), and when the accuracy was calculated in 132 lesions (omitting 21 inconclusive cases), the rate increased to 82.6% (109

Table 2 Clinical characteristics of the 21 inconclusive cases

Tumor-related factors	No. of inconclusive cases (%)	P value
Macroscopic type		< 0.0001
I ($n = 9$)	9 (100)	
IIa ($n = 51$)	7 (13.7)	
IIc ($n = 92$)	5 (5.4)	
Location		0.03
Upper ($n = 45$)	3 (6.7)	
Middle ($n = 69$)	8 (11.6)	
Lower ($n = 39$)	10 (25.6)	
Histology		0.16
Differentiated ($n = 118$)	19 (16.1)	
Undifferentiated ($n = 35$)	2 (5.7)	
Ulcer scar		0.37
Positive ($n = 29$)	2 (6.9)	
Negative ($n = 124$)	19 (15.3)	
Criteria for ER		0.58
Absolute ($n = 51$)	9 (17.6)	
Expanded ($n = 38$)	5 (13.2)	
Non-indication ($n = 64$)	7 (10.3)	

ER: Endoscopic resection.

of 132).

The sensitivity of EUS for diagnosing M/SM1 lesions was 85.3% (81 of 95 cases), the specificity was 75.7% (28 of 37), the positive predictive value (PPV) was 90.0% (81 of 90), and the negative predictive value (NPV) was 66.7% (28 of 42). The diagnostic accuracy of EUS was not significantly different among the three macroscopic types or the three tumor locations, or between the histological types, *i.e.*, the differentiated type and the undifferentiated type.

However, UL(+) and the non-indication criteria for ER were significantly associated with the incorrect diagnosis of tumor invasion depth by EUS ($P < 0.0001$ and $P = 0.0004$, respectively). In addition, UL(+) (OR = 4.49; 95%CI: 1.68-11.97; $P = 0.003$) and the non-indication criteria for ER (OR = 3.02; 95%CI: 1.14-8.00; $P = 0.03$) were significant and independent risk factors affecting misdiagnosis by EUS in our multivariate logistic regression analysis.

There were no significant differences in the accuracy or other parameters between EUS and CE; the sensitivity of CE diagnosis for M/SM1 was 88.2% (97 of 110 cases), the specificity was 58.1% (25 of 43), the PPV was 84.3% (97 of 115), and the NPV was 65.8% (25 of 38). As shown in Table 3, the accuracy rate obtained for the absolute-indication criteria lesions was very high for both modalities, and was significantly higher than that of the non-indication criteria lesions ($P < 0.0001$ in EUS and $P = 0.01$ in CE). There were also significant differences in the accuracy between the lesions with the expanded-indication criteria and those with the non-indication criteria for ER ($P = 0.02$ in both EUS and CE). However, no significant differences in diagnostic accuracy between the two modalities were observed within the expanded-indication criteria group or the

Table 3 Comparison of the invasion depth diagnosis between endoscopic ultrasonography and conventional endoscopy

	Clinical diagnosis	Histologic diagnosis		EUS diagnosis		P^2	Histologic diagnosis		Accuracy	P (vs EUS)
		M/SM1	SM2	Overall accuracy	Accuracy ¹		M/SM1	SM2		
Diagnosis	M/SM1	81	9	71.2	82.6	0.30	97	18	79.7	0.54
	SM2	14	28				13	25		
Macroscopic type										
I	M/SM1	-	-	-	-	0.55	5	1	88.9	-
	SM2	-	-				0	3		
Ila/Ilb	M/SM1	26	4	67.3	77.8		32	5	78.8	0.90
	SM2	6	9				6	9		
Ilc	M/SM1	55	5	80.4	85.1	0.79	60	12	79.3	0.32
	SM2	8	19				7	13		
Location										
Upper	M/SM1	21	2	74.4	80	< 0.0001	24	4	80.0	> 0.99
	SM2	6	11				5	12		
Middle	M/SM1	40	7	69.9	78.5		44	11	78.3	0.98
	SM2	7	11				4	10		
Lower	M/SM1	19	2	62.2	85.2	0.02	29	3	82.1	> 0.99
	SM2	2	4				4	3		
Histology										
Diff.	M/SM1	71	10	70.4	83	< 0.0001	77	12	80.5	0.63
	SM2	8	17				11	18		
Undiff.	M/SM1	9	1	75.0	84		20	6	77.1	> 0.99
	SM2	4	12				2	7		
Ulcer scar						< 0.0001				
Positive	M/SM1	3	2	46.7	50		7	4	58.6	0.51
	SM2	12	11				8	10		
Negative	M/SM1	77	7	75.6	89.4	< 0.0001	90	14	84.7	0.29
	SM2	4	16				5	15		
Indication for ER										
Absolute	M/SM1	37	-	80.4	97.4 ^b	< 0.0001	43	-	84.3 ^f	0.07
	SM2	1	-				8	-		
Expanded	M/SM1	28	-	75.7	87.5 ^d		33	-	86.8 ^h	> 0.99
	SM2	4	-				5	-		
Non-indication	M/SM1	12	13	56.1	62.7 ^{b,d}	< 0.0001	16	18	64.1 ^{f,h}	> 0.99
	SM2	9	25				5	25		

Accuracy¹ was calculated with the exception of 21 inconclusive cases of EUS; P^2 indicates a significant difference in Accuracy¹. ^b $P < 0.0001$; ^d $P = 0.02$; ^f $P = 0.02$; ^h $P = 0.01$. EUS: Endoscopic ultrasonography; CE: conventional endoscopy; Diff: Differentiated-type; Undiff: Undifferentiated-type; ER: Endoscopic resection.

non-indication criteria group (Table 3).

Diagnostic concordance between EUS and CE

As shown in Table 4, the number of lesions that showed a correct diagnosis by CE and an incorrect diagnosis by EUS was almost the same as the number of lesions that showed an incorrect diagnosis by CE and a correct diagnosis by EUS in both the expanded-indication criteria group and the non-indication criteria group, irrespective of histology. This result may indicate that there is no additive effect of EUS in the diagnosis of invasion depth.

In the subgroup analysis of a total of 13 differentiated-type cancers without UL and with SM2 invasion diagnosed by CE, three (23.1%) cases that were misdiagnosed by CE were correctly diagnosed as M/SM1 lesions by EUS (Table 5 and Figure 1). We identified two cases (20.0%, 2 of 10) lesions that were ≤ 2 cm and three cases (25.0%, 3 of 12) that were 3 cm in size. These cases were subsequently treated with ESD, avoiding surgery. The reverse phenomenon, *i.e.*, cases misdiagnosed by EUS but correctly diagnosed by CE -

was not seen.

Similarly, in our subgroup analysis of 13 undifferentiated-type cases that met the expanded-indication criteria for ER, which were judged endoscopically as M/SM1 lesions, UL(-) and ≤ 2 cm in size, three cases (23.1%) were correctly diagnosed by EUS as having SM2 invasion (Table 6 and Figure 2). These three cases were thus adequately treated with surgery.

DISCUSSION

Although there have been many investigations comparing the efficacy of EUS and CE for the pretreatment staging of EGCs, much controversy remains. In our present study, the overall accuracy of EUS for diagnosing invasion depth was lower than that of CE, but not significantly so. The accuracy of EUS was 82.6% (71.1% in overall accuracy), which was similar to the values reported in previous studies^[13,14,19,22-25,27] but higher than the values obtained in other studies^[9,11,12,15,20,21,26]. In recent meta-analyses, most of the cited studies showed that EUS has only a limited effect on determining the

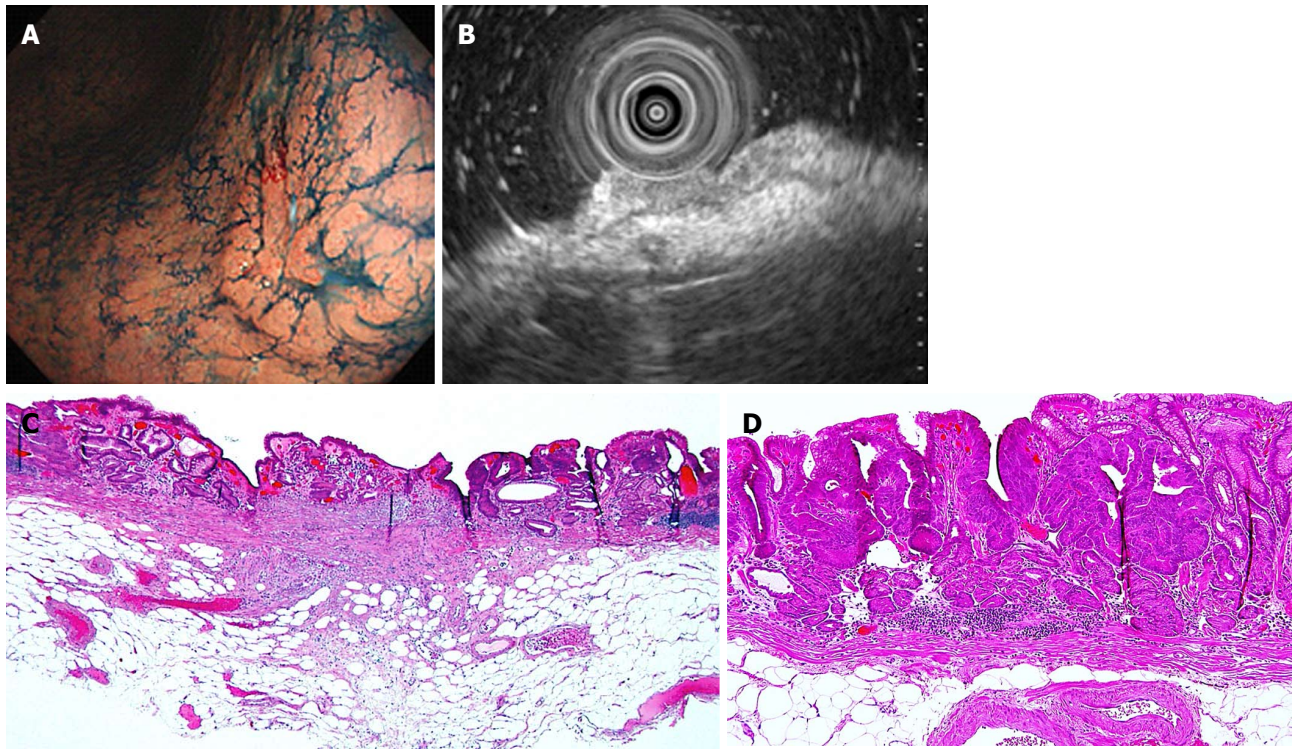


Figure 1 Case diagnosed correctly by endoscopic ultrasonography but misdiagnosed by endoscopy. A: Chromoendoscopy shows an irregular surface in a depressed lesion diagnosed as SM2; B: On this EUS image, irregular narrowing of sonographic layer 3 was not observed, and thus this lesion was considered an M/SM1 lesion; C: The histology by endoscopic submucosal dissection showed a differentiated-type intramucosal cancer with slightly fibrosis by biopsy; D: Histologic specimen of the lesion shows well differentiated-type adenocarcinoma limited to the mucosae ($\times 200$). EUS: Endoscopic ultrasonography.

Table 4 Diagnostic concordance between endoscopic ultrasonography and conventional endoscopy

Diagnosis		Indication for endoscopic resection		
		Absolute criteria	Expanded criteria	Non-indication
Differentiated-type cancer ($n = 99$)				
EUS	CE	($n = 42$) (%)	($n = 25$) (%)	($n = 32$) (%)
Correct	Correct	39 (92.9)	19 (76)	20 (62.5)
Incorrect	Incorrect	0 (0)	3 (12)	11 (34.4)
Correct	Incorrect	1 (4.8)	1 (4)	1 (3.1)
Incorrect	Correct	1 (2.4)	2 (8)	0 (0)
Undifferentiated-type cancer ($n = 33$)				
EUS	CE		($n = 8$) (%)	($n = 25$) (%)
Correct	Correct	-	8 (100)	15 (60)
Incorrect	Incorrect	-	0 (0)	1 (4)
Correct	Incorrect	-	0 (0)	5 (20)
Incorrect	Correct	-	0 (0)	4 (16)

EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

optimal therapeutic strategy^[15,18-20,25]. Our present findings clearly demonstrated the limitations of EUS and the characteristics of EGCs that make them suitable for analysis by EUS.

In the present study, all nine of the 0-I-type cancers (protruded-type) yielded low-quality EUS images and were thus judged as inconclusive cases, as mentioned above^[11,22]. The main cause of inconclusiveness was ultrasound attenuation due to the use of a high-frequency ultrasound probe (20 MHz); the submucosal layer could not be clearly visualized. If a low-frequency EUS or probe had been used, the number

of inconclusive cases among those types of cancers might have been lower. However, in 0-I-type cancer the mucosa is thick and the muscularis mucosae elevates toward the mucosa from the submucosa, and it may thus be difficult to make an accurate diagnosis even if low-frequency EUS is performed.

In addition, the accuracy rate of EUS in the UL(+) lesions was extremely low ($\leq 50\%$), and significantly lower than that in the UL(-) lesions ($P < 0.0001$). Regarding the reason for this finding, most of the lesions (80%, 12 of 15) of M/SM1 cancers with UL were over-diagnosed due to submucosal fibrosis,

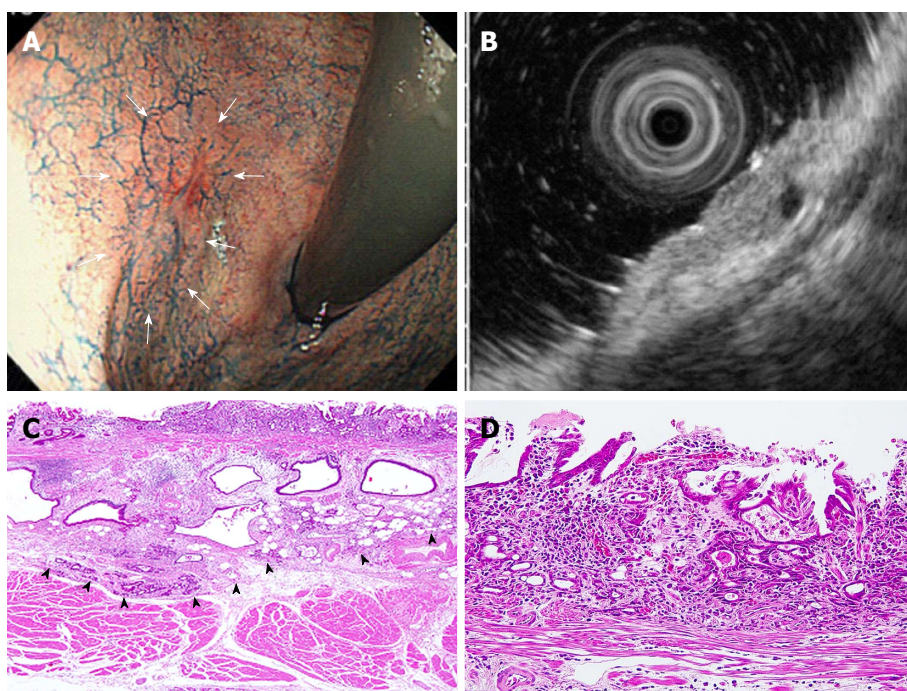


Figure 2 Case diagnosed correctly by endoscopic ultrasonography but misdiagnosed by endoscopy. A: Chromoendoscopy shows a reddish and smooth surface in a shallow depressed lesion diagnosed as M/SM1 (arrows). Histologically, the biopsy sample indicated a moderately to poorly differentiated adenocarcinoma; B: EUS image showing that a hypoechoic mass invaded the submucosal layer (sonographic layer 3). This lesion was diagnosed as SM2; C: Histology revealed that undifferentiated type adenocarcinoma massively invaded the submucosal layer (arrowheads); D: Moderately to poorly differentiated adenocarcinoma cells were observed in the gastric mucosae ($\times 200$). EUS: Endoscopic ultrasonography.

Table 5 Subgroup analysis of 13 differentiated-type cancers without UL and with SM2 diagnosed by conventional endoscopy¹

EUS	CE	n (%)
Correct	Correct	10 (76.9)
Correct	Incorrect	3 (23.1)
Incorrect	Correct	0 (0)
Incorrect	Incorrect	0 (0)

SM2 indicates invasion $\geq 500 \mu\text{m}$ into the submucosal layer. ¹The lesions with an ulcer scar or 0-I macroscopic type were excluded from this analysis because the diagnostic capability for those lesions was extremely low. EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

Table 6 Subgroup analysis of 13 undifferentiated-type cancers diagnosed as meeting the expanded criteria for endoscopic treatment by conventional endoscopy¹

EUS	CE	n (%)
Correct	Correct	10 (76.9)
Correct	Incorrect	3 (23.1)
Incorrect	Correct	0 (0)
Incorrect	Incorrect	0 (0)

¹One 0-I macroscopic type lesion was excluded from this analysis because the diagnostic capability of this type of lesions was extremely low. EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

which is in agreement with previous reports^[12,15,19,21,23]. In the report by Mandai *et al.*^[21], the accuracy rate of EUS decreased from 86.5% to 28.9% in the UL(-) lesions. Although a few studies have introduced a method that distinguishes cancer invasion from ulcer fibrosis^[13,27], it may be difficult in practice to differentiate between those two conditions. In our multivariate logistic regression analysis, UL was a significant and independent risk factor affecting misdiagnosis by EUS, and thus it may be futile to perform EUS for UL(+) lesions.

There was no significant difference in the accuracy rate of EUS among the three tumor locations of the stomach, but inconclusive cases were observed significantly more frequently in the lower third of the stomach than in the other portions ($P = 0.03$). Several studies

showed that the diagnostic accuracy of the invasion depth was diminished for lesions in the upper portion of the stomach^[8,12,14,15,19,23]. Tsuzuki *et al.*^[25] reported that the submucosal layer in the upper third of the stomach is relatively thin and tends to have fibrosis and many vessels, making signs of submucosal invasion difficult to diagnosis and leading to incorrect staging. For other reasons, it is considered that it is difficult to fill this region with deaerated water^[8,19,25]. However, this problem can be overcome by adjusting the volumes of air and deaerated water. In our patient population, it was often difficult to achieve the necessary pool of deaerated water in the lower third of the stomach, and there were technical problems with scanning this portion.

The diagnostic accuracy of EUS has been reported to be low for undifferentiated-type lesions^[10-12,14,18,22] and

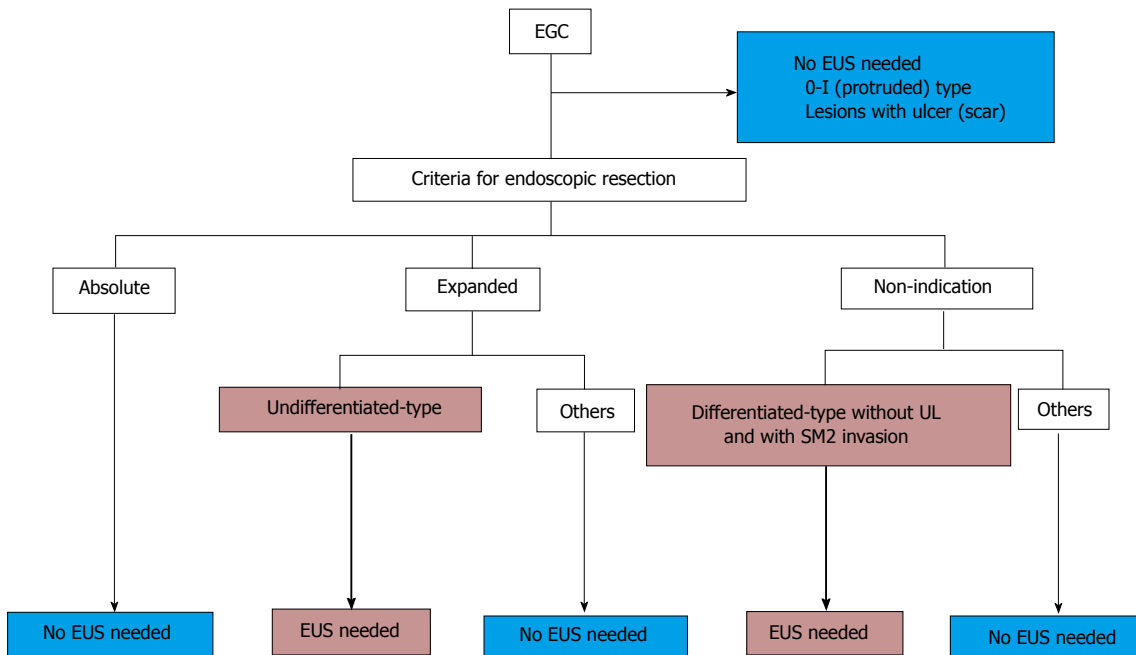


Figure 3 Flowchart of endoscopic ultrasonography diagnostic strategy for early gastric cancer. EUS should be considered performing the following lesions: (1) differentiated-type cancers without UL diagnosed as invading to SM2; and (2) undifferentiated-type cancers diagnosed by conventional endoscopy as meeting the expanded-indication criteria for endoscopic resection. In cases rather than those lesions, however, EUS may not be needed for the preoperative determination of the depth of EGCs. SM2 indicates invasion $\geq 500 \mu\text{m}$ into the submucosal layer. EGC: Early gastric cancer; EUS: Endoscopic ultrasonography.

larger-size lesions^[11,12,18,19,21], which were categorized mainly as meeting the expanded-indication criteria or non-indication criteria for ER. In the present study, the diagnostic accuracy for the lesions meeting the absolute-indication criteria for ER was very high for both EUS (97.4%) and CE (84.3%) as expected, whereas the accuracy rates of EUS and CE were significantly lower for the lesions that met the non-indication criteria for ER compared to those that met other criteria for ER.

If EUS is going to be performed for many lesions meeting the absolute-indication criteria for ER, the overall accuracy of EUS may naturally increase, but not to a clinically significant degree. It has been reported that magnifying endoscopy with narrow-band imaging (ME-NBI) is useful for determining the invasion depth diagnosis of EGC^[29,30]; however the diagnostic criteria for SM2 are complex^[29] and the diagnostic specificity of ME-NBI may be relatively low^[30]. Actually, when the staging of an EGC is doubtful by CE, EUS is likely to provide helpful information to stage the EGC, *i.e.*, to determine the M/SM1 or SM2 status^[16]. In such cases EUS may correct a misdiagnosis by CE, especially with respect to the expanded-indication and non-indication criteria for ER.

Taking past findings into consideration along with our present results, we propose that EUS may be considered for the following lesions: (1) differentiated-type cancers without UL diagnosed as invading to SM2; and (2) undifferentiated-type cancers diagnosed by CE as meeting the expanded-indication criteria for ER. When EUS is performed for these lesions, the additive effect of EUS will increase the accuracy by 23.1%. It

should be noted, however, that we studied only a small number of either type of lesions, *i.e.*, three lesions of type (1) and three lesions of type (2). In contrast, it should also be emphasized that there were no lesions of either type which were correctly diagnosed by CE and incorrectly diagnosed by EUS. Based on our conclusion, we have summarized the indications of EUS for the pretreatment diagnosis of EGCs in Figure 3.

Our study has several potential limitations. First, it was a retrospective study at a single institution. Second, the sample size was relatively small. However, we did not perform EUS for most of the lesions that met the absolute-indication criteria, which could be definitely diagnosed as mucosal cancer by CE as mentioned above. Indeed, of the 186 EGCs that met the absolute-indication criteria for ER and that were treated with ER during this study period, only 50 lesions (26.9%) underwent EUS. This result may thus have resulted in a selection bias because there were no eligibility criteria for performing EUS in this study. Third, only the patients with histologically confirmed EGC who underwent EUS and ESD or surgery were evaluated, which might also have introduced a potential selection bias. Fourth, since EUS was performed under CE by an endosonographer, the construction of EUS images may have been affected by the endoscopic appearance of the lesions and the experience of the endosonographer^[31]. In addition, one observer might have been involved in both of the examinations, *i.e.*, CE and EUS, in some cases. In general, the observer who validates the criteria should not have been involved in the evaluation of the EUS and CE images^[24].

In conclusion, our analyses revealed that: (1) EUS may not be necessary to determine the pretreatment staging of 0-I type and UL(+) or absolute-indication criteria lesions; and (2) EUS may be considered for the following lesions: (1) differentiated-type cancers diagnosed without UL and with invasion to SM2; and (2) undifferentiated-type cancers diagnosed as meeting the expanded-indication criteria for ER by CE.

COMMENTS

Background

It is sometimes difficult to establish diagnostic criteria for differentiating mucosal cancer from submucosal invasive cancer by conventional endoscopy (CE) alone. Although endoscopic ultrasonography (EUS) permits a more objective assessment by providing a tomographic image, recent meta-analyses showed that EUS has relatively low accuracy for staging the depth of early gastric cancer (EGC) invasion.

Research frontiers

According to the previous studies, some of these reports clearly demonstrated the superiority of EUS for diagnosing EGC invasion depth whereas others did not. The authors retrospectively investigated the application of EUS in the pretreatment staging of EGD.

Innovations and breakthrough

All protruded-type EGCs were "inconclusive" cases with low-quality EUS images. There was no significant difference in the diagnostic accuracy between CE and EUS. The lesions with ulcer scar (UL) and non-indication criteria for endoscopic resection (ER) were significant independent risk factors for misdiagnosis by EUS. In the subgroup analysis, however, the additive effect of EUS was found in the lesions with the differentiated-type cancers exhibiting SM2 invasion (submucosal invasion $\geq 500 \mu\text{m}$) by CE and the undifferentiated-type EGCs meeting the expanded-indication criteria for ER.

Applications

EUS may not be necessary to determine the pretreatment staging of protruded (0-I)-type and the lesions with UL or absolute-indication criteria for ER; and EUS may be considered for the following lesions: (1) differentiated-type cancers diagnosed without UL and with invasion to SM2; and (2) undifferentiated-type cancers diagnosed as meeting the expanded-indication criteria for ER by CE.

Terminology

EUS is a reliable method for predicting the invasion depth diagnosis of EGC. However, there is no need to perform EUS for the EGCs with the absolute-indication criteria, UL(+) or 0-I-type. The modality should be considered performing the limited lesions.

Peer-review

This is a good article to describe the indications for EUS staging of invasion depth in EGCs.

REFERENCES

- 1 **Japanese Gastric Cancer Association.** Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123 [PMID: 21573742 DOI: 10.1007/s10120-011-0042-4]
- 2 **Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y.** Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/PL00011720]
- 3 **Ohkuwa M, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S.** New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221-226 [PMID: 11293753 DOI: 10.1055/s-2001-12805]
- 4 **Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S.** Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]
- 5 **Yamamoto H, Sekine Y, Higashizawa T, Kihira K, Kaneko Y, Hosoya Y, Ido K, Saito K, Sugano K.** Successful en bloc resection of a large superficial gastric cancer by using sodium hyaluronate and electrocautery incision forceps. *Gastrointest Endosc* 2001; **54**: 629-632 [PMID: 11677485 DOI: 10.1067/mge.2001.118643]
- 6 **Miyamoto S, Muto M, Hamamoto Y, Boku N, Ohtsu A, Baba S, Yoshida M, Ohkuwa M, Hosokawa K, Tajiri H, Yoshida S.** A new technique for endoscopic mucosal resection with an insulated-tip electrosurgical knife improves the completeness of resection of intramucosal gastric neoplasms. *Gastrointest Endosc* 2002; **55**: 576-581 [PMID: 11923778 DOI: 10.1067/mge.2002.122579]
- 7 **Gotoda T, Yamamoto H, Soetikno RM.** Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]
- 8 **Sano T, Okuyama Y, Kobori O, Shimizu T, Morioka Y.** Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig Dis Sci* 1990; **35**: 1340-1344 [PMID: 2226095 DOI: 10.1007/BF01536738]
- 9 **Yanai H, Noguchi T, Mizumachi S, Tokiyama H, Nakamura H, Tada M, Okita K.** A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut* 1999; **44**: 361-365 [PMID: 10026321 DOI: 10.1136/gut.44.3.361]
- 10 **Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS.** Endoscopic prediction of tumor invasion depth in early gastric cancer. *Gastrointest Endosc* 2011; **73**: 917-927 [PMID: 21316050 DOI: 10.1016/j.gie.2010.11.053]
- 11 **Akahoshi K, Chijiwa Y, Hamada S, Sasaki I, Nawata H, Kabemura T, Yasuda D, Okabe H.** Pretreatment staging of endoscopically early gastric cancer with a 15 MHz ultrasound catheter probe. *Gastrointest Endosc* 1998; **48**: 470-476 [PMID: 9831834 DOI: 10.1016/S0016-5107(98)70087-2]
- 12 **Hizawa K, Iwai K, Esaki M, Matsumoto T, Suekane H, Iida M.** Is endoscopic ultrasonography indispensable in assessing the appropriateness of endoscopic resection for gastric cancer? *Endoscopy* 2002; **34**: 973-978 [PMID: 12471541 DOI: 10.1055/s-2002-35851]
- 13 **Yoshida S, Tanaka S, Kunihiro K, Mitsuoka Y, Hara M, Kitadai Y, Hata J, Yoshihara M, Haruma K, Hayakawa N, Chayama K.** Diagnostic ability of high-frequency ultrasound probe sonography in staging early gastric cancer, especially for submucosal invasion. *Abdom Imaging* 2005; **30**: 518-523 [PMID: 15688103 DOI: 10.1007/s00261-004-0287-z]
- 14 **Mouri R, Yoshida S, Tanaka S, Oka S, Yoshihara M, Chayama K.** Usefulness of endoscopic ultrasonography in determining the depth of invasion and indication for endoscopic treatment of early gastric cancer. *J Clin Gastroenterol* 2009; **43**: 318-322 [PMID: 19077733 DOI: 10.1097/MCG.0b013e3181775966]
- 15 **Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS.** Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. *Endoscopy* 2010; **42**: 705-713 [PMID: 20652857 DOI: 10.1055/s-0030-1255617]
- 16 **Pei Q, Wang L, Pan J, Ling T, Lv Y, Zou X.** Endoscopic ultrasonography for staging depth of invasion in early gastric cancer: A meta-analysis. *J Gastroenterol Hepatol* 2015; **30**: 1566-1573 [PMID: 26094975 DOI: 10.1111/jgh.13014]
- 17 **Mocellin S, Pasquali S.** Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. *Cochrane Database Syst Rev* 2015; **(2)**: CD009944 [PMID: 25914908 DOI: 10.1002/14651858.CD009944.pub2]
- 18 **Kim JH, Song KS, Youn YH, Lee YC, Cheon JH, Song SY, Chung JB.** Clinicopathologic factors influence accurate endosonographic assessment for early gastric cancer. *Gastrointest Endosc* 2007; **66**: 901-908 [PMID: 17963876 DOI: 10.1016/j.gie.2007.06.012]

- 19 **Okada K**, Fujisaki J, Kasuga A, Omae M, Yoshimoto K, Hirasawa T, Ishiyama A, Yamamoto Y, Tsuchida T, Hoshino E, Igarashi M, Takahashi H. Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection. *Surg Endosc* 2011; **25**: 841-848 [PMID: 20734082 DOI: 10.1007/s00464-010-1279-4]
- 20 **Park JM**, Ahn CW, Yi X, Hur H, Lee KM, Cho YK, Han SU. Efficacy of endoscopic ultrasonography for prediction of tumor depth in gastric cancer. *J Gastric Cancer* 2011; **11**: 109-115 [PMID: 22076211 DOI: 10.5230/jgc.2011.11.2.109]
- 21 **Mandai K**, Yasuda K. Accuracy of endoscopic ultrasonography for determining the treatment method for early gastric cancer. *Gastroenterol Res Pract* 2012; **2012**: 245390 [PMID: 23213325 DOI: 10.1155/2012/245390]
- 22 **Kim GH**, Park DY, Kida M, Kim DH, Jeon TY, Kang HJ, Kim DU, Choi CW, Lee BE, Heo J, Song GA. Accuracy of high-frequency catheter-based endoscopic ultrasonography according to the indications for endoscopic treatment of early gastric cancer. *J Gastroenterol Hepatol* 2010; **25**: 506-511 [PMID: 20074167 DOI: 10.1111/j.1440-1746.2009.06111.x]
- 23 **Yamamoto S**, Nishida T, Kato M, Inoue T, Hayashi Y, Kondo J, Akasaka T, Yamada T, Shinzaki S, Iijima H, Tsujii M, Takehara T. Evaluation of endoscopic ultrasound image quality is necessary in endosonographic assessment of early gastric cancer invasion depth. *Gastroenterol Res Pract* 2012; **2012**: 194530 [PMID: 23024651]
- 24 **Tsujii Y**, Kato M, Inoue T, Yoshii S, Nagai K, Fujinaga T, Maekawa A, Hayashi Y, Akasaka T, Shinzaki S, Watabe K, Nishida T, Iijima H, Tsujii M, Takehara T. Integrated diagnostic strategy for the invasion depth of early gastric cancer by conventional endoscopy and EUS. *Gastrointest Endosc* 2015; **82**: 452-459 [PMID: 25841580 DOI: 10.1016/j.gie.2015.01.022]
- 25 **Tsuzuki T**, Okada H, Kawahara Y, Nasu J, Takenaka R, Inoue M, Kawano S, Kita M, Hori K, Yamamoto K. Usefulness and problems of endoscopic ultrasonography in prediction of the depth of tumor invasion in early gastric cancer. *Acta Med Okayama* 2011; **65**: 105-112 [PMID: 21519368 DOI: 10.1016/j.gie.2011.03.362]
- 26 **Lee JY**, Choi IJ, Kim CG, Cho SJ, Kook MC, Ryu KW, Kim YW. Therapeutic Decision-Making Using Endoscopic Ultrasonography in Endoscopic Treatment of Early Gastric Cancer. *Gut Liver* 2016; **10**: 42-50 [PMID: 26087792 DOI: 10.5009/gnl14401]
- 27 **Kida M**, Tanabe S, Watanabe M, Kokutou M, Kondou I, Yamada Y, Sakaguchi T, Saigenji K. Staging of gastric cancer with endoscopic ultrasonography and endoscopic mucosal resection. *Endoscopy* 1998; **30** Suppl 1: A64-A68 [PMID: 9765088 DOI: 10.1055/s-2007-1001474]
- 28 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 2nd English Edition - *Gastric Cancer* 1998; **1**: 10-24 [PMID: 11957040 DOI: 10.1007/s101200050051]
- 29 **Kobara H**, Mori H, Fujihara S, Kobayashi M, Nishiyama N, Nomura T, Kato K, Ishihara S, Morito T, Mizobuchi K, Iwama H, Masaki T. Prediction of invasion depth for submucosal differentiated gastric cancer by magnifying endoscopy with narrow-band imaging. *Oncol Rep* 2012; **28**: 841-847 [PMID: 22752002 DOI: 10.3892/or.2012.1889]
- 30 **Kikuchi D**, Iizuka T, Hoteya S, Yamada A, Furuhashi T, Yamashita S, Domon K, Nakamura M, Matsui A, Mitani T, Ogawa O, Watanabe S, Kaise M. Usefulness of magnifying endoscopy with narrow-band imaging for determining tumor invasion depth in early gastric cancer. *Gastroenterol Res Pract* 2013; **2013**: 217695 [PMID: 23401676 DOI: 10.1155/2013/217695]
- 31 **Roubein LD**, Lynch P, Gloor G, Sinicrope FA. Interobserver variability in endoscopic ultrasonography: a prospective evaluation. *Gastrointest Endosc* 1996; **44**: 573-577 [PMID: 8934164 DOI: 10.1016/S0016-5107(96)70011-1]

P- Reviewer: Arigami T, Sugimoto S, Zhang CW
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL



Small bowel Dieulafoy lesions: An uncommon cause of obscure bleeding in cirrhosis

Grainne Holleran, Mary Hussey, Deirdre McNamara

Grainne Holleran, Mary Hussey, Deirdre McNamara, Trinity Academic Gastroenterology Group, Trinity College Dublin, Trinity Centre for Health Sciences, Tallaght Hospital, Dublin 24, Ireland

Author contributions: All authors contributed to this paper.

Institutional review board statement: This case series was exempt from approval by the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee (REC).

Informed consent statement: All involved subjects were contacted and gave verbal consent to their anonymised inclusion in this report.

Conflict-of-interest statement: None of the authors have any conflicts of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Grainne Holleran, Gastroenterology Registrar, Trinity Academic Gastroenterology Group, Trinity College Dublin, Trinity Centre for Health Sciences, Tallaght Hospital, Dublin 24, Ireland. hollerag@tcd.ie
Telephone: +353-18-963844
Fax: +353-18-962988

Received: March 29, 2016
Peer-review started: March 31, 2016
First decision: May 17, 2016
Revised: May 28, 2016
Accepted: June 27, 2016
Article in press: June 29, 2016
Published online: August 25, 2016

Abstract

Dieulafoy lesions (DLs) are an uncommon cause of gastrointestinal bleeding, accounting for up to 2% of cases overall. They are largely under recognised and difficult to treat. Up to 95% occur in the stomach, and only case reports document their occurrence in the small bowel (SB). Little is known about their pathophysiology, although there have been associations made previously with chronic liver disease, thought to be due to the erosive effects of alcohol on the mucosa overlying the abnormally dilated vessels. We present a case series of 4 patients with a long duration of obscure gastrointestinal bleeding, who were diagnosed with small intestinal DLs and incidentally diagnosed with chronic liver disease. The histories describe the challenges in both diagnosis and treatment of small intestinal DLs. Our case series suggest a previously unreported link between chronic liver disease and SB DLs which may be due to anatomical vasculature changes or a shift in angiogenic factors as a consequence of portal hypertension or liver cirrhosis.

Key words: Obscure gastrointestinal bleeding; Dieulafoy lesions; Cirrhosis; Portal hypertension; Capsule endoscopy; Double balloon enteroscopy

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Patients with advanced liver disease are known to have a high rate of obscure gastrointestinal bleeding, the cause of which is often left undetected. Our case series suggests that there may be an increased risk of small intestinal Dieulafoy lesions (DLs) in patients with cirrhosis. Although the pathophysiology of DLs is unknown, our case series of jejunal lesions in patients with cirrhosis raises the question of a potential alteration in the vasculature secondary to portal hypertension, as either an anatomical abnormality or due to a shift in angiogenic factors in these patients.

Holleran G, Hussey M, McNamara D. Small bowel Dieulafoy lesions: An uncommon cause of obscure bleeding in cirrhosis. *World J Gastrointest Endosc* 2016; 8(16): 568-571 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i16/568.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i16.568>

INTRODUCTION

Dieulafoy lesions (DLs) are an uncommon cause of gastrointestinal bleeding (GIB), accounting for up to 2%, and are largely under recognised and difficult to treat. Endoscopically they are characterised by the following diagnostic criteria: Active bleeding from a mucosal defect < 3 mm in size, an isolated protruding vessel with or without a minute mucosal defect, or an adherent clot with a narrow point of attachment to a tiny mucosal defect or occasionally normal appearing mucosa^[1]. The majority, up to 95%, of DLs are found in the stomach, generally within 6 cm of the oesophagogastric junction, with over 60% on the lesser curvature of the stomach, however they also occur in the colon, duodenum, and rarely in the small bowel (SB). The presentation of bleeding is usually acute overt haemorrhage, and due to the intermittent nature of bleeding, rates of diagnosis at initial endoscopy can be as low as 70%^[2]. Endoscopic treatment with argon plasma coagulation (APC), clipping, injection of adrenaline or banding is successful in up to 90% of cases, with angiographic embolization or surgical resection reserved for cases unresponsive to endoscopic therapy^[3]. Although the initial response is very high, recurrence is common, and up to 10% of patients present with massive acute GIB, and despite advances in endoscopic treatment mortality rates are as high as 8%^[4]. DLs in the SB are rare, however with the increasing availability of SB endoscopy, there have been a number of case series in recent years, understandably suggesting that SB lesions are more difficult to treat^[5,6]. Several hypotheses have been put forward as to the cause of bleeding from these DLs, and although an association has been suggested between the use of non-steroidal anti-inflammatories (NSAIDs) and anticoagulants, no causal link or pathophysiological basis for their development has been established. Interestingly a number of small studies have identified an association between advanced liver disease and DLs, suggesting a similarity of these lesions to spider naevi, however the numbers in each study have been small^[7-9]. We present a case series of 4 patients with SB DLs who were found incidentally to have advanced liver disease during their workup for obscure GIB. These patients presented consecutively to our institution over approximately a two year time period.

CASE REPORT

Case 1

PS: A 67-year-old female was referred for investigation

of obscure overt GIB ongoing for 2 years. Her past history included rheumatic fever, with metallic aortic and mitral valve replacements, for which she was anticoagulated, and congestive cardiac failure. She had initially presented with recurrent episodes of melaena and underwent multiple upper and lower endoscopies and a CT mesenteric angiogram which failed to reveal the source of her bleeding. Cross sectional imaging revealed cirrhosis, without significant varices. A serological screen failed to show any cause of cirrhosis and it was presumed to be secondary to her cardiac failure. She was initially treated empirically with iron and red cell transfusions, however her requirements increased and she became dependent on fortnightly transfusions to maintain her haemoglobin above 8 g/dL. At this stage she was admitted electively and underwent SB capsule endoscopy (SBCE) which showed a large volume of fresh bleeding in the proximal jejunum, with melaena and transported clots throughout the SB. Double balloon enteroscopy (DBE) showed no active bleeding but an isolated protruding vessel in the proximal jejunum, consistent with a DL was detected, and APC and endoclips were applied. Following this she was treated with 20 mg of a long-acting intramuscular somatostatin analogue and she remained bleed free for 12 wk. Unfortunately she then suffered an acute haemorrhage, presenting with haemoglobin of 5 g/dL. She underwent repeat SBCE and DBE which again showed active bleeding from the DL in the proximal jejunum which was again treated with APC and endoclips which initially controlled the bleeding. However PS suffered a massive further haemorrhage, a bleeding source could not be identified by CT mesenteric angiography and despite undergoing an emergency jejunal resection; she died post operatively due to cardiac complications.

Case 2

MF: A 74-year-old lady was referred with intermittent melaena ongoing for 18 mo. She had a history of rheumatic fever, a mitral valve replacement, requiring anticoagulation, congestive cardiac failure and a SB resection in the 1990s for angiodysplasia. Similarly, MF had undergone multiple upper and lower endoscopies which had been unyielding and again, she was found to have features of cirrhosis and portal hypertension on cross sectional imaging, the cause of which was idiopathic. Prior to referral to our services she had received over 50 units of red cell transfusions. She underwent SBCE which showed active bleeding and a minute mucosal defect in her proximal jejunum consistent with a DL, with clots of likely transported blood seen more distally. Her DL was treated with APC via DBE on 4 occasions due to early re-bleeding, along with 20 mg of long-acting somatostatin analogue. MF developed cholecystitis secondary to choledocholithiasis, which was managed conservatively, requiring her to discontinue the somatostatin analogue. She has been bleed-free for the last 24 mo, with a most recent

haemoglobin level of 12.1 g/dL.

Case 3

MB: A 76-year-old lady was admitted electively for investigation of a 12-mo history of recurrent obscure overt bleeding in the form of melaena. She had a background of a mitral valve replacement requiring anticoagulation, chronic myeloid leukaemia, cirrhosis of unknown aetiology, and hypertension. MB had undergone embolization of a bleeding source in her proximal jejunum *via* mesenteric angiography prior to her referral to our services; however her melaena recurred within 4 mo of the procedure, and she was requiring weekly red cell transfusions. SBCE showed active bleeding in her proximal jejunum; however at DBE although fresh blood was seen in her proximal jejunum no active bleeding or mucosal abnormalities were seen. During her admission she suffered a number of large volume overt bleeds requiring multiple red cell transfusions, again DBE showed active bleeding in the proximal jejunum. However this was not detected by either CT mesenteric angiogram or a formal heparin-provoked angiogram. After prolonged consideration and discussion, MB underwent a laparoscopic resection of her proximal jejunum, with histology findings consistent with that of a DL. Her haemoglobin remained stable without any red cell transfusions for over 9 mo at which point she re-presented with melaena. On this occasion she was not found to have and SB bleeding, however a new DL was found in her gastric fundus.

Case 4

EN: A 75-year-old lady was referred to our institution for investigation of recurrent melaena. She had undergone multiple upper and lower endoscopies which had not revealed a source of bleeding. Her past medical history included congestive cardiac failure, atrial fibrillation for which she was anticoagulated, type 2 diabetes mellitus, hypertension and cirrhosis, again diagnosed incidentally by imaging during her workup for GIB. SBCE showed fresh blood in the proximal jejunum and she underwent a DBE where a small amount of fresh bleeding was noted in the first part of her duodenum, with the visualisation of a pinpoint vessel consistent with a DL. The area was injected with adrenaline and endoclips were applied with initial haemostasis. However due to the need for ongoing anticoagulation the lesion continued to ooze and a definitive treatment was sought. EN underwent a CT mesenteric angiogram which revealed an occluded coeliac artery with retrograde filling of the gastroduodenal artery from the superior mesenteric artery. Due to the anatomical abnormalities in her vasculature, embolization therapy was not possible and an ileohepatic artery bypass was planned. However, despite previously normal imaging, at laparotomy EN was found to have macro nodular cirrhosis with multiple small intra-abdominal varices. The proposed bypass was abandoned and multiple small DLs around D1 were ligated and/or clipped. EN recommenced anticoagulation shortly after her surgery

and has not had any recurrent bleeding episodes in over 10 mo.

DISCUSSION

The above 4 cases outline the challenges in both diagnosis and treatment of SB DLs, and they also present a number of potentially new associations with SB DLs. Firstly regarding demographics, in keeping with the published literature, our patients were elderly with multiple comorbidities, however in contrast to the suggested male preponderance, our 4 patients with SB DLs were all female. In addition, all 4 patients had SB without coexistent lesions in the stomach, where 95% of DLs reportedly occur, although the third case was found to have a *de novo* gastric DL over 9 mo later. There was also no history of NSAID, or alcohol use, although all patients were anticoagulated, which has been proven to increase the risk of bleeding. Each of the cases highlights the difficulties in diagnosis of SB DLs and reiterates the importance of heightened vigilance in patients with obscure GIB. Despite active bleeding causing systemic compromise and large red cell transfusion requirements, none of the DLs were detected by mesenteric angiography, and were only diagnosed by mucosal visualisation with SB endoscopy, either *via* SBCE or DBE.

Previous associations between cirrhosis and DLs have been thought to be due to the erosive effect of alcohol on the mucosa overlying the dilated DL vessel; however alcohol was not a factor in any of our 4 patients. As mentioned in the introduction, comparisons have been made between the appearances of DLs and spider naevi, a known feature of chronic liver disease, with the suggestion that DLs are gastrointestinal forms of spider naevi; however the pathophysiology for the development of spider naevi is also unknown. Cirrhosis can increase the risk of GIB, mainly due to portal hypertension, leading to portal gastropathy and intraluminal varices; however in our case series all patients had undergone multiple endoscopies, out ruling varices as a cause of bleeding. Patients with advanced liver disease are known to have a high rate of obscure GIB, the cause of which is often left undetected, however; our case series suggests that there may be an increased risk of DLs in patients with cirrhosis. In general the most common cause of obscure GIB is SB angiodysplasias, which have a similar clinical presentation to DL; however there were no characteristic endoscopic features of angiodysplasias in the vascular lesions in any of these 4 patients. We have recently identified an association between the abnormalities in the Angiopoietin pathway along with other angiogenic factors, with the presence of SB angiodysplasias^[10]. Our finding of jejunal DLs in patients with cirrhosis raises the question of a potential alteration in the vasculature secondary to portal hypertension, as either an anatomical abnormality, as was described in case 4, or potentially due to a shift in angiogenic factors in these patients. As referenced in the case series by Akhras *et al*^[9], the examination of biopsies

from DLs is likely to yield more information about their pathophysiology. Finally, 3 of our 4 patients were treated both medically with long-acting somatostatin analogues and endoscopically, due to a combination of their long history of bleeding and its significant burden on their quality of life, and their need for long-term anticoagulation. Somatostatin analogues are known to reduce GIB due to a combination of effects, including reducing the splanchnic and portal pressure and *via* an anti-angiogenic effect on vascular endothelial growth factor. This makes it difficult to determine which treatment modality was effective in controlling further bleeding episodes but the seemingly successful use of somatostatin analogues in these patients would support both a “vascular pressure system” and an “angiogenic disarray” hypothesis in the pathogenesis of SB DLs. Further work in the field of portal hypertension and angiogenic factors in the pathophysiology of SB DLs and other vascular lesions including angiodysplasias will be interesting and could lead to more targeted treatment options in cases of refractory bleeding.

COMMENTS

Case characteristics

All cases had a long history of significant gastrointestinal bleeding from small intestinal Dieulafoy lesions (DLs) and were found to have cirrhosis and portal hypertension, suggesting a potential association between the two conditions.

Clinical diagnosis

Small intestinal DLs were diagnosed by a combination of capsule endoscopy and double balloon enteroscopy in all patients, with a diagnosis of cirrhosis initially suggested by radiological imaging and confirmed by clinical examination \pm laboratory features of cirrhosis.

Differential diagnosis

There are a number of other vascular lesions which can affect the small intestine and share similar endoscopic features with DLs including: Angiodysplasias, telangiectasias, arteriovenous malformations, mucosal ulceration and trauma.

Laboratory diagnosis

All patients presented with iron deficiency anaemia, in addition features of cirrhosis including thrombocytopaenia and a low serum albumin were found in 2 patients.

Imaging diagnosis

Small intestinal DLs were diagnosed endoscopically by characteristic visual appearances, using either capsule endoscopy or double balloon enteroscopy.

Pathological findings

When examined histologically, DLs are found to consist of abnormally large calibre sub-mucosal end arteries which lie close to the surface of the mucosa, making them delicate and prone to rupture and bleeding.

Treatment

Treatments included endoscopic; a combination of injection of adrenaline, application of endoclips, and/or thermal coagulation, *via* angiographic embolization, or ultimately *via* surgical resection of the segment of affected

bowel, or ligation of the vessels feeding the DLs.

Related reports

Small intestinal DLs are reported only rarely in the literature and are thought to be difficult to treat. An association between patients with advanced liver disease and DLs outside the small intestine has also been made in a few other case reports, although the pathophysiology linking the two conditions is still unknown.

Term explanation

DLs are uncommon causes of gastrointestinal bleeding characterised by tiny defects in the gastrointestinal mucosa.

Experiences and lessons

This case series highlights the difficulties in the diagnosis of DLs and the need for heightened vigilance and repeated investigation in patients with obscure gastrointestinal bleeding, particularly in patients with cirrhosis. It also highlights the difficulties and poor outcomes following treatment, which addresses the need for further research in the area to identify the pathophysiology of DLs and develop targeted therapies.

Peer-review

The paper is a useful addition to the literature concerning this difficult to treat lesion.

REFERENCES

- 1 **Baxter M**, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. *Ann R Coll Surg Engl* 2010; **92**: 548-554 [PMID: 20883603 DOI: 10.1308/003588410X12699663905311]
- 2 **Marangoni G**, Cresswell AB, Faraj W, Shaikh H, Bowles MJ. An uncommon cause of life-threatening gastrointestinal bleeding: 2 synchronous Dieulafoy lesions. *J Pediatr Surg* 2009; **44**: 441-443 [PMID: 19231553 DOI: 10.1016/j.jpedsurg.2008.09.033]
- 3 **Chung IK**, Kim EJ, Lee MS, Kim HS, Park SH, Lee MH, Kim SJ, Cho MS. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. *Gastrointest Endosc* 2000; **52**: 721-724 [PMID: 11115902 DOI: 10.1067/mge.2000.108040]
- 4 **Alshumrani G**, Almuaikael M. Angiographic findings and endovascular embolization in Dieulafoy disease: a case report and literature review. *Diagn Interv Radiol* 2006; **12**: 151-154 [PMID: 16972222]
- 5 **Fox A**, Ravi K, Leeder PC, Britton BJ, Warren BF. Adult small bowel Dieulafoy lesion. *Postgrad Med J* 2001; **77**: 783-784 [PMID: 11723319 DOI: 10.1136/pmj.77.914.783]
- 6 **Blecker D**, Bansal M, Zimmerman RL, Fogt F, Lewis J, Stein R, Kochman ML. Dieulafoy's lesion of the small bowel causing massive gastrointestinal bleeding: two case reports and literature review. *Am J Gastroenterol* 2001; **96**: 902-905 [PMID: 11280574 DOI: 10.1111/j.1572-0241.2001.03641.x]
- 7 **Madhira MS**, Tobi M. Isolated gastrointestinal spider nevi: potential clinical significance. *Am J Gastroenterol* 2000; **95**: 3009-3010 [PMID: 11051406 DOI: 10.1111/j.1572-0241.2000.03233.x]
- 8 **Campbell S**, Mee A. Gastrointestinal spider nevi. *Gastrointest Endosc* 2004; **59**: 401 [PMID: 14997143 DOI: 10.1016/s0016-5107(03)02337-x]
- 9 **Akhras J**, Patel P, Tobi M. Dieulafoy's lesion-like bleeding: an underrecognized cause of upper gastrointestinal hemorrhage in patients with advanced liver disease. *Dig Dis Sci* 2007; **52**: 722-726 [PMID: 17237996 DOI: 10.1007/s10620-006-9468-7]
- 10 **Holleran G**, Hall B, O'Regan M, Smith S, McNamara D. Expression of Angiogenic Factors in Patients With Sporadic Small Bowel Angiodysplasia. *J Clin Gastroenterol* 2015; **49**: 831-836 [PMID: 25319741 DOI: 10.1097/MCG.0000000000000260]

P-Reviewer: Butterworth J, Ogata H, Rimbas M
S-Editor: Ji FF **L-Editor:** A **E-Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 September 16; 8(17): 572-634





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

ASSOCIATE EDITORS

Chisato Hamashima, *Tokyo*

GUEST EDITORIAL BOARD MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Dimitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *Udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Naoki Hotta, *Nagoya*

Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurionhoj*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iruru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satohiro Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Nosho, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *UiJeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornnotin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentis, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *Albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciaccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

REVIEW

- 572 Current role of capsule endoscopy in Crohn's disease
Luján-Sanchis M, Sanchis-Artero L, Larrey-Ruiz L, Peño-Muñoz L, Núñez-Martínez P, Castillo-López G, González-González L, Boix Clemente C, Albert Antequera C, Durá-Ayet A, Sempere-García-Argüelles J

MINIREVIEWS

- 584 Blood thinners and gastrointestinal endoscopy
Ahmed M
- 591 Endoscopic management of post-bariatric surgery complications
Boules M, Chang J, Haskins IN, Sharma G, Froylich D, El-Hayek K, Rodriguez J, Kroh M
- 600 Review of small-bowel cleansing scales in capsule endoscopy: A panoply of choices
Ponte A, Pinho R, Rodrigues A, Carvalho J
- 610 Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges
Zheng D, Huang CS, Huang SB, Zheng CX

ORIGINAL ARTICLE

Retrospective Study

- 616 Predictors of suboptimal bowel preparation in asymptomatic patients undergoing average-risk screening colonoscopy
Govani SM, Elliott EE, Menees SB, Judd SL, Saini SD, Anastassiades CP, Urganus AL, Boyce SJ, Schoenfeld PS
- 623 Transanal endoscopic microsurgery as optimal option in treatment of rare rectal lesions: A single centre experience
Ortenzi M, Ghiselli R, Cappelletti Trombettoni MM, Cardinali L, Guerrieri M

Observational Study

- 628 Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection
Arantes V, Uedo N, Pedrosa MS, Tomita Y

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 17 September 16, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Mahesh K Goenka, FACP, FASGE, MD, MNAMS, MNAMS, Director, Institute of Gastrosciences, Apollo Gleneagles Hospitals, Kolkata 700054, India

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Dan Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com>

www.wjgnet.com/1948-5190/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
Fang-Fang Ji, Vice Director
World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
September 16, 2016

COPYRIGHT
© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

Current role of capsule endoscopy in Crohn's disease

Marisol Luján-Sanchis, Laura Sanchis-Artero, Laura Larrey-Ruiz, Laura Peño-Muñoz, Paola Núñez-Martínez, Génesis Castillo-López, Lara González-González, Carlos Boix Clemente, Cecilia Albert Antequera, Ana Durá-Ayet, Javier Sempere-García-Argüelles

Marisol Luján-Sanchis, Laura Sanchis-Artero, Laura Larrey-Ruiz, Laura Peño-Muñoz, Paola Núñez-Martínez, Génesis Castillo-López, Lara González-González, Carlos Boix Clemente, Cecilia Albert Antequera, Ana Durá-Ayet, Javier Sempere-García-Argüelles, Digestive Diseases Unit, General University Hospital of Valencia, 46014 Valencia, Spain

Author contributions: Luján-Sanchis M designed the research, reviewed the literature and wrote the paper; Sanchis-Artero L made the tables, figures and illustrations; Larrey-Ruiz L ordered the references; Sempere-García-Argüelles J performed critical final revision of manuscript; rest of authors contributed equally to collecting the data.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest (including to commercial, personal, political, intellectual or religious interests). No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Marisol Luján-Sanchis, MD, PhD, Digestive Diseases Unit, General University Hospital of Valencia, Avenida Tres Cruces, 2, 46014 Valencia, Spain. marisol.lujan@hotmail.es
Telephone: +34-96-3131800
Fax: +34-96-1972148

Received: April 13, 2016
Peer-review started: April 16, 2016
First decision: May 19, 2016
Revised: May 25, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: September 16, 2016

Abstract

Capsule endoscopy (CE) currently plays an important role in Crohn's disease (CD). It is a noninvasive technique that has led to a breakthrough in the endoscopic diagnosis of diseases of the small intestine. Its superior diagnostic performance and excellent safety profile lead to its considerable acceptance on the part of the patient. This paper reviews current indications of CE in three stages of clinical practice: Suspected CD, unclassified colitis and its extensive role in diagnosed CD. The diagnostic and therapeutic impact of the results of CE on the monitoring of this disease is also reviewed. Knowledge of its applications, the interpretation of its results in an appropriate context and the existence of a validated endoscopic activity index could change the way in which these patients are managed. The definition of mucosal healing and postoperative recurrence by means of endoscopic scoring systems will endow CE with new applications in the management of CD in the near future.

Key words: Capsule endoscopy; Inflammatory bowel disease; Crohn's disease

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We expose current indications and practical uses of capsule endoscopy in Crohn's disease based on the most relevant published evidence. Likewise, we describe the diagnostic and therapeutic impact on this disease and an exhaustive summary of where it plays an extensive role.

Luján-Sanchis M, Sanchis-Artero L, Larrey-Ruiz L, Peño-Muñoz L, Núñez-Martínez P, Castillo-López G, González-González L, Boix Clemente C, Albert Antequera C, Durá-Ayet A, Sempere-García-Argüelles J. Current role of capsule endoscopy in Crohn's disease. *World J Gastrointest Endosc* 2016; 8(17): 572-583
Available from: URL: <http://www.wjgnet.com/1948-5190/full/>

INTRODUCTION

Early diagnosis of inflammatory bowel disease (IBD) is crucial, as the progression of inflammatory activity leads to irreversible damage^[1-4]. There is currently no test for the diagnosis of Crohn's disease (CD)^[5,6]; therefore, the techniques used must be interpreted in the appropriate context^[7]. Since its approval by the Food and Drug Administration (FDA) in 2001, capsule endoscopy (CE) has revolutionized the diagnostic imaging of diseases of the small bowel (SB). The endoscopic capsule is a small instrument that takes hundreds of photographs while moving naturally with intestinal movements, thus facilitating direct, noninvasive visualization of the intestinal mucosa. CE is currently the most important indicator of CD in children between 10 and 18 years age^[8,9]; in adults and young children, its importance as an indicator is second only to bleeding of unknown origin^[8].

This review presents the principal indications of CD based on the available evidence^[10-17] in three scenarios: Suspected CD (SCD), unclassified colitis (UNC) and diagnosed CD (DCD). This is the best procedure for viewing mucosal lesions attributable to CD in the SB^[11] and of identifying superficial lesions that go unnoticed by other endoscopic and radiological techniques^[7,11,14,18-20].

These characteristics establish its indication as the technique of choice in the evaluation of the SB with CD in the absence of stenosis or fistulas^[14,21], and particularly when it will lead to a change in patient management^[6,10,14,15].

DIAGNOSTIC CRITERIA FOR CD USING CE

Lesions consistent with CD should be described according to a structured and standardized terminology called Capsule Endoscopy Structured Terminology, which was described in 2005^[22]. The terminology is based on the presence of stenosis, ulcers, erosions, cankers, pseudopolyps and fistulas (Figure 1), and it enables the use of a common language to interpret lesions consistent with CD. These lesions are not specific; therefore, other diseases with the same endoscopic features (infections, ischemia, vasculitis, iatrogenesis, tumors, lymphoma and Behcet's disease, among others) need to be ruled out. Other lesions such as erythema, nodularity, denudation or petechiae are not considered to be related to inflammation of the mucous membranes. Most studies have used the diagnostic criteria for CD by means of CE, defined by Mow *et al*^[23] in 2004, as the existence of more than three diffuse or multiple ulcerations when nonsteroidal anti-inflammatory drugs (NSAIDs) are not being taken. This criterion provides a sensitivity (S) of 77%, specificity (SP) of 89%, positive predictive value (PPV) of 55% and a negative predictive value (NPV) of

96% for the diagnosis of CD in relation to clinical, endoscopic, radiological and histological findings. The rate of mucosal lesions missed by CE is minimal (0.5%); therefore, CD can be excluded after two years of monitoring^[24].

Other authors have described criteria used less commonly in clinical practice such as the presence of multiple aphthous or erosive lesions (> 10), whether distributed continuously or discontinuously^[25], or the presence of four or more ulcers, erosions, or a region with exudate, hyperemia and edema^[26].

The current guidelines of both ASGE^[27] and ECCO^[14] recommend the use of two endoscopic indices that quantify the inflammatory activity of the CD by means of CE. Both have been prospectively validated^[28,29] and enable the objective assessment of severity of the disease. They focus more on the presence or absence of inflammatory activity than on its extent and location. The first is the Niv or Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) score (Table 1), which was published by Gal *et al*^[30] and defines the size of ulcers and the extent of inflammation and stenosis, dividing the SB into two segments, proximal and distal. The total score (from 0 to 36) is the sum of both segments. The CECDAI does not have a specific threshold; however, an increase in its value indicates more severe mucosal inflammation.

The second is the Lewis score described in 2008 by Gralnek *et al*^[31] (Table 2). It divides the SB into three equal parts and also quantifies the edema of the villi, the ulcer and the stenosis. A score of < 135 indicates a normal mucosa or insignificant inflammation, a score of between 135 and 790 represents mild inflammation, and a score of ≥ 790 represents moderate or severe inflammation^[32]. This index has been more widely used in clinical practice than the CECDAI, because there is an automatic calculation tool in a CE reading program (Rapid Reader® workstation of PillCam® capsules). It has been demonstrated that, the more lesions that are detected, the greater the endoscopic score and the more specific the diagnosis of CD by means of CE^[33]. Similarly, with a Lewis score of < 135, the probability of it being a case of CD is unlikely^[29,32,34]. In healthy patients (who do not take NSAIDs, have not had an intestinal resection, and do not have ankylosing spondylitis or digestive symptoms), only 9% may exhibit mucosal lesions similar to CD, and in all cases, the Lewis score would indicate mild activity (< 450)^[33].

It is important to remember that the endoscopic findings themselves are not diagnostic of CD, and there is no cutoff value above which the diagnosis can be firmly established^[35]. Moreover, endoscopic activity shows no correlation with the clinical evidence; consequently, in a symptomatic patient, CE detects lesions in only half of the cases^[36,37] and conversely, when the patient is in clinical remission (Crohn's disease activity index < 150), CE will show signs of inflammation in 62%^[38]. This means that, once the objective assessment of CD activity has been performed by means of CE, decisions can be made regarding the management of the patient.

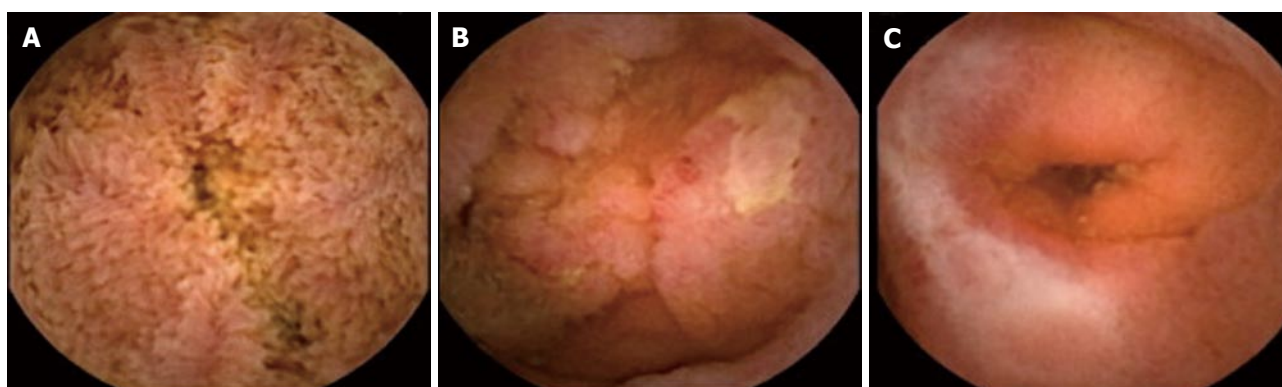


Figure 1 Lesions compatible with Crohn's disease by capsule endoscopy. A: Edema; B: Ulcers; C: Strictures.

Table 1 Capsule endoscopy Crohn's disease activity index

Inflammation score
0: None
1: Mild to moderate edema/hyperemia/denudation
2: Severe edema/hyperemia/denudation
3: Bleeding, exudate, aphtha, erosion, small ulcer (< 0.5 cm)
4: Moderate ulcer (0.5-2 cm), pseudopolyp
5: Large ulcer (> 2 cm)
Disease extension score
0: No disease - normal exploration
1: Focal disease (single segment involvement)
2: Patchy disease (2-3 segments involved)
3: Diffuse disease (> 3 segments involved)
Stricture score
0: None
1: Single - passed
2: Multiple - passed
3: Obstructing (not passed)
Segmentary score (proximal or distal): $(A \times B) + C$
Total score: Proximal $[(A \times B) + C]$ + distal $[(A \times B) + C]$

Table 2 Lewis score for mucosal inflammatory changes

Lesions in the proximal, mid, and distal small bowel thirds
Villous appearance
0: Normal
1: Edema
8: Short segment
12: Long segment; 20: The whole third
1: Single; 14: Patchy
Ulcers
0: None; 3: One; 5: Few; 10: Multiple
5: Short segment; 10: Long segment; 15: The whole third
9: 1/4; 12: 1/4-1/2; 18: > 1/2
Strictures
0: None; 14: One
2: Non ulcerated; 24: Ulcerated
7: No retention; 10: Capsule retention
Score calculation: Stricture score is added to the sum total for highest scoring villous edema and segment ulcers

INDICATIONS OF CE IN SUSPECTED CD

There is no gold standard for the diagnosis of CD; therefore, all techniques are complementary and should be interpreted with an appropriate degree of skepticism. Thus, CE and enteroscopy are useful for the early diagnosis and assessment of the extent and activity of the disease; radiology is better for studying the progression of damage and extraintestinal complications; and serological and fecal markers of inflammation are generally used to decide on the indication of radiological and endoscopic techniques. The selection of these will depend on the availability at the center, operator experience, its practical usefulness and cost^[39].

The appropriate indication of CE for SCD was defined at the International Conference on CE through the selection of the following criteria: Existence of consistent symptoms, associated or not associated with extraintestinal manifestations and laboratory and/or radiological abnormalities^[7]. In these cases, an ileocolonoscopy (IC) with biopsies should be performed, and regardless of the outcome, it would be advisable to assess the proximal extension of the disease into the stomach and/or intestine for its prognostic implications^[5,14,15,27,40].

CE is the diagnostic technique of first resort when the IC and radiology are negative or inconclusive^[14,15,27,41], because it detects subtle inflammatory changes that go unnoticed by radiological techniques or are unachievable by conventional endoscopy (Figure 2)^[42,43]. Thus, two broad meta-analyses^[44,45] show that its performance in cases of SCD is superior to that of IC, barium follow-through examinations (BFT) and computerized tomography (CT) at 22%, 32% and 47%, respectively. Faced with lesions consistent with CD, enteroscopy may be useful for taking biopsies, but its routine performance is not indicated according to the ASGE^[27] and ECCO^[14] guidelines.

The capsule's diagnostic performance with respect to CD varies as a function of how early the disease is suspected as well as the extension, activity and distribution of the disease^[46,47]. The findings of CE have diagnostic value when they are interpreted with an adequate degree of skepticism. Overall performance is higher when additional data besides clinical evidence such as intestinal manifestations and/or serum or fecal markers of inflammation^[7,14,26,32,48-50], are presented. Thus, when the disease is suspected based on one criterion, CE shows mild activity, and the diagnosis is confirmed in 20% of cases; however, when it is based on three criteria, activity will be more severe, and the

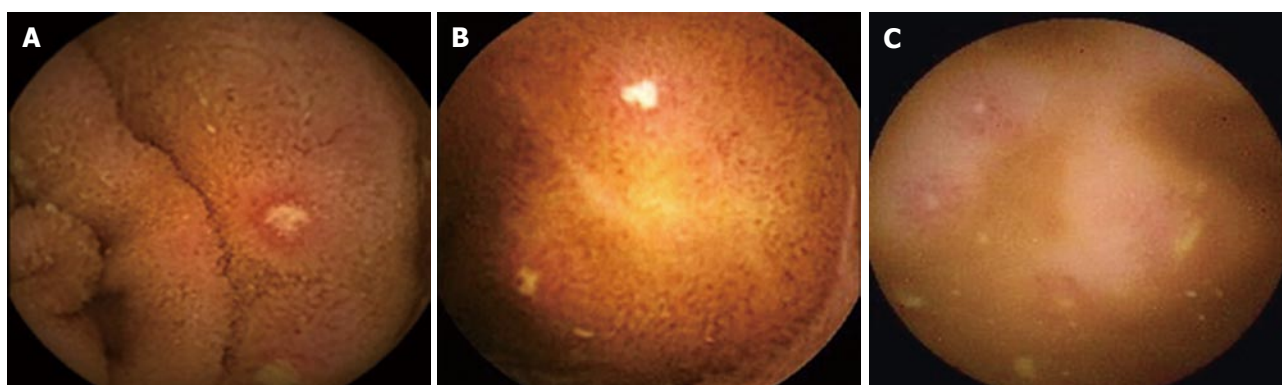


Figure 2 Aphthous erosions detected by capsule endoscopy. A: Aphtha; B: Surface erosion; C: Aphthoid erosions. The capsule may detect superficial intestinal lesions in a patient with Crohn's disease that are overlooked by radiographic techniques and inaccessible to ileocolonoscopy.

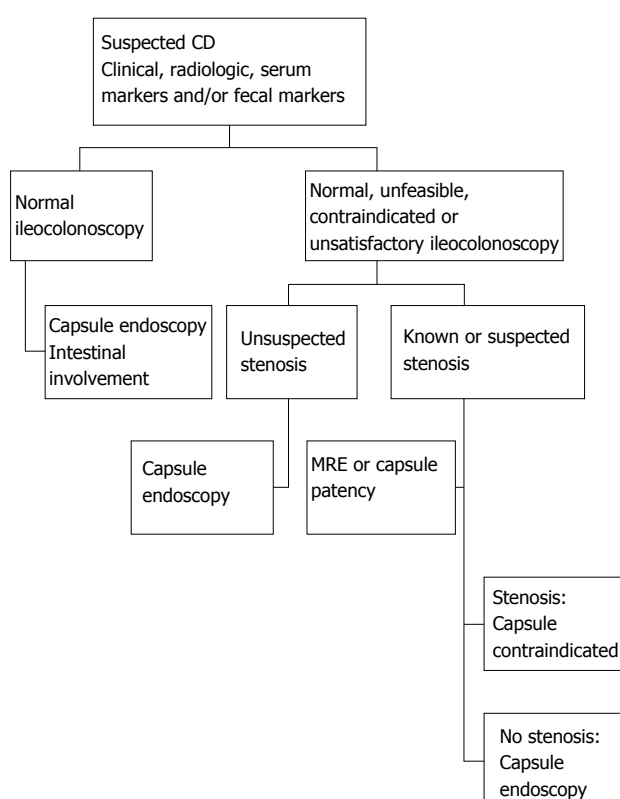


Figure 3 A diagnostic protocol for suspected Crohn's disease^[127]. When CD is suspected ileocolonoscopy should be the first study to be performed, with capsule endoscopy ensuing when results are normal, unsatisfactory or not are achieved ileoscopy. If intestinal stenosis is suspected, a test capsule should be used to confirm the feasibility of capsule endoscopy. CD: Crohn's disease; MRE: Enterography with nuclear magnetic resonance.

diagnosis is confirmed in 80%^[32]. In accordance with the above, Figure 3 sets out a proposal to focus on the diagnosis of SCD.

INDICATIONS OF CE FOR DIAGNOSED CD

In the context of DCD, the indication of CE should be considered when providing for a change in the management of the disease^[6,10,11,40]. It has been demonstrated that the investigation of proximal extension into the SB using CE has prognostic and therapeutic implications in

disease progression^[14,51]. Therefore, given its superior diagnostic performance in DCD (85.7%), its findings can influence a change in the management and clinical follow-up for 64% of these patients^[52].

As with SCD, several meta-analyses^[44,45] show that performance in cases of DCD is superior to that of push enteroscopy, BFT and CT at 57%, 38% and 32% respectively. The identification of mucosal lesions in the SI is better than with BFT (78% vs 32%) and can be better than enterotomography (ETC) (68% vs 38%) or enterography with nuclear magnetic resonance (MRE) (93% vs 79%), although the clinical significance of these differences is not defined in prospective studies. The primary role of CE in cases of DCD is when there are symptoms or signs which cannot be explained by the normal or inconclusive result of radiology and/or IC, as it can detect lesions between the duodenum and terminal ileum which are inaccessible with conventional endoscopy or imperceptible with radiology which substantiate the clinical picture^[14,40,53]. The applications of CE for DCD in habitual clinical practice are set out below.

Investigation of the extent of CD

Currently, at the time of the initial diagnosis of CD, it is advisable to assess the extent throughout the entire gastrointestinal tract^[14,54]. The SB is affected in 80% of patients with CD^[51]. In general, in more than half of the patients with ileal CD, the proximal SB is also involved, with the most frequent distribution being in the proximal ileum (67%) followed by the proximal jejunum (53%) and/or proximal duodenum (32%)^[36,55]. After the entire SB was able to be accessed with CE, it was observed that this location could coexist with the ileal and the colonic. Therefore, the Vienna classification was replaced by Montreal in 2005, adding the involvement of the upper digestive tract through to the proximal ileum (that which is called L4)^[56] to the rest of the locations. The advantage of the phenotypic classification of DCD using the Montreal classification is important for predicting the progression of the disease and the selection of the best management strategy.

Flamant *et al.*^[51] found that jejunal (L4) involvement was 40% when the ileum (L1) was affected and 12%

when the colon (L2) was affected. Isolated jejunal involvement occurred in 17% of the cases, and this figure has been corroborated by other authors^[57]; however, other authors have observed jejunal involvement in a third of patients with normal IC^[58]. In the pediatric population, these figures are superimposable, with L4 involvement in 24% of patients with DCD, 30% being associated with L1, 18% with L2 and 21% if the phenotype is ileocolonic (L3)^[59].

Recent findings published by Lazarev *et al.*^[60] have been decisive in understanding the involvement of the SB in CD. Of the 2015 patients analyzed, 14% exhibited proximal involvement, and this location is associated with younger age groups, non-smoking patients, coexistence with ileal involvement and a pattern of stenosis. Specifically, jejunal involvement is associated with patterns of stenosis which necessitate further surgery. Based on these findings, this author proposes revising the Montreal classification, as jejunal involvement should be viewed as a separate phenotype due to the prognostic implications of this location. The behavior of the proximal location is similar to that of the ileal location and most frequently develops into a pervasive, stenotic pattern in contrast with the colonic location^[61].

Isolated CD in the small bowel

The diagnosis of isolated CD in the SB is a true challenge, and as it occurs with colonic involvement, it is not correlated with endoscopic activity. Population-based epidemiological studies show that more than 50% of Western patients with CD and 77%-87% of Asian patients exhibit involvement of the SB at the time of diagnosis^[62-65]. The use of CE with DCD is currently considered to be complementary to other techniques, and the selection thereof will depend on the experience of each center^[66].

As for radiology, ETC and MRE evaluate the progression of transmural damage and the complications (transmural extension, abscesses, fistulas, stenosis and collections); therefore, studies are preceded or completed with CE when there is interest in identifying these^[10]. Its primary advantage over radiological techniques is its elevated sensitivity for the detection of superficial mucosal lesions^[42], as there are few series, which provide sensitivity similar to that of MRE (75% vs 77.8%, respectively)^[67]. The advantage of CE over MRE focuses principally on jejunal lesions, as the jejunum has a larger mucosal surface than the ileum as well as more numerous and redundant folds and a relative minor distension, which leads to false positives and negatives with MRE in this section^[68]. Similarly, it has been observed that its diagnostic performance when combined with IC and CE is 97.3% vs 57.3% when IC and BFT^[69] are performed, so the use of the BFT in this context is currently controversial in addition to its being rejected due to the radiation which it involves^[70].

As regards inflammation markers, fecal calprotectin (FC) studies inflammatory activity noninvasively and indirectly but does not differentiate the location thereof in the SB or colon^[71]. Some authors have observed a good

correlation with the results of CE with a S of 83%, SP of 100%, PPV of 100% and NPV of 80%^[37]; however, more recent studies have demonstrated that the elevation of C-reactive protein, FC, or a combination of the two are poorly correlated with significant inflammation of the SB^[72]. In general, the Lewis score has demonstrated a good correlation with FC in cases of mild inflammation, so when it is < 100 µg/g, the Lewis score is normal, but it is less useful when the CBF is elevated^[73]. For SCD with a normal IC, a FC of > 100 mg/g may suggest the indication of CE, and a value of approximately 200 µg/g is associated with a diagnostic performance of 65%^[74].

Assessment of the activity and severity of DCD

CE enables the assessment of both the extent and the inflammatory activity in the SI. When CD is suspected based on the presence of anemia, thrombocytosis, weight loss and/or fecal inflammatory markers which are not justified by the findings of the IC or radiology, the performance of CE is indicated in order to look for activity in the SB^[40,46]. In this context, the Lewis score diagnoses CD with a PPV of 82.6%, NPV of 87.9%, S of 82.6% and SP of 87.9% for the diagnosis of CD with respect to the clinical, analytical, radiological, endoscopic and/or histological evaluation^[32]. Endoscopic score systems maintain a good correlation with each other, with CECDAI levels of 3.8 and 5.8 proportional to Lewis scores of 135 and 790 respectively, with the first values for mild activity and the last values for moderate to severe activity^[73]. Recently, other authors have identified a higher CECDAI threshold of 23.5 for severe inflammation, which may be helpful for guiding clinical management^[75]. The use of these indices in the therapeutic algorithm decision, requires prospective studies^[14]; therefore, the findings should currently be seen as complementary to the rest of the panel of diagnostic tests^[66].

Mucosal healing

Achieving deep remission (clinical, biological and mucosal healing) improves the prognosis for CD^[3], with mucosal healing being an objective of treatment^[76]. The various radiological modalities, as opposed to endoscopic modalities, cannot provide direct visualization of the mucosa of the SB; consequently, they have an inherent limitation in the objective assessment of mucosal healing.

Mucosal healing is considered the initial event in the suppression of inflammation of the deeper layers of the intestinal wall^[77] and, as occurs with colonic lesions, this healing is not correlated with the clinical evidence^[78]; therefore, it is necessary to evaluate it endoscopically in order to detect it. In this sense, endoscopic evaluation of the whole intestinal mucosa should be crucial for measuring the treatment response and establishing a treatment strategy.

In the few studies that have focused on mucosal healing of the SB using CE for CD (not fistulizing or pervasive), it has been observed, paradoxically, that ulcers improve one month after immunosuppressive treatment and cankers can take up to 6 mo^[79]. Current

recommendations on the monitoring of mucosal healing indicate first conducting an IC in patients with involvement of the ileum and/or colon; in those with SB involvement that cannot be reached by IC, MRE would probably be the standard test. However, given the modest NPV of MRE to exclude mucosal lesions, CE should be considered if symptoms persist despite normal MRE results, or if there is suspicion of activity^[80].

Currently, there is no agreed definition for mucosal healing through CE. It has been suggested that it could be the resolution of all active inflammatory lesions^[37] or the absence of all visible ulcers (according to the International Organization for the Study of Inflammatory Bowel Diseases)^[81]. In both cases, quantification of inflammatory activity by means of the validated Lewis score and CECDAI index is recommended^[14].

Perianal disease

CE detects SB involvement in 24% of cases involving perianal disease patients with a normal IC, and these findings lead to a change in therapeutic management in all patients. In these cases, the predictors of a positive outcome from the CE are not associated with laboratory abnormalities, family history of IBD or age^[82].

Association with other intestinal diseases

According to the recommendations of the ASGE^[8], there are other indications of CE such as suspected intestinal tumors and malabsorption syndromes, and both can be associated during the progression of DCD.

The relative risk of intestinal tumors presented by IBD in the long term (10-25 years) is low (0.2%-2%), although this is higher than in the general population^[83,84]. According to ECCO's recommendations, CE is recommended for suspected intestinal tumors. In CD with a long-term, pervasive stenotic pattern, the abrupt onset of symptoms after a prolonged remission or with refractory strictures should be suspected to medical treatment^[85].

Moreover, celiac disease and its complications can be associated with DCD. CE has shown lesions consistent with CD in 6% of doubtful cases of celiac disease with negative antibodies and signs of atrophy in the duodenal biopsy^[85].

INDICATIONS OF CE IN POSTSURGICAL RECURRENCE

The management of postsurgical recurrence of DCD by means of endoscopic monitoring and its management is determined by the risk factors among which is extension into the SB^[86,87]. IC is currently the reference technique for evaluating postoperative recurrence, which is measured using the Rutgeerts index^[86,88]. Although the clinical relevance of the findings has not been studied, CE exhibits a S of 62%-76% and a SP of 100% over ileoscopy for this indication^[10]. CE is performed when endoscopy is contraindicated or unsatisfactory^[40], and it is selected with anastomosis that is difficult to access or

when preferred by the patient^[10,15,40,89,90].

It is recommended to perform it six months to one year after surgery depending on the association with other risk factors^[89] in order to identify the recurrence and the proximal lesions not attainable with ileoscopy^[40,53,91]. Some authors have used the Buchmann activity index^[92] to classify lesions, but the use of the Lewis score is currently recommended in the context of clinical trials^[35].

However, prospective studies are lacking in this context for evaluating the prognosis and clinical significance of the results of CE for this indication. Recurrence has only been assessed in one study using CE at one month and six months after surgery, and recurrence in the SB is defined as being when the residual lesions at one month after surgery have progressed after 6 mo, with an increase of 100 points in the Lewis score^[93].

INDICATIONS OF CE IN UNCLASSIFIED COLITIS

Population-based studies have shown that, for up to 10% of adult patients and 30% of children with IBD and the exclusive involvement of the colon, it is difficult to distinguish between CD and ulcerative colitis (UC). This entity is called unclassified or UNC, and in most cases, the final diagnosis is established during the first 8 years of development^[94-96]. In these cases, CE can identify lesions consistent with CD in 17%-70% of the cases^[96], which is better than BFT or enteroclysis. There are no comparative data for ETC or MRE. Similarly, when the CE is normal, a future diagnosis is not excluded^[14], and its repetition can be recommended in the medium term^[10].

Several retrospective studies have suggested that CE produces a definitive diagnosis of CD, has resulted in management changes, or has had a potential impact on prediction of the prognosis with this fact being particularly significant in young patients. In one pediatric study, 50% of UC or UNC were ultimately diagnosed as CD^[97].

THERAPEUTIC IMPACT OF CE IN CD

It has been demonstrated that the extension of CD into the SB and/or its proximal location are two poor prognostic factors and determine therapeutic decisions through early indication of immunosuppression^[6,51,98-100].

The management changes that CE findings prompt are related to the initiation of a new treatment, the change or suspension thereof, or the indication of surgery^[52,101,102]. On a practical level, the impact on management of the disease depends on the reason why CE is indicated. This impact is particularly relevant in the pediatric age group, as CE reclassifies 50% of ulcerative colitis and UNC as CD, as it detects proximal lesions undetected by other techniques; in 78% of these cases, there is a change in the therapeutic decision^[101].

In general, current publications report the diagnostic performance of CE for CD at 60%-85%^[52,103], which gives rise to an overall therapeutic impact of 50% (40%-67%)^[27].

In long-term studies (6 years), this will lead to changes in decision-making based on the indication: 90% of patients when CE is requested for SCD, 88% for UNC and 73% for DCD^[104].

In the case of DCD, therapeutic management is modified in 64% of patients^[52]. In studies involving more than 900 patients with CD^[102], the decision to change the medication is made three months after the CE for 61.6%, and for 39.5%, a new treatment is initiated. Pathologic findings of CE compared with none or minimal findings, resulted in significant differences in treatment modifications (73.2% vs 51.1%, $P = 0.04$), the addition of drugs (58.5% vs 22.2%, $P < 0.01$), and the indication of surgery (21.9% vs 4.4%, $P = 0.01$). Treatment is intensified after CE when activity of the lesions is more severe: In 14.5%, 48% and 87% of patients with Lewis score < 135 , 135-790 and ≥ 790 , respectively^[72].

COMPLICATIONS

The most significant complication of CE, and almost the only one, is retention, which is still very rare with this disease, as the exploration of the entire SB is achieved in 85.4% (from 79% to 90.8%) of the cases^[105]. DCD is considered a risk factor for retention with CE, although the overall figures in long series are low at 2.6% (1.6-3.9) and very similar to other indications^[105]. Currently, when intestinal stenosis is suspected, the recommended approach is to assess the contraindication of CE in a test of intestinal permeability with the degradable capsule Patency (PC) (Given Imaging, Yoqneam, Israel), approved by the FDA in 2006 for this purpose, or to perform radiology depending on its local availability and the experience of the center^[14,106-108]. For pediatric patients, the choice is between the PC and MRE due to the safety of both types of exploration for this age range^[109].

It has been observed that, in most capsule retention cases with CE, radiology was not adequate to suspect its risk^[110]; otherwise, for suspected radiation stenosis (CT or BFT) the retention rate is low (21%). Therefore, it is proposed that radiology be avoided (especially in young patients), unless the permeability test is abnormal^[111]. For some authors, it is a "therapeutic" complication, because it diagnoses stenoses that have gone unnoticed by other techniques and results in a change in patient management^[112]. The treatment of retention depends on the diameter and nature of the stenosis and provides for the wait-and-see approach with monitoring for the expulsion of the capsule and medical or endoscopic treatment if there is not complete obstruction, in which case surgery is indicated^[113]. Most cases are resolved conservatively^[114]. Medical treatment includes the administration of laxatives or corticosteroids depending on the etiology of the retention. Enteroscopy indicates whether to recover the endoscopic capsule, biopsy the stenosis and/or treat with dilation.

The risk of retention in DCD and SCD are not the same. Accordingly, the highest percentage was published in a single retrospective study of 102 patients, with the

risk for DCD being 13% (5.6%-28%), whereas in cases of SCD, the figure dropped to 1.6% (0.2%-10%)^[115], and that was a decade ago, when the PC did not exist. However, a multicenter Japanese study was recently published which shows no difference between retention in DCD (7.4%) and SCD (6.4%)^[116].

Retention in suspected CD

In general, the retention rates with SCD are low and vary from 0% to 5%^[105,112,117-119]. In 22 of the 1000 patients of the series of Li *et al.*^[120] CE was performed for SCD (2.2%), and of those, there were only 3 retentions.

In a retrospective study involving 78 patients with SCD, there were 3 retentions (5%)^[121], and similar data were obtained in the study of Cheon, with retention rates of 5.4% (2/37)^[113].

Retention in diagnosed CD

In patients with DCD, the retention rate oscillates between 1.8% and 13%^[23,102,105,112,113,116,122]. The first publications, such as Cheifetz *et al.*^[115], estimate higher retention figures while in more recent publications, the figures have dropped considerably^[116]. Cotter *et al.*^[99] presented a retention rate of 6% and Dussault *et al.*^[47] rates of 4%. However, in studies with active CD, where mucosal healing is assessed, retentions account for only 1.8%^[123].

Retention with intestinal obstruction in CD

In CD, a rigorous selection of the indication of CE is required due to the risk of retention in patients with known intestinal stenosis^[8,10]. It should be noted that, in the preliminary studies in which tests with the PC were not available, retention rates in this context were 21%^[112]. However, in a more recent study involving 19 patients with active CD in which 43 sequential scans were performed, no retentions were recorded despite the inclusion of patients with multiple stenosis and intestinal surgery^[124]. This study confirms that the PC is an excellent predictor of intestinal permeability with respect to CE for these patients^[14,125]. However, the latest reports indicate that the retention rate is not affected by the selective use of the PC, as the retention rate is 2.3%, which is similar to when it is not performed (1.5%) as well as when the PC is negative (2.1%). When the PC is positive, the retention rate is 11.1%^[126].

CONCLUSION

In summary, CE is a noninvasive technique, which plays a wide-ranging role in CD. Its principal advantages over other diagnostic techniques are the absence of invasiveness and irradiation and the direct study of the mucosa of the entire SB. It enables the early diagnosis of CD due to its ability to detect superficial mucosal lesions, which go unnoticed by radiology or cannot be accessed with IC. These characteristics, along with its excellent level of safety, define it as the best exploratory method for the study of inflammatory activity in the mucosa of

the SI with CD. Its only contraindication is the objective presence of intestinal stenosis.

Its primary use is well defined in the early diagnosis of SCD, the assessment of the extent of DCD and the study of unclassifiable colitis. After ruling out intestinal stenosis, CE is the technique of first resort for patients with SCD who have had negative evaluations with radiology and IC. For patients diagnosed with CD, if cross-sectional imaging tests are normal or non-diagnostic, CE is performed if the result implies a change in patient management.

The systematic use of validated indices for scoring endoscopic activity enables the interpretation of lesions and monitoring of the developmental history of each patient to be standardized. Its use in future prospective studies will enable the definition of the criteria for mucosal healing and postoperative recurrence, which may suggest guidance for treatment. As is the case with other diagnostic tests and current treatments, the involvement of all these applications of CE in changing the natural history of this disease has yet to be established.

REFERENCES

- 1 Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250 [PMID: 12131607]
- 2 Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV, Louis E, Michetti P, Munkholm P, Oresland T, Panés J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lémann M. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis* 2011; **17**: 1415-1422 [PMID: 21560202 DOI: 10.1002/ibd.21506]
- 3 Panaccione R, Hibi T, Peyrin-Biroulet L, Schreiber S. Implementing changes in clinical practice to improve the management of Crohn's disease. *J Crohns Colitis* 2012; **6** Suppl 2: S235-S242 [PMID: 22463930 DOI: 10.1016/S1873-9946(12)60503-0]
- 4 Peyrin-Biroulet L, Loftus EV, Colombel JF, Sandborn WJ. Early Crohn disease: a proposed definition for use in disease-modification trials. *Gut* 2010; **59**: 141-147 [PMID: 20176633 DOI: 10.1136/gut.2009.187120]
- 5 Stange EF, Travis SP, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, Feakins R, Fléjou JF, Herfarth H, Hommes DW, Kupcinskas L, Lakatos PL, Mantzaris GJ, Schreiber S, Villanacci V, Warren BF. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. *J Crohns Colitis* 2008; **2**: 1-23 [PMID: 21172194 DOI: 10.1016/j.crohns.2007.11.001]
- 6 Van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, Ochsenkühn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010; **4**: 7-27 [PMID: 21122488 DOI: 10.1016/j.crohns.2009.12.003]
- 7 Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy* 2007; **39**: 895-909 [PMID: 17968807]
- 8 Early DS, Ben-Menachem T, Decker GA, Evans JA, Fanelli RD, Fisher DA, Fukami N, Hwang JH, Jain R, Jue TL, Khan KM, Malpas PM, Maple JT, Sharaf RS, Dominitz JA, Cash BD. Appropriate use of GI endoscopy. *Gastrointest Endosc* 2012; **75**: 1127-1131 [PMID: 22624807 DOI: 10.1016/j.gie.2012.01.011]
- 9 Fritscher-Ravens A, Scherbakov P, Bufler P, Torroni F, Ruuska T, Nuutinen H, Thomson M, Tabbers M, Milla P. The feasibility of wireless capsule endoscopy in detecting small intestinal pathology in children under the age of 8 years: a multicentre European study. *Gut* 2009; **58**: 1467-1472 [PMID: 19625281 DOI: 10.1136/gut.2009.177774]
- 10 Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, Despott EJ, Fortun PF, Heuschkel R, Kammermeier J, Leighton JA, Mantzaris GJ, Moussata D, Lo S, Paulsen V, Panés J, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger JM, Yamamoto H, Travis S, Colombel JF, Van Gossum A. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009; **41**: 618-637 [PMID: 19588292 DOI: 10.1055/s-0029-1214790]
- 11 Ladas SD, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; **42**: 220-227 [PMID: 20195992 DOI: 10.1055/s-0029-1243968]
- 12 Doherty GA, Moss AC, Cheifetz AS. Capsule endoscopy for small-bowel evaluation in Crohn's disease. *Gastrointest Endosc* 2011; **74**: 167-175 [PMID: 21497806 DOI: 10.1016/j.gie.2011.01.067]
- 13 Lucendo AJ, Guagnozzi D. Small bowel video capsule endoscopy in Crohn's disease: What have we learned in the last ten years? *World J Gastrointest Endosc* 2011; **3**: 23-29 [PMID: 21403813 DOI: 10.4253/wjge.v3.i2.23]
- 14 Annesse V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kieblisch R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: 982-1018 [PMID: 24184171 DOI: 10.1016/j.crohns.2013.09.016]
- 15 Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: 25826168 DOI: 10.1055/s-0034-1391855]
- 16 Luján-Sanchis M, Sanchis-Artero L, Suárez-Callol P, Medina-Chuliá E. Indications of capsule endoscopy in Crohn's disease. *Rev Esp Enferm Dig* 2014; **106**: 37-44 [PMID: 24689714]
- 17 Wang A, Banerjee S, Barth BA, Bhat YM, Chauhan S, Gottlieb KT, Konda V, Maple JT, Murad F, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Rodriguez SA. Wireless capsule endoscopy. *Gastrointest Endosc* 2013; **78**: 805-815 [PMID: 24119509 DOI: 10.1016/j.gie.2013.06.026]
- 18 Leighton JA, Shen B, Baron TH, Adler DG, Davila R, Egan JV, Faigel DO, Gan SI, Hirota WK, Lichtenstein D, Qureshi WA, Rajan E, Zuckerman MJ, VanGuilder T, Fanelli RD. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointest Endosc* 2006; **63**: 558-565 [PMID: 16564852]
- 19 Rey JF, Ladas S, Alhassani A, Kuznetsov K. European Society of Gastrointestinal Endoscopy (ESGE). Video capsule endoscopy: update to guidelines (May 2006). *Endoscopy* 2006; **38**: 1047-1053 [PMID: 17058174]
- 20 Sidhu R, Sanders DS, Morris AJ, McAlindon ME. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. *Gut* 2008; **57**: 125-136 [PMID: 18094205]
- 21 Pohl J, Delvaux M, Ell C, Gay G, May A, Mulder CJ, Pennazio M, Perez-Cuadrado E, Vilmann P. European Society of Gastrointestinal

- Endoscopy (ESGE) Guidelines: flexible enteroscopy for diagnosis and treatment of small-bowel diseases. *Endoscopy* 2008; **40**: 609-618 [PMID: 18612948 DOI: 10.1055/s-2008-1077371]
- 22 **Delvaux M**, Friedman S, Keuchel M, Hagenmüller F, Weinstein M, Cave D, de Franchis R, Gay G, Korman LY. Structured terminology for capsule endoscopy: results of retrospective testing and validation in 766 small-bowel investigations. *Endoscopy* 2005; **37**: 945-950 [PMID: 16189766]
 - 23 **Mow WS**, Lo SK, Targan SR, Dubinsky MC, Treyzon L, Abreu-Martin MT, Papadakis KA, Vasilias EA. Initial experience with wireless capsule endoscopy in the diagnosis and management of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2004; **2**: 31-40 [PMID: 15017630]
 - 24 **Hall B**, Holleran G, Costigan D, McNamara D. Capsule endoscopy: High negative predictive value in the long term despite a low diagnostic yield in patients with suspected Crohn's disease. *United European Gastroenterol J* 2013; **1**: 461-466 [PMID: 24917998 DOI: 10.1177/2050640613508551]
 - 25 **Voderholzer WA**, Beinhörl J, Rogalla P, Murr S, Schachschal G, Lochs H, Ortner MA. Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut* 2005; **54**: 369-373 [PMID: 15710985]
 - 26 **Fidder HH**, Nadler M, Lahat A, Lahav M, Bardan E, Avidan B, Bar-Meir S. The utility of capsule endoscopy in the diagnosis of Crohn's disease based on patient's symptoms. *J Clin Gastroenterol* 2007; **41**: 384-387 [PMID: 17413607]
 - 27 **Shergill AK**, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Foley K, Hwang JH, Jue TL, Khashab MA, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD, DeWitt JM. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc* 2015; **81**: 1101-1121.e1-e13 [PMID: 25800660 DOI: 10.1016/j.gie.2014.10.030]
 - 28 **Niv Y**, Ilani S, Levi Z, Hershkowitz M, Niv E, Fireman Z, O'Donnel S, O'Morain C, Eliakim R, Scapa E, Kalantzis N, Kalantzis C, Apostolopoulos P, Gal E. Validation of the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score): a multicenter prospective study. *Endoscopy* 2012; **44**: 21-26 [PMID: 22125196 DOI: 10.1055/s-0031-1291385]
 - 29 **Cotter J**, Dias de Castro F, Magalhães J, Moreira MJ, Rosa B. Validation of the Lewis score for the evaluation of small-bowel Crohn's disease activity. *Endoscopy* 2015; **47**: 330-335 [PMID: 25412092 DOI: 10.1055/s-0034-1390894]
 - 30 **Gal E**, Geller A, Fraser G, Levi Z, Niv Y. Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). *Dig Dis Sci* 2008; **53**: 1933-1937 [PMID: 18034304]
 - 31 **Gralnek IM**, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008; **27**: 146-154 [PMID: 17956598]
 - 32 **Rosa B**, Moreira MJ, Rebelo A, Cotter J. Lewis Score: a useful clinical tool for patients with suspected Crohn's Disease submitted to capsule endoscopy. *J Crohns Colitis* 2012; **6**: 692-697 [PMID: 22398099 DOI: 10.1016/j.crohns.2011.12.002]
 - 33 **Lewis JR**, Pashinsky Y, Tindley A, Lewis BS. Capsule endoscopy in healthy individuals. *Gastroenterology* 2012; **142**: 52-53 [DOI: 10.1016/S0016-5085(12)60204-2]
 - 34 **Monteiro S**, Boal Carvalho P, Dias de Castro F, Magalhães J, Machado F, Moreira MJ, Rosa B, Cotter J. Capsule Endoscopy: Diagnostic Accuracy of Lewis Score in Patients with Suspected Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 2241-2246 [PMID: 26197449 DOI: 10.1097/MIB.0000000000000517]
 - 35 **Rosa B**, Pinho R, Mão de Ferro S, Almeida N, Cotter J, Mascarenhas M. Endoscopic Scores for Evaluation of Crohn's Disease Activity at Small Bowel Capsule Endoscopy: General Principles and Current Applications. *GE Port J Gastroenterol* 2016; **23**: 36-41 [DOI: 10.1016/j.jgge.2015.08.004]
 - 36 **Mehdizadeh S**, Chen GC, Barkodar L, Enayati PJ, Pirouz S, Yadegari M, Ippoliti A, Vasilias EA, Lo SK, Papadakis KA. Capsule endoscopy in patients with Crohn's disease: diagnostic yield and safety. *Gastrointest Endosc* 2010; **71**: 121-127 [PMID: 19863957 DOI: 10.1016/j.gie.2009.06.034]
 - 37 **De Cruz P**, Kamm MA, Prideaux L, Allen PB, Moore G. Mucosal healing in Crohn's disease: a systematic review. *Inflamm Bowel Dis* 2013; **19**: 429-444 [PMID: 22539420 DOI: 10.1002/ibd.22977]
 - 38 **Aggarwal V**, Day SD, Connor SJ, Leach ST, Brown GJ, Singh R, Friedman A, Grimm MC, Craig PI. Multicenter Capsule Endoscopy Study of Small Bowel Crohn's Disease Patients in Clinical Remission: Long-Term Follow-up and Correlation With Faecal Biomarkers and Clinical Outcome. *Gastroenterology* 2012; **142** suppl 1: 169 [DOI: 10.1016/S0016-5085(12)60636-2]
 - 39 **Park SJ**, Kim WH. A look into the small bowel in Crohn's disease. *Clin Endosc* 2012; **45**: 263-268 [PMID: 22977814 DOI: 10.5946/ce.2012.45.3.263]
 - 40 **Papay P**, Ignjatovic A, Karmiris K, Amarante H, Milheller P, Feagan B, D'Haens G, Marteau P, Reinisch W, Sturm A, Steinwurz F, Egan L, Panés J, Louis E, Colombel JF, Panaccione R. Optimising monitoring in the management of Crohn's disease: a physician's perspective. *J Crohns Colitis* 2013; **7**: 653-669 [PMID: 23562672 DOI: 10.1016/j.crohns.2013.02.005]
 - 41 **Jensen MD**, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. *Clin Gastroenterol Hepatol* 2011; **9**: 124-129 [PMID: 21056692 DOI: 10.1016/j.cgh.2010.10.019]
 - 42 **Costamagna G**, Shah SK, Riccioni ME, Foschia F, Mutignani M, Perri V, Vecchioli A, Brizi MG, Piccicocchi A, Marano P. A prospective trial comparing small bowel radiographs and video capsule endoscopy for suspected small bowel disease. *Gastroenterology* 2002; **123**: 999-1005 [PMID: 12360460 DOI: 10.1053/gast.2002.35988]
 - 43 **Dubcenco E**, Jeejeebhoy KN, Petroniene R, Tang SJ, Zalev AH, Gardiner GW, Baker JP. Capsule endoscopy findings in patients with established and suspected small-bowel Crohn's disease: correlation with radiologic, endoscopic, and histologic findings. *Gastrointest Endosc* 2005; **62**: 538-544 [PMID: 16185968 DOI: 10.1016/j.gie.2005.06.026]
 - 44 **Triester SL**, Leighton JA, Leontiadis GI, Gurudu SR, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol* 2006; **101**: 954-964 [PMID: 16696781 DOI: 10.1111/j.1572-0241.2006.00506.x]
 - 45 **Dionisio PM**, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010; **105**: 1240-1248; quiz 1249 [PMID: 20029412]
 - 46 **de Melo SW**, Di Palma JA. The role of capsule endoscopy in evaluating inflammatory bowel disease. *Gastroenterol Clin North Am* 2012; **41**: 315-323 [PMID: 22500520 DOI: 10.1016/j.gtc.2012.01.005]
 - 47 **Dussault C**, Gower-Rousseau C, Salleron J, Vernier-Massouille G, Branche J, Colombel JF, Maunoury V. Small bowel capsule endoscopy for management of Crohn's disease: a retrospective tertiary care centre experience. *Dig Liver Dis* 2013; **45**: 558-561 [PMID: 23238033 DOI: 10.1016/j.dld.2012.11.004]
 - 48 **De Bona M**, Bellumat A, Cian E, Valiante F, Moschini A, De Boni M. Capsule endoscopy findings in patients with suspected Crohn's disease and biochemical markers of inflammation. *Dig Liver Dis* 2006; **38**: 331-335 [PMID: 16569524 DOI: 10.1016/j.dld.2006.02.004]
 - 49 **Valle J**, Alcántara M, Pérez-Grueso MJ, Navajas J, Muñoz-Rosas C, Legaz ML, Cuena R, Carrobbles JM. Clinical features of patients with negative results from traditional diagnostic work-up and Crohn's disease findings from capsule endoscopy. *J Clin Gastroenterol* 2006; **40**: 692-696 [PMID: 16940880 DOI: 10.1097/00004836-200609000-00006]

- 50 **Shim KN**, Kim YS, Kim KJ, Kim YH, Kim TI, Do JH, Ryu JK, Moon JS, Park SH, Hee Park C, Lee KM, Lee IS, Chun HJ, Jung IS, Choi MG. Abdominal pain accompanied by weight loss may increase the diagnostic yield of capsule endoscopy: a Korean multicenter study. *Scand J Gastroenterol* 2006; **41**: 983-988 [PMID: 16803698 DOI: 10.1080/00365520600548974]
- 51 **Flamant M**, Trang C, Maillard O, Sacher-Huvelin S, Le Rhun M, Galmiche JP, Bourreille A. The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 1390-1396 [PMID: 23552764 DOI: 10.1097/MIB.0b013e31828133c1]
- 52 **Lorenzo-Zúñiga V**, de Vega VM, Domènech E, Cabré E, Mañosa M, Boix J. Impact of capsule endoscopy findings in the management of Crohn's Disease. *Dig Dis Sci* 2010; **55**: 411-414 [PMID: 19255845 DOI: 10.1007/s10620-009-0758-8]
- 53 **Bourreille A**, Jarry M, D'Halluin PN, Ben-Soussan E, Maunoury V, Bulois P, Sacher-Huvelin S, Vahedy K, Lerebours E, Heresbach D, Bretagne JF, Colombel JF, Galmiche JP. Wireless capsule endoscopy versus ileocolonoscopy for the diagnosis of postoperative recurrence of Crohn's disease: a prospective study. *Gut* 2006; **55**: 978-983 [PMID: 16401689 DOI: 10.1136/gut.2005.081851]
- 54 **Baumgart DC**, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380**: 1590-1605 [PMID: 22914295 DOI: 10.1016/S0140-6736(12)60026-9]
- 55 **Petruzzello C**, Onali S, Calabrese E, Zorzi F, Ascolani M, Condino G, Lolli E, Naccarato P, Pallone F, Biancone L. Wireless capsule endoscopy and proximal small bowel lesions in Crohn's disease. *World J Gastroenterol* 2010; **16**: 3299-3304 [PMID: 20614486 DOI: 10.3748/wjg.v16.i26.3299]
- 56 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]
- 57 **Pérez-Cuadrado Martínez E**, Pérez-Cuadrado Robles E. Capsule endoscopy and deep enteroscopy. *Gastrointest Endosc* 2014; **80**: 396-399 [PMID: 25127943 DOI: 10.1016/j.gie.2014.07.006]
- 58 **Hall B**, Holleran G, McNamara D. Small bowel Crohn's disease: an emerging disease phenotype? *Dig Dis* 2015; **33**: 42-51 [PMID: 25531496 DOI: 10.1159/000366047]
- 59 **de Bie CI**, Paerregaard A, Kolacek S, Ruemmele FM, Koletzko S, Fell JM, Escher JC. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUOKIDS Registry. *Inflamm Bowel Dis* 2013; **19**: 378-385 [PMID: 22573581 DOI: 10.1002/ibd.23008]
- 60 **Lazarev M**, Huang C, Bitton A, Cho JH, Duerr RH, McGovern DP, Proctor DD, Regueiro M, Rioux JD, Schumm PP, Taylor KD, Silverberg MS, Steinhart AH, Hutfless S, Brant SR. Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. *Am J Gastroenterol* 2013; **108**: 106-112 [PMID: 23229423 DOI: 10.1038/ajg.2012.389]
- 61 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]
- 62 **Molinié F**, Gower-Rousseau C, Yzet T, Merle V, Grandbastien B, Marti R, Lerebours E, Dupas JL, Colombel JF, Salomez JL, Cortot A. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988-1999). *Gut* 2004; **53**: 843-848 [PMID: 15138211 DOI: 10.1136/gut.2003.025346]
- 63 **Lashner B**. Clinical features, laboratory findings, and course of Crohn's disease. In: Kirsner JV, editor. *Inflamm Bowel Dis*. 5th ed. Philadelphia: Saunders, 2000: 305-314
- 64 **Rameshshanker R**, Arebi N. Endoscopy in inflammatory bowel disease when and why. *World J Gastrointest Endosc* 2012; **4**: 201-211 [PMID: 22720120 DOI: 10.4253/wjge.v4.i6.201]
- 65 **Yang DH**, Keum B, Jeon YT. Capsule Endoscopy for Crohn's Disease: Current Status of Diagnosis and Management. *Gastroenterol Res Pract* 2016; **2016**: 8236367 [PMID: 26819612 DOI: 10.1155/2016/8236367]
- 66 **Gurudu SR**, Leighton JA. Correlation of two capsule endoscopy scoring systems with fecal calprotectin: does it really matter? *Dig Dis Sci* 2012; **57**: 827-829 [PMID: 22322365 DOI: 10.1007/s10620-012-2079-6]
- 67 **Kovanlikaya A**, Watson E, Hayward J, Beneck D, Sockolow R, Solomon A, Christos P, Brill PW. Magnetic resonance enterography and wireless capsule endoscopy in the evaluation of patients with inflammatory bowel disease. *Clin Imaging* 2013; **37**: 77-82 [PMID: 23206611 DOI: 10.1016/j.clinimag.2012.03.011]
- 68 **Lee SM**, Kim WS, Choi YH. Pediatric Magnetic Resonance Enterography: Focused on Crohn's Disease. *Pediatr Gastroenterol Hepatol Nutr* 2015; **18**: 149-159 [PMID: 26473134 DOI: 10.5223/pghn.2015.18.3.149]
- 69 **Leighton JA**, Gralnek IM, Cohen SA, Toth E, Cave DR, Wolf DC, Mullin G, Ketover S, Legnani P, Seidman E, Crowell M, Bergwek A, PeledR, Eliakim R. Capsule endoscopy is superior to small-bowel follow-through and equivalent to ileocolonoscopy in suspected Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 609-15 [PMID: 24075891 DOI: 10.1016/j.cgh.2013.09.028]
- 70 **Cave D**, Legnani P, de Franchis R, Lewis BS. ICCE consensus for capsule retention. *Endoscopy* 2005; **37**: 1065-1067 [PMID: 16189792 DOI: 10.1055/s-2005-870264]
- 71 **Jensen MD**, Kjeldsen J, Nathan T. Fecal calprotectin is equally sensitive in Crohn's disease affecting the small bowel and colon. *Scand J Gastroenterol* 2011; **46**: 694-700 [PMID: 21456899 DOI: 10.3109/00365521.2011.560680]
- 72 **Kopylov U**, Nemeth A, Koulaouzis A, Makins R, Wild G, Afif W, Bitton A, Johansson GW, Bessissow T, Eliakim R, Toth E, Seidman EG. Small bowel capsule endoscopy in the management of established Crohn's disease: clinical impact, safety, and correlation with inflammatory biomarkers. *Inflamm Bowel Dis* 2015; **21**: 93-100 [PMID: 25517597 DOI: 10.1097/MIB.0000000000000255]
- 73 **Koulaouzis A**, Douglas S, Plevris JN. Lewis score correlates more closely with fecal calprotectin than Capsule Endoscopy Crohn's Disease Activity Index. *Dig Dis Sci* 2012; **57**: 987-993 [PMID: 22057284 DOI: 10.1007/s10620-011-1956-8]
- 74 **Koulaouzis A**, Douglas S, Rogers MA, Arnott ID, Plevris JN. Fecal calprotectin: a selection tool for small bowel capsule endoscopy in suspected IBD with prior negative bi-directional endoscopy. *Scand J Gastroenterol* 2011; **46**: 561-566 [PMID: 21269246 DOI: 10.3109/00365521.2011.551835]
- 75 **Holleran G**, Hall B, Hussey M, Thornton O, Dobson M, McNamara D. How accurate are capsule endoscopy scoring systems in Crohn's disease. 8th Congress ECCO; 2013 Feb 14; Vienna, Austria. Abstract 233
- 76 **Bouguen G**, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, Hanauer SB, Sandborn WJ. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol* 2015; **13**: 1042-1050.e2 [PMID: 24036054 DOI: 10.1016/j.cgh.2013.09.006]
- 77 **Laughlin DM**, Friedmacher F, Puri P. Total colonic aganglionosis: a systematic review and meta-analysis of long-term clinical outcome. *Pediatr Surg Int* 2012; **28**: 773-779 [PMID: 22842648 DOI: 10.1136/gutjnl-2012-302830]
- 78 **Eftymiou A**, Viazis N, Mantzaris G, Papadimitriou N, Tzourmakliotis D, Raptis S, Karamanolis DG. Does clinical response correlate with mucosal healing in patients with Crohn's disease of the small bowel? A prospective, case-series study using wireless capsule endoscopy. *Inflamm Bowel Dis* 2008; **14**: 1542-1547 [PMID: 18521929 DOI: 10.1002/ibd.20509]
- 79 **Tsibouris P**, Periklis A, Chrissostomos K, Antonios Z, Panagiota M, Erasmia V, Georgios A. When Crohn's disease is in remission, more patients complete capsule endoscopy study but less lesions are identified. *Saudi J Gastroenterol* 2013; **19**: 63-68 [PMID: 23481131 DOI: 10.4103/1319-3767.108468]
- 80 **Dulai PS**, Levesque BG, Feagan BG, D'Haens G, Sandborn WJ.

- Assessment of mucosal healing in inflammatory bowel disease: review. *Gastrointest Endosc* 2015; **82**: 246-255 [PMID: 26005012 DOI: 10.1016/j.gie.2015.03.1974]
- 81 **D'Haens GR**, Fedorak R, Lémann M, Feagan BG, Kamm MA, Cosnes J, Rutgeerts PJ, Marteau P, Travis S, Schölmerich J, Hanauer S, Sandborn WJ. Endpoints for clinical trials evaluating disease modification and structural damage in adults with Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1599-1604 [PMID: 19653291 DOI: 10.1002/ibd.21034]
 - 82 **Adler SN**, Yoav M, Eitan S, Yehuda C, Eliakim R. Does capsule endoscopy have an added value in patients with perianal disease and a negative work up for Crohn's disease? *World J Gastrointest Endosc* 2012; **4**: 185-188 [PMID: 22624070 DOI: 10.4253/wjge.v4.i5.185]
 - 83 **Jess T**, Gamborg M, Matzen P, Munkholm P, Sørensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005; **100**: 2724-2729 [PMID: 16393226 DOI: 10.1111/j.1572-0241.2005.00287]
 - 84 **Canavan C**, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1097-1104 [PMID: 16611269]
 - 85 **Kurien M**, Evans KE, Aziz I, Sidhu R, Drew K, Rogers TL, McAlindon ME, Sanders DS. Capsule endoscopy in adult celiac disease: a potential role in equivocal cases of celiac disease? *Gastrointest Endosc* 2013; **77**: 227-232 [PMID: 23200728]
 - 86 **Buisson A**, Chevaux JB, Bommelaer G, Peyrin-Biroulet L. Diagnosis, prevention and treatment of postoperative Crohn's disease recurrence. *Dig Liver Dis* 2012; **44**: 453-460 [PMID: 22265329 DOI: 10.1016/j.dld.2011.12.018]
 - 87 **De Cruz P**, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, Liew D, Prideaux L, Lawrance IC, Andrews JM, Bampton PA, Gibson PR, Sparrow M, Leong RW, Florin TH, Gearry RB, Radford-Smith G, Macrae FA, Debinski H, Selby W, Kronborg I, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Desmond PV. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; **385**: 1406-1417 [PMID: 25542620]
 - 88 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963
 - 89 **De Cruz P**, Kamm MA, Prideaux L, Allen PB, Desmond PV. Postoperative recurrent luminal Crohn's disease: a systematic review. *Inflamm Bowel Dis* 2012; **18**: 758-777 [PMID: 21830279 DOI: 10.1002/ibd.21825]
 - 90 **Goenka MK**, Majumder S, Goenka U. Capsule endoscopy: Present status and future expectation. *World J Gastroenterol* 2014; **20**: 10024-10037 [PMID: 25110430 DOI: 10.3748/wjg.v20.i29.10024]
 - 91 **Pons Beltrán V**, Nos P, Bastida G, Beltrán B, Argüello L, Aguas M, Rubin A, Pertejo V, Sala T. Evaluation of postsurgical recurrence in Crohn's disease: a new indication for capsule endoscopy? *Gastrointest Endosc* 2007; **66**: 533-540 [PMID: 17725942 DOI: 10.1016/j.gie.2006.12.059]
 - 92 **Buchman AL**, Miller FH, Wallin A, Chowdhry AA, Ahn C. Videocapsule endoscopy versus barium contrast studies for the diagnosis of Crohn's disease recurrence involving the small intestine. *Am J Gastroenterol* 2004; **99**: 2171-2177 [PMID: 15554999 DOI: 10.1111/j.1572-0241.2004.40253]
 - 93 **Kono T**, Hida N, Nogami K, Iimuro M, Ohda Y, Yokoyama Y, Kamikozuru K, Tozawa K, Kawai M, Ogawa T, Hori K, Ikeuchi H, Miwa H, Nakamura S, Matsumoto T. Prospective postsurgical capsule endoscopy in patients with Crohn's disease. *World J Gastrointest Endosc* 2014; **6**: 88-98 [PMID: 24634713 DOI: 10.4253/wjge.v6.i3.88]
 - 94 **Vind I**, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, Bak Andersen I, Wewer V, Nørregaard P, Moesgaard F, Bendtsen F, Munkholm P. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; **101**: 1274-1282 [PMID: 16771949 DOI: 10.1111/j.1572-0241.2006.00552]
 - 95 **Stewénus J**, Adnerhill I, Ekelund G, Florén CH, Fork FT, Janzon L, Lindström C, Mars I, Nyman M, Rosengren JE. Ulcerative colitis and indeterminate colitis in the city of Malmö, Sweden. A 25-year incidence study. *Scand J Gastroenterol* 1995; **30**: 38-43 [PMID: 7701248]
 - 96 **Mehdizadeh S**, Chen G, Enayati PJ, Cheng DW, Han NJ, Shaye OA, Ippoliti A, Vasilias EA, Lo SK, Papadakis KA. Diagnostic yield of capsule endoscopy in ulcerative colitis and inflammatory bowel disease of unclassified type (IBDU). *Endoscopy* 2008; **40**: 30-35 [PMID: 18058654 DOI: 10.1055/s-2007-995359]
 - 97 **Min SB**, Le-Carlson M, Singh N, Nylund CM, Gebbia J, Haas K, Lo S, Mann N, Melmed GY, Rabizadeh S, Dubinsky MC. Video capsule endoscopy impacts decision making in pediatric IBD: a single tertiary care center experience. *Inflamm Bowel Dis* 2013; **19**: 2139-2145 [PMID: 23867872 DOI: 10.1097/MIB.0b013e31829a749c]
 - 98 **Park SK**, Yang SK, Park SH, Kim JW, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Yu CS, Kim JH. Long-term prognosis of the jejunal involvement of Crohn's disease. *J Clin Gastroenterol* 2013; **47**: 400-408 [PMID: 23269310 DOI: 10.1097/MCG.0b013e3182705f9e]
 - 99 **Cotter J**, Dias de Castro F, Moreira MJ, Rosa B. Tailoring Crohn's disease treatment: the impact of small bowel capsule endoscopy. *J Crohns Colitis* 2014; **8**: 1610-1615 [PMID: 24631311 DOI: 10.1016/j.crohns.2014.02.018]
 - 100 **Dias de Castro F**, Boal Carvalho P, Monteiro S, Rosa B, Firmino-Machado J, Moreira MJ, Cotter J. Lewis Score--Prognostic Value in Patients with Isolated Small Bowel Crohn's Disease. *J Crohns Colitis* 2015; **9**: 1146-1151 [PMID: 26377028 DOI: 10.1093/ecco-jcc/jjv166]
 - 101 **Gralnek IM**, Cohen SA, Ephrath H, Napier A, Gobin T, Sherrod O, Lewis J. Small bowel capsule endoscopy impacts diagnosis and management of pediatric inflammatory bowel disease: a prospective study. *Dig Dis Sci* 2012; **57**: 465-471 [PMID: 21901253 DOI: 10.1007/s10620-011-1894-5]
 - 102 **Long MD**, Barnes E, Isaacs K, Morgan D, Herfarth HH. Impact of capsule endoscopy on management of inflammatory bowel disease: a single tertiary care center experience. *Inflamm Bowel Dis* 2011; **17**: 1855-1862 [PMID: 21830264 DOI: 10.1002/ibd.21571]
 - 103 **Kalla R**, McAlindon ME, Drew K, Sidhu R. Impact of capsule endoscopy on management in patients with established Crohn's disease-experience from a single tertiary centre. *Gut* 2011; **60**: A216-A217 [DOI: 10.1136/gut.2011.239301.457]
 - 104 **Kalla R**, McAlindon ME, Drew K, Sidhu R. Clinical utility of capsule endoscopy in patients with Crohn's disease and inflammatory bowel disease unclassified. *Eur J Gastroenterol Hepatol* 2013; **25**: 706-713 [PMID: 23325280 DOI: 10.1097/MEG.0b013e3182835ddb85]
 - 105 **Liao Z**, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010; **71**: 280-286 [PMID: 20152309 DOI: 10.1016/j.gie.2009.09.031]
 - 106 **Herrerias JM**, Leighton JA, Costamagna G, Infantolino A, Eliakim R, Fischer D, Rubin DT, Manten HD, Scapa E, Morgan DR, Bergwerk AJ, Koslowsky B, Adler SN. Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. *Gastrointest Endosc* 2008; **67**: 902-909 [PMID: 18355824 DOI: 10.1016/j.gie.2007.10.063]
 - 107 **Saurin JC**, Maunoury V, Lapalus MG, Cellier C, Delvaux M, Favre O, Gay G, Heresbach D. [International consensus in Paris, 2006, on the indications and use of the endoscopic videocapsule test. Report of the SFED Capsule Commission]. *Gastroenterol Clin Biol* 2007; **31**: 798-805 [PMID: 18166856]
 - 108 **Postgate AJ**, Burling D, Gupta A, Fitzpatrick A, Fraser C. Safety, reliability and limitations of the given patency capsule in patients at risk of capsule retention: a 3-year technical review. *Dig Dis Sci* 2008; **53**: 2732-2738 [PMID: 18320313 DOI: 10.1007/s10620-008-0210-5]

- 109 **Nuutinen H**, Kolho KL, Salminen P, Rintala R, Koskenpato J, Koivusalo A, Sipponen T, Färkkilä M. Capsule endoscopy in pediatric patients: technique and results in our first 100 consecutive children. *Scand J Gastroenterol* 2011; **46**: 1138-1143 [PMID: 21615227 DOI: 10.3109/00365521.2011.584900]
- 110 **Rondonotti E**, Herreras JM, Pennazio M, Caunedo A, Mascarenhas-Saraiva M, de Franchis R. Complications, limitations, and failures of capsule endoscopy: a review of 733 cases. *Gastrointest Endosc* 2005; **62**: 712-716; quiz 752, 754 [PMID: 16246685]
- 111 **Leighton JA**, Legnani P, Seidman EG. Role of capsule endoscopy in inflammatory bowel disease: where we are and where we are going. *Inflamm Bowel Dis* 2007; **13**: 331-337 [PMID: 17206673]
- 112 **Cheifetz AS**, Lewis BS. Capsule endoscopy retention: is it a complication? *J Clin Gastroenterol* 2006; **40**: 688-691 [PMID: 16940879]
- 113 **Cheon JH**, Kim YS, Lee IS, Chang DK, Ryu JK, Lee KJ, Moon JS, Park CH, Kim JO, Shim KN, Choi CH, Cheung DY, Jang BI, Seo GS, Chun HJ, Choi MG. Can we predict spontaneous capsule passage after retention? A nationwide study to evaluate the incidence and clinical outcomes of capsule retention. *Endoscopy* 2007; **39**: 1046-1052 [PMID: 18072054]
- 114 **Richards J**, Wass A. Small bowel obstruction after a capsule enteroscopy. *BMJ Case Rep* 2013; **2013**: pii: bcr2013008606 [PMID: 23429030 DOI: 10.1136/bcr-2013-008606]
- 115 **Cheifetz AS**, Kornbluth AA, Legnani P, Schmelkin I, Brown A, Lichtiger S, Lewis BS. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. *Am J Gastroenterol* 2006; **101**: 2218-2222 [PMID: 16848804]
- 116 **Esaki M**, Matsumoto T, Watanabe K, Arakawa T, Naito Y, Matsuura M, Nakase H, Hibi T, Matsumoto T, Nouda S, Higuchi K, Ohmiya N, Goto H, Kurokawa S, Motoya S, Watanabe M. Use of capsule endoscopy in patients with Crohn's disease in Japan: a multicenter survey. *J Gastroenterol Hepatol* 2014; **29**: 96-101 [PMID: 24354993 DOI: 10.1111/jgh.12411]
- 117 **Cheraskin E**, Ringsdorf WM, Medford FH. Letter: Relationship of fatigue to smoking. *South Med J* 1976; **69**: 522 [PMID: 1265525]
- 118 **Fireman Z**, Mahajna E, Broide E, Shapiro M, Fich L, Sternberg A, Kopelman Y, Scapa E. Diagnosing small bowel Crohn's disease with wireless capsule endoscopy. *Gut* 2003; **52**: 390-392 [PMID: 12584221]
- 119 **Herreras JM**, Caunedo A, Rodríguez-Téllez M, Pellicer F, Herreras JM. Capsule endoscopy in patients with suspected Crohn's disease and negative endoscopy. *Endoscopy* 2003; **35**: 564-568 [PMID: 12822090]
- 120 **Li F**, Gurudu SR, De Petris G, Sharma VK, Shiff AD, Heigh RI, Fleischer DE, Post J, Erickson P, Leighton JA. Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. *Gastrointest Endosc* 2008; **68**: 174-180 [PMID: 18513723 DOI: 10.1016/j.gie.2008.02.037]
- 121 **Figueiredo P**, Almeida N, Lopes S, Duque G, Freire P, Lérias C, Gouveia H, Sofia C. Small-bowel capsule endoscopy in patients with suspected Crohn's disease-diagnostic value and complications. *Diagn Ther Endosc* 2010; **2010**: pii: 101284 [PMID: 20811612 DOI: 10.1155/2010/101284]
- 122 **Lewis B**. How to prevent endoscopic capsule retention. *Endoscopy* 2005; **37**: 852-856 [PMID: 16116537]
- 123 **Hall B**, Holleran G, Chin JL, Smith S, Ryan B, Mahmud N, McNamara D. A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. *J Crohns Colitis* 2014; **8**: 1601-1609 [PMID: 25257546 DOI: 10.1016/j.crohns.2014.09.005]
- 124 **Niv E**, Fishman S, Kachman H, Arnon R, Dotan I. Sequential capsule endoscopy of the small bowel for follow-up of patients with known Crohn's disease. *J Crohns Colitis* 2014; **8**: 1616-1623 [PMID: 24666976 DOI: 10.1016/j.crohns.2014.03.003]
- 125 **Spada C**, Riccioni ME, Costamagna G. Patients with known small bowel stricture or with symptoms of small bowel obstruction secondary to Crohn's disease should not perform video capsule endoscopy without being previously tested for small bowel patency. *Am J Gastroenterol* 2007; **102**: 1542-1543; author reply 1543-1544 [PMID: 17593167]
- 126 **Nemeth A**, Kopylov U, Koulaouzidis A, Wurm Johansson G, Thorlacius H, Amre D, Eliakim R, Seidman EG, Toth E. Use of patency capsule in patients with established Crohn's disease. *Endoscopy* 2016; **48**: 373-379 [PMID: 26561918 DOI: 10.1055/s-0034-139356]
- 127 **Van de Bruaene C**, De Looze D, Hindryckx P. Small bowel capsule endoscopy: Where are we after almost 15 years of use? *World J Gastrointest Endosc* 2015; **7**: 13-36 [PMID: 25610531 DOI: 10.4253/wjge.v7.i1.13]

P- Reviewer: Actis GC, Akyuz F, Koulaouzidis A, Sipahi AM

S- Editor: Qiu S **L- Editor:** A **E- Editor:** Li D



Blood thinners and gastrointestinal endoscopy

Monjur Ahmed

Monjur Ahmed, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Thomas Jefferson University, Philadelphia, PA 19107, United States

Author contributions: Ahmed M solely contributed to this work.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Monjur Ahmed, MD, FRCP, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Thomas Jefferson University, 132 South 10th Street, Suite 565, Main Building, Philadelphia, PA 19107, United States. monjur.ahmed@jefferson.edu
Telephone: +1-215-9521493
Fax: +1-215-7551850

Received: March 25, 2016

Peer-review started: March 25, 2016

First decision: May 17, 2016

Revised: June 8, 2016

Accepted: July 20, 2016

Article in press: July 22, 2016

Published online: September 16, 2016

prior to endoscopic procedures. Gastrointestinal bleeding or thromboembolism can occur in this category of patients in the periendoscopic period. To better manage these patients, endoscopists should have a clear concept about the various blood thinners in the market. Patients' risk of thromboembolism off anticoagulation, and the risk of bleeding from endoscopic procedures should be assessed prior to endoscopy. The endoscopic procedure should be done when it is safe to do it.

Key words: Acute coronary syndrome; Gastrointestinal bleeding and endoscopy; Blood thinners; Antiplatelet agents and endoscopy; Gastrointestinal bleeding and endoscopy; Anticoagulation bridge before endoscopy; Anticoagulants and endoscopy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: While patients on blood thinners undergoing endoscopic procedures are encountered in our clinical practice frequently, endoscopists need to be familiar with the various blood thinners and have a strategy to manage these patients efficiently. This article will discuss the various blood thinners including their mechanism and duration of action, and the current guidelines of performing gastrointestinal endoscopies when the patients are on those blood thinners.

Ahmed M. Blood thinners and gastrointestinal endoscopy. *World J Gastrointest Endosc* 2016; 8(17): 584-590 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i17/584.htm>
DOI: <http://dx.doi.org/10.4253/wjge.v8.i17.584>

Abstract

As the number of diagnostic and therapeutic gastrointestinal endoscopies is increasing, and there is an increase in number of patients taking blood thinners, we are seeing more and more patients on blood thinners

INTRODUCTION

Blood thinners include antiplatelet agents, anticoagulants and thrombolytic agents. In the United States, more than 2 million people have been taking blood thinners every day for various cardiovascular, pulmonary and

hypercoagulable disorders^[1]. Gastrointestinal tract is the most common site of significant bleeding in patients on blood thinners. Thousands of people per day and millions of people per year are having gastrointestinal endoscopies in the United States^[2,3] and throughout the world. The various gastrointestinal endoscopic procedures performed are esophagogastroduodenoscopy, colonoscopy, endoscopic retrograde cholangiopancreatography (ERCP), flexible sigmoidoscopy, pouch/stoma endoscopy, enteroscopy (push, spiral, balloon assisted, *i.e.*, single balloon or double balloon), endoscopic ultrasound (EUS - mediastinal, pancreatic, rectal), capsule endoscopy and capsule colonoscopy. All these procedures have diagnostic and therapeutic potentials except capsule endoscopy and capsule colonoscopy in which neither any diagnostic biopsy nor any intervention can be done. Blood thinners may potentiate the risk of bleeding during or after performing these procedures. In the last few years, new blood thinners have been introduced in the market. As safety is the most important concern before performing a procedure, endoscopists should be very familiar with the different blood thinners available in the market.

BLOOD THINNERS

Anti-platelet agents

These include irreversible cyclooxygenase inhibitor, adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, glycoprotein II b/IIIa inhibitors and protease-activated receptor-1 (PAR-1) inhibitor.

Irreversible cyclooxygenase inhibitor

Aspirin: Low dose aspirin irreversibly inhibits platelet cyclooxygenase-1, thus decreasing production of prostaglandin H₂ (PGH₂) from arachidonic acid. As a result, production of thromboxane A₂ (TxA₂) derived from PGH₂ is decreased. TxA₂ is responsible for platelet aggregation and vasoconstriction. Low dose aspirin works as a weak antiplatelet agent. Aspirin is widely used in coronary artery disease, cerebrovascular disease and atrial fibrillation. Aspirin can be continued for low risk and high-risk elective procedures.

Adenosine diphosphate receptor inhibitors

They competitively inhibit ADP from binding to ADP receptors on platelets, and thus prevent ADP mediated up-regulation of glycoprotein II b/IIIa receptor, leading to inhibition of platelet aggregation. They include Clopidogrel (Plavix), Prasugrel (Effient), Ticagrelor (Brilinta) and Ticlopidine (Ticlid). Clopidogrel is widely used in acute coronary syndrome, post-coronary artery stenting, cerebrovascular accidents and peripheral vascular diseases. Prasugrel is used in acute coronary syndrome. It has rapid onset of action and more bleeding risk. Ticagrelor is used in acute coronary syndrome, post-myocardial infarction and post-coronary artery stenting. Ticlopidine is approved for the prevention of stroke when combined with aspirin, and also for the prevention

of coronary artery thrombosis after coronary artery stenting. But because of its rare but serious side effect of neutropenia and thrombocytopenia, it is rarely used nowadays. These medications are thienopyridines which inhibit platelet aggregation by irreversibly binding to P2Y₁₂ ADP receptors on platelets^[4]. Clopidogrel, prasugrel and ticagrelor should be withheld for 5-7 d and ticlopidine for 10-14 d prior to any endoscopic procedures.

Phosphodiesterase inhibitors

Cilostazol (Pletal): It prevents platelets from sticking together to form clots and is a direct vasodilator. It reduces intermittent claudication in peripheral vascular diseases. Cilostazol should be withheld for 2 d prior to endoscopic procedures.

Dipyridamole: It inhibits phosphodiesterase and prevents adenosine reuptake into platelets, red blood cells and endothelial cells. As it prevents platelets aggregation, it is used to prevent clot formation after cardiac valve replacement, and also to prevent myocardial infarction and stroke. It should be withheld for 2 to 3 d before performing any endoscopic procedure.

Glycoprotein IIB/IIIA inhibitors

This group of medications blocks the receptor on the platelet for fibrinogen and von Willebrand factor and thus prevent cross-linking of platelets and platelet aggregation. They are intravenous drugs used in acute coronary syndrome and percutaneous coronary intervention. The 3 agents available in this group are tirofiban (Aggrastat) - a synthetic non-peptide with a plasma half-life of 1.5 to 2 h and 80% of platelet aggregation returns 4 h after stopping the medication, abciximab (ReoPro) - a murine-human chimeric antibody with a plasma half-life of 10 min and platelet function recovery over 48 h after discontinuing the medication, and Eptifibatide (Integrilin) - a synthetic peptide with a plasma half life of 2.5 h and 50% of platelet aggregation returns 4 h after stopping the medication^[5]. Elective gastrointestinal procedures are not done while patients are on these medications. Urgent procedures should be on hold until recovery of platelet aggregation occurs.

PAR-1 inhibitor

Proteolytic activation of cell surface of PAR-1 by thrombin activates platelets. Selective inhibition of PAR-1 by Vorapaxar (Zontivity) leads to potent antiplatelet effect^[6]. Vorapaxar has been approved as an adjunct to dual anti-platelet therapy to reduce myocardial infarction, cerebrovascular accidents, cardiovascular death and to use during revascularization procedures. It can cause moderate to severe bleeding including intracranial hemorrhage^[7]. It is contraindicated in patients with transient ischemic attacks, stroke and intracerebral bleeding. Endoscopic procedures should be held for about 2 wk as its duration of action is 5 to 13 d.

Anticoagulants

These include parenteral and oral agents. Parenteral agents include unfractionated heparin, low molecular heparin and fondaparinux. Oral agents include warfarin and novel oral anticoagulants (NOAC) which are oral direct factor Xa inhibitors and direct thrombin inhibitors.

Unfractionated heparin

Unfractionated heparin is an injectable blood thinner widely used in the prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism. It is also used in atrial fibrillation, acute coronary syndrome, indwelling peripheral or central venous catheters, hemodialysis/hemofiltration and extracorporeal membrane oxygenation (ECMO) circuit for extracorporeal life support. Heparin exerts its major anticoagulant effect by activating anti-thrombin III which inactivates thrombin and activated factor X (Factor Xa). Inactivation of thrombin inhibits formation of fibrin from fibrinogen and also inhibits thrombin-induced activation of platelets and factor V and VIII^[8]. The main side effect is bleeding. Other side effects include hyperkalemia, abnormal liver function test, heparin-induced thrombocytopenia (due to formation of IgG antibody against heparin-platelet factor 4 complex in the blood), osteoporosis and alopecia. The plasma half-life varies with the dose of heparin but is approximately 90 min. In case of intravenous administration of heparin, endoscopy should be held for 4 to 6 h and in case of subcutaneous administration of heparin, endoscopy should be held for 12 to 24 h after stopping heparin. The action of heparin can be reversed by protamine (1 mg of protamine can neutralize 100 units of heparin).

Low molecular weight heparins

Low molecular weight heparins (LMWH) are derived from fractionation of standard heparin so that each fragment is about one third the size of the original compound. As the number of long chains is reduced, there is less binding to thrombin. LMWH (containing majority of short chains) mainly works by inhibiting factor Xa without inactivating thrombin. Thus partial thromboplastin time (PTT), a measure of anti-thrombin activity is not affected by LMWH. The anti-coagulation effect of LMWH is measured by anti-Xa activity. The short chains of LMWH do not bind to plasma and cellular proteins and as a result, the dose-response relationship is predictable, and the half-life becomes 2 to 4 times that of Unfractionated heparin. There is less binding of LMWH to platelets and osteoclasts leading to less heparin-induced thrombocytopenia and osteopenia respectively. Currently, the LMWH available are enoxaparin (Lovenox) and dalteparin (Fragmin). They are associated with greater efficacy and less bleeding episodes^[9]. As the duration of action of LMWH is 24 h, endoscopic procedures should be done 1 d after stopping LMWH. LMWH can also be partially reversed by protamine which neutralizes 60% activity of anti-factor Xa.

Fondaparinux (Arixtra)

Fondaparinux (Arixtra) is a specific inhibitor of factor Xa without any effect on thrombin or other clotting factors but it needs antithrombin III as a cofactor for inhibition of factor Xa. A fixed dose is given subcutaneously and does not require monitoring of PTT. It is used for the treatment of DVT with or without pulmonary embolism, and for the prevention of DVT in high-risk individuals who are immobilized or who have undergone abdominal or orthopedic surgery. As it has no affinity for PF-4 antigen, the chance of developing heparin-induced thrombocytopenia is very rare. Fondaparinux is eliminated mainly unchanged through the urine and the elimination half-life is 17 to 21 h. It should be discontinued 36 to 48 h prior to any high-risk endoscopic procedure. Fondaparinux activity can be reversed by protamine sulfate and rVIIa.

Warfarin

Warfarin is the most commonly used oral anticoagulant throughout the world. It is used in various clinical conditions like DVT, pulmonary embolism, atrial fibrillation, following cardiac valve replacement, following hip/knee surgery, to prevent stroke and myocardial infarction. It inhibits formation of vitamin K dependent clotting factors - II, VII, IX and X and natural anticoagulants Protein C and protein S by inhibiting C1 subunit of vitamin K epoxide reductase. The major side effect is bleeding. The duration of action of warfarin is 2 to 5 d. Endoscopy should be held for 5 d after stopping warfarin.

Oral direct factor Xa inhibitors

Oral direct factor Xa inhibitors are rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Savaysa). Factor X is activated by both extrinsic and intrinsic pathways. Unlike heparin and warfarin which inhibit multiple coagulation factors, they are specific for factor Xa. They have rapid onset of action (time to maximal effect: Rivaroxaban-2 to 4 h, Apixaban-1 to 3 h) with good oral bioavailability and they do not need any bridging therapy. Their plasma half-lives range from 8 to 15 h. They have both renal and fecal excretion. As a result they have less accumulation in the body in renal failure. Edoxaban should be stopped at least 24 h before any high-risk endoscopic procedure. Rivaroxaban and apixaban should be stopped 1 to 4 d, i.e., at least 2 half-lives before high-risk endoscopic procedures depending on the creatinine clearance. These medications are approved for prevention of stroke in patients with non-valvular atrial fibrillation (NVAf), DVT and pulmonary embolism. In ENGAGE AF-TIMI 48 Trial^[10], both high dose (60 mg/d) and low dose (30 mg/d) Edoxaban were found to be non-inferior to warfarin for the prevention of recurrent symptomatic thromboembolism. The annual rate of major gastrointestinal bleeding was higher with high dose Edoxaban than with warfarin (1.51% vs 1.23%) but lowest with low dose Edoxaban (0.82%). Although gastrointestinal bleeding risk (GIB) is similar in patients using warfarin and NOAC in the young and middle-aged

population, in the elderly (age > 75) population, there is increased risk of GIB in patients taking NOAC^[11].

Direct thrombin inhibitors

Direct thrombin inhibitors are oral Dabigatran (Pradaxa) and subcutaneous Desirudin (Iprivask). Dabigatran is an oral anticoagulant which has been approved for: (1) the treatment of patients with DVT and pulmonary embolism (PE) after 5 to 10 d of parenteral anticoagulant; (2) the prevention of DVT and PE in patients who have been treated previously; and (3) the prevention of stroke and systemic embolism in patients with NVAf. Dabigatran was found to be non-inferior to warfarin in the treatment and prevention of DVT and PE but carried increased risk of bleeding^[12] particularly gastrointestinal bleeding than the placebo group (5.3% vs 1.8%). Its anticoagulant activity can be assessed by Ecarin Clotting Time or dilute thrombin time. Dabigatran is fixed dose, does not require monitoring by international normalized ratio (INR) and excessive bleeding can be reversed by a monoclonal antibody^[13] called idarucizumab (Praxbind). Dabigatran has a half life of 12-24 h. It should be stopped 2 to 6 d (i.e., at least for 4 half-lives) prior to high risk endoscopic procedures depending on the creatinine clearance. Desirudin has been approved for the prevention of DVT in patients after elective hip replacement surgery. As this medication is metabolized and excreted renally similar to Dabigatran, the dose is adjusted according to creatinine clearance. The anticoagulant activity can be monitored by aPTT. The terminal half-life is 2 h after subcutaneous administration. High-risk endoscopic procedures should be done 10 h after discontinuation of desirudin.

Thrombolytic agents

Thrombolytic agents are clot busters used in acute myocardial infarction, cerebral infarction and occasionally in massive pulmonary embolism. Thrombolytics have also been used as provocative agents to induce bleeding during endoscopic procedures, bleeding scan and angiogram to evaluate obscure gastrointestinal bleeding. The five thrombolytics currently available in the United States have different plasma half-lives: Streptokinase - 20 min, tissue plasminogen activator- 5 min, anistreplase - 2 h, reteplase - 18 min and tenecteplase - 20 min. Five percent of patients on thrombolytics can have minor bleeding, 1% serious bleeding including intracranial hemorrhage. At the present time, there is no guideline about doing endoscopic procedures on patients who received thrombolytic therapy. In patients with acute myocardial infarction and overt upper gastrointestinal bleeding, upper endoscopy prior to cardiac catheterization has been advocated as platelet inhibition and anticoagulation are needed post percutaneous coronary intervention^[14].

GUIDELINES

Before doing an elective endoscopic procedure for

patients on blood thinners, we must evaluate whether the patient has high-risk or low-risk condition and whether it is a high-risk or low-risk endoscopic procedure.

Low-risk conditions

Low-risk conditions have low risk of thromboembolic events after temporary interruption of blood thinners (absolute risk less than 2 per 1000 patients). These include DVT, NVAf, biologic heart valve, mechanical heart valve in the aortic position^[15].

High-risk conditions

High-risk conditions have high risk of thromboembolic events after temporary interruption of blood thinners (absolute risk more than 2 per 1000 patients). These include valvular atrial fibrillation (AF) or AF associated with other risk factors (prosthetic heart valve, congestive heart failure with ejection fraction of < 35%, history of thromboembolism, diabetes mellitus, hypertension or age > 75), coronary artery stenting - bare metal less than 1 mo, drug-eluting less than 12 mo, mechanical heart valve in the mitral position, mechanical heart valve in any position with history of thromboembolism, acute coronary artery syndrome, percutaneous coronary intervention without coronary artery stenting after myocardial infarction.

Low-risk procedures

In the absence of blood thinners, the risk of clinically significant bleeding is less than 1%^[16]. These include diagnostic esophagogastroduodenoscopy, colonoscopy and flexible sigmoidoscopy with or without biopsy, Argon plasma coagulation, Barrett's ablation, ERCP without sphincterotomy, EUS without FNA, push enteroscopy with or without biopsy, diagnostic balloon-assisted enteroscopy, capsule endoscopy and enteral stent placement without dilation (controversial).

High-risk procedures

The risk of clinically significant bleeding is more than 1% in the absence of blood thinners. These include polypectomy, treatment of varices, endoscopic hemostasis, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, pneumatic or bougie dilation, pneumatic balloon dilation for achalasia, endoscopic therapy of Zenker's diverticulum, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic tumor ablation by any technique (esophagus, stomach, colon and rectum), therapeutic balloon-assisted enteroscopy (other than argon plasma coagulation), endoscopic sphincterotomy, ampullary resection, EUS with FNA, cystogastrostomy, cystoenterostomy, per-oral endoscopic myotomy^[17].

Risk stratification

Aspirin and non-steroidal anti-inflammatory drugs are safe in both low-risk and high-risk procedures except EMR, ESD and ampullectomy.

Table 1 Summary of recommendations for elective endoscopic procedure

	Low-risk conditions	High-risk conditions
Low-risk procedures	Continue APA, warfarin and NOAC	Continue APA, warfarin and NOAC
	Keep INR in therapeutic range in case of warfarin	Keep INR in therapeutic range in case of warfarin
High-risk procedures	Hold thienopyridines for 5 to 7 d before the procedure. Resume theonopyridine once hemostasis is obtained	Hold thienopyridines for 5 to 7 d before the procedure after discussion with the cardiologist. Resume theonopyridine once hemostasis is obtained
	In case of dual APA, hold thienopyridines for 5 to 7 d before the procedure but continue aspirin	In case of dual APA, hold thienopyridines for 5 to 7 d before the procedure but continue aspirin
	Hold warfarin 5 d before the procedure. Resume warfarin on the same day as the procedure	Delay endoscopic procedure if coronary artery stenting done and thienopyridines cannot be discontinued
	Hold NOAC: Rivaroxaban 2 to 4 d, apixaban 2 to 4 d, edoxaban 1 d and dabigatran 2 to 6 d before the procedure depending on creatinine clearance. Resume NOAC when adequate hemostasis is obtained	If the patient is on warfarin, bridge therapy with LMWH

APA: Antiplatelet agents; NOAC: Novel oral anticoagulants; LMWH: Low molecular weight heparins; INR: International normalized ratio.

Low-risk endoscopic procedures irrespective of low-risk or high-risk condition

If the patient is on antiplatelet agent or anticoagulant, it should be continued. In case of warfarin, the INR should be in therapeutic range. If the INR is supra-therapeutic, warfarin dose should be adjusted to keep the INR in therapeutic range before doing the endoscopic procedure^[18]. The morning dose of NOAC should be missed on the day of the procedure.

High-risk procedure but low-risk condition

If the patient is on aspirin and clopidogrel, clopidogrel should be stopped 5 to 7 d prior to the procedure but aspirin should be continued. If the patient is on warfarin, it should be discontinued 5 d prior to the procedure. INR should be less than 1.5 prior to the procedure. Warfarin should be restarted after the procedure on the same day with the usual daily dose. Patient's INR should be rechecked one week after the procedure to make sure that the patient is getting enough anticoagulation.

NOAC should be discontinued 48 h prior to the procedure in patients with normal renal function. If the creatinine clearance is 30 to 50 mL/min, last dose of NOAC should be given 72 h prior to the procedure.

High-risk procedure and high-risk condition

If the patient is on aspirin and clopidogrel, clopidogrel should only be discontinued after discussion with the cardiologist taking care of the patient. Aspirin should be continued. As the risk of thromboembolism is always a concern, elective endoscopic procedure should be delayed. Clopidogrel should not be stopped in certain high-risk conditions such as within one month of placing of a bare metal coronary stent and within 12 mo of placing a drug-eluting coronary stent. After these periods, clopidogrel can be temporarily stopped 7 d prior to the endoscopic procedure and then can be restarted on the day after the procedure. If the patient is on warfarin, bridge therapy should be utilized. The risk of systemic thromboembolism must be taken into consideration against the risk of bleeding during bridge therapy.

Warfarin should be held 5 d prior to the procedure and LMWH should be started two days after discontinuing warfarin. On the night of the procedure, regular dose of warfarin should be started. LMWH should be started the following day and continued until therapeutic INR is achieved. NOAC are not used for high-risk conditions.

Bleeding risk

In patients with history of venous thromboembolism on warfarin, bridge therapy for invasive procedures was associated with increased risk of bleeding^[19].

Thrombosis risk

There is also increased risk of thrombosis in patients receiving LMWH for mechanical heart valve (Table 1).

Emergency endoscopic procedures

Frequently we encounter acute gastrointestinal bleeding in patients: (1) who are on antiplatelet or anticoagulant therapy for various reasons; (2) who had coronary vascular stent placed recently; and (3) who have acute coronary syndrome (ACS): Unstable angina or acute myocardial infarction.

The risk of bleeding to death should be assessed against the risk of thromboembolism due to discontinuation of antiplatelet or anticoagulant therapy on an individual basis. Patients on antiplatelet therapy should be discussed with their cardiologists. In case of significant gastrointestinal bleeding, the antiplatelet agent should be stopped after discussing with the cardiologist, and platelet transfusion can be given. In case of baby aspirin induced peptic ulcer bleeding, aspirin should be continued and proton pump therapy should be started. As soon as endoscopic hemostasis is obtained, antiplatelet therapy should be resumed^[20].

The risk factors for GIB in patients on anticoagulant therapy are prior history of GIB, use of aspirin and supra-therapeutic INR.

Anticoagulation therapy should be discontinued in patients with active gastrointestinal (GI) bleeding. If the patient is on warfarin and the bleeding is massive, rapid

Table 2 Summary of recommendations for emergency endoscopic procedures

Anticoagulant	APA
Active GI bleed	Do not stop thienopyridines without discussion with the cardiologist in high risk situations like within 3 mo of ACS, within 1 mo of placing a bare metal coronary stent and within 12 mo of placing a drug eluting coronary stent
Hold the anticoagulant	
If on warfarin, give FFP, 4-factor PCC or IV Vitamin K to improve INR	
Avoid vitamin K in case of mechanical heart valve	
Hemodialysis in case of Dabigatran	
Endoscopic therapy when INR is less than 2.5	

APA: Antiplatelet agents; PCC: Prothrombin complex; ACS: Acute coronary syndrome; GI: Gastrointestinal; FFP: Fresh frozen plasma; INR: International normalized ratio; IV: Intravenous injection.

reversal of INR can be done with fresh frozen plasma (FFP), 4-factor prothrombin complex (PCC) containing factors II, VII, IX and X, or intravenous vitamin K. In case of mechanical heart valve and massive GI bleeding, FFP or PCC can be given but vitamin K should be avoided because of the risk of hypercoagulable state^[21]. Endoscopic therapy should be given in patients with active bleeding and INR < 2.5. In high-risk patients, heparin infusion should be started after endoscopic hemostasis. Hemodialysis should be done in case of dabigatran-induced massive GI bleeding.

Patients with active gastrointestinal bleeding with history of coronary artery stent placement - *i.e.*, within one month of bare metal stenting and within one year of drug eluting stenting, should be discussed with the cardiologist. Clopidogrel should not be discontinued without permission from the cardiologist as there is high risk of coronary artery thrombosis and myocardial infarction. Discontinuation of clopidogrel should not exceed 5 d because of the risk of increased stent thrombosis.

Patients with ACS and GIB are unique group of patients who require close communication between the cardiologist and the gastroenterologist. This is a serious entity as ACS and GIB are independent risk factors for ischemic complications, higher morbidity and mortality. There are two distinct settings: (1) patients develop gastrointestinal bleeding first, then develop ACS. This group of patients have primary gastrointestinal lesions which have caused GIB. As GIB is the inciting event leading to ACS, endoscopic treatment would be more beneficial for this group of patients^[22]; and (2) patients develop ACS first, then develop gastrointestinal bleeding. This is the commoner entity as this group of patients receive antiplatelet and/or antithrombotic agents for their ACS, either treated conservatively or by PCI. One study showed 1.3% of patients developed GIB within 30 d of acute coronary syndrome^[23]. There was significantly increased incidence of stent thrombosis in the GIB group than non-GIB group (5.8% vs 2.4%). Predictors of post-ACS GIB were old age, female sex, smoking status, baseline anemia, diabetes mellitus, hypertension, heart failure, ST-segment elevation ≥ 1 mm, longer duration of blood thinner administration before angiogram^[23,24]. There was 8 fold increase in mortality when ACS patients developed GIB. Another study showed that patients with ACS who had also upper GIB had 30% mortality within 30 d of their ACS^[25]. Upper endoscopy can have

procedural and anesthetic risk like hypotension, EKG changes, hypoxia and life threatening arrhythmia in the setting of ACS. One study done in a tertiary care center found upper endoscopy to be relatively safe in the diagnosis and management of upper GIB within 30 d of having myocardial infarction^[26] (Table 2).

CONCLUSION

Because a good number of blood thinners are available in the market, sound knowledge about these blood thinners is necessary. Anti-platelet agents, heparin and warfarin have been in our clinical practice for many years. NOAC introduced over the last few years are being increasingly used as they do not need Lab test monitoring like warfarin. Their onset of action is short and the duration of action depends on creatinine clearance. So serum creatinine and half-life of these medications should be considered in the periendoscopic period. Whether it is an elective case or an emergent case, an endoscopist should always evaluate high-risk and low-risk conditions and procedures, and bleeding and thrombotic risk. The main aim is success of the procedure maintaining safety of the patient.

REFERENCES

- 1 Blood Thinner Pills: Your Guide to Using Them Safely. Rockville, MD: Agency for Healthcare Research and Quality. [updated 2015 Sep]. Available from: URL: <http://www.ahrq.gov/patients-consumers/diagnosis-treatment/treatments/btpills/btpills.html>
- 2 Seeff LC, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS, Dong FB, Wings LD, McKenna MT. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastroenterology* 2004; **127**: 1670-1677 [PMID: 15578503]
- 3 Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibanaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-87.e1-3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]
- 4 Nguyen TV, Lac TH, Ishkhakova M, Srbliak A. A prescriber's guides to oral antiplatelet therapy. *J Nur Practit* 2011; **7**: 847-852
- 5 Oprea AD, Popescu WM. Perioperative management of antiplatelet therapy. *Br J Anaesth* 2013; **111** Suppl 1: i3-i17 [PMID: 24335397 DOI: 10.1093/bja/aet402]
- 6 Abdulsattar Y, Ternas T, Garcia D. Vorapaxar: targeting a novel antiplatelet pathway. *P T* 2011; **36**: 564-568 [PMID: 22346324]
- 7 Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby

- AJ, Fish MP, Fox KA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012; **366**: 1404-1413 [PMID: 22443427 DOI: 10.1056/NEJMoa1200933]
- 8 **Hirsch J**, Anand SS, Halperin JL, Fuster V. Mechanism of action and Pharmacology of Unfractionated Heparin (Editorial). *Arterioscl Thromb Vasc Biol* 2001; **21**: 1094-1096 [DOI: 10.1161/hq0701.093686]
- 9 **Hirsh J**. Low-molecular-weight heparin: A review of the results of recent studies of the treatment of venous thromboembolism and unstable angina. *Circulation* 1998; **98**: 1575-1582 [PMID: 9769312 DOI: 10.1161/01.CIR.98.15.1575]
- 10 **Giugliano RP**, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104 [PMID: 24251359 DOI: 10.1056/NEJMoa1310907]
- 11 **Abraham NS**, Singh S, Alexander GC, Heien H, Haas LR, Crown W, Shah ND. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ* 2015; **350**: h1857 [PMID: 25910928 DOI: 10.1136/bmj.h1857]
- 12 **Schulman S**, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ, RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. *New England J Med* 2013; **368**: 709-718 [DOI: 10.1056/NEJMoa1113697]
- 13 **Pollack CV**, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI. Idarucizumab for Dabigatran Reversal. *N Engl J Med* 2015; **373**: 511-520 [PMID: 26095746 DOI: 10.1056/NEJMoa1502000]
- 14 **Yachinski P**, Hur C. Upper endoscopy in patients with acute myocardial infarction and upper gastrointestinal bleeding: results of a decision analysis. *Dig Dis Sci* 2009; **54**: 701-711 [PMID: 18661236 DOI: 10.1007/s10620-008-0403-y]
- 15 **Anderson MA**, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Lichtenstein DR, Maple JT, Shen B, Strohmeyer L, Baron T, Dominitz JA. Management of anti-thrombotic agents for endoscopic procedures. *Gastroint Endosc* 2009; **70**: 1060-1070 [DOI: 10.1016/j.gie.2009.09.040]
- 16 **Eisen GM**, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, Mallory JS, Raddawi HM, Vargo JJ, Waring JP, Fanelli RD, Wheeler-Harborough J. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastrointest Endosc* 2002; **55**: 775-779 [PMID: 12024126]
- 17 **Acosta RD**, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaikat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016; **83**: 3-16 [PMID: 26621548 DOI: 10.1016/j.gie.2015.09.035]
- 18 **Veitch AM**, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Endoscopy* 2016; **48**: 385-402 [PMID: 26890676 DOI: 10.1136/gutjnl-2015-311110]
- 19 **Clark NP**, Witt DM, Davies LE, Saito EM, McCool KH, Douketis JD, Metz KR, Delate T. JAMA Intern Med. Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures. *JAMA Intern Med* 2015; **175**: 1163-1168 [PMID: 26010033 DOI: 10.1001/jamaintern.2015.1843]
- 20 **Becker RC**, Scheiman J, Dauerman HL, Spencer F, Rao S, Sabatine M, Johnson DA, Chan F, Abraham NS, Quigley EM; American College of Cardiology; American College of Gastroenterology. Management of platelet directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. *Am J Gastroenterol* 2009; **104**: 2903-2917 [PMID: 19935784 DOI: 10.1038/ajg.2009.667]
- 21 **Nishimura RA**, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: 2438-2488 [PMID: 24603192 DOI: 10.1161/CIR.000000000000029]
- 22 **Lin S**, Konstance R, Jollis J, Fisher DA. The utility of upper endoscopy in patients with concomitant upper gastrointestinal bleeding and acute myocardial infarction. *Dig Dis Sci* 2006; **51**: 2377-2383 [PMID: 17151907 DOI: 10.1007/s10620-006-9326-7]
- 23 **Nikolsky E1**, Stone GW, Kirtane AJ, Dangas GD, Lansky AJ, McLaurin B, Lincoff AM, Feit F, Moses JW, Fahy M, Manoukian SV, White HD, Ohman EM, Bertrand ME, Cox DA, Mehran R. Gastrointestinal bleeding in patients with acute coronary syndromes: incidence, predictors, and clinical implications: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am College Cardiol* 2009; **54**: 1293-1302 [DOI: 10.1016/j.jacc.2009.07.019]
- 24 **Al-Mallah M**, Bazari RN, Jankowski M, Hudson MP. Predictors and outcomes associated with gastrointestinal bleeding in patients with acute coronary syndromes. *J Thromb Thrombolysis* 2007; **23**: 51-55 [PMID: 17186397]
- 25 **Shalev A**, Zahger D, Novack V, Etzion O, Shimony A, Gilutz H, Cafri C, Ilia R, Fich A. Incidence, predictors and outcome of upper gastrointestinal bleeding in patients with acute coronary syndromes. *Int J Cardiol* 2012; **157**: 386-390 [PMID: 21277643 DOI: 10.1016/j.ijcard.2010.12.081]
- 26 **Lim RG**, Cobell WJ, Theivanayagam S, Kilgore TW, Matteson ML, Puli SR, Bechtold ML. Endoscopy after acute myocardial infarction: an evaluation of safety. *South Med J* 2013; **106**: 545-549 [PMID: 24096947 DOI: 10.1097/SMJ.000000000000001]

P- Reviewer: Armellini E, Braden B, Zhang QS
S- Editor: Qi Y **L- Editor:** A **E- Editor:** Li D



Endoscopic management of post-bariatric surgery complications

Mena Boules, Julietta Chang, Ivy N Haskins, Gautam Sharma, Dvir Froylich, Kevin El-Hayek, John Rodriguez, Matthew Kroh

Mena Boules, Julietta Chang, Ivy N Haskins, Gautam Sharma, Dvir Froylich, Kevin El-Hayek, John Rodriguez, Matthew Kroh, Department of General Surgery, Digestive Disease Institute, Cleveland Clinic, Cleveland, OH 44195, United States

Author contributions: Boules M contributed to writing of the manuscript, literature review, incorporating revisions, and final review; Chang J contributed to writing of the manuscript and literature review; Haskins IN contributed to writing of the manuscript, literature review, and incorporating revisions; Sharma G contributed to literature review; Froylich D contributed to literature review and revisions; El-Hayek K contributed to writing of the manuscript, final review; Rodriguez J contributed to writing of the manuscript and revision review; Kroh M contributed to writing of the manuscript, revisions review, study concept, and final review of the manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors on this manuscript. All authors approve the final version of this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Matthew Kroh, MD, Director of Surgical Endoscopy, Associate Professor of Surgery Cleveland Clinic Lerner College of Medicine, Department of General Surgery, Digestive Disease Institute, Cleveland Clinic, 9500 Euclid Avenue, A100, Cleveland, OH 44195, United States. krohm@ccf.org
Telephone: +1-216-4446664
Fax: +1-216-4442153

Received: April 29, 2016
Peer-review started: May 3, 2016

First decision: June 17, 2016
Revised: July 2, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: September 16, 2016

Abstract

Understanding the technical constructs of bariatric surgery is important to the treating endoscopist to maximize effective endoluminal therapy. Post-operative complication rates vary widely based on the complication of interest, and have been reported to be as high as 68% following adjustable gastric banding. Similarly, there is a wide range of presenting symptoms for post-operative bariatric complications, including abdominal pain, nausea and vomiting, dysphagia, gastrointestinal hemorrhage, and weight regain, all of which may provoke an endoscopic assessment. Bleeding and anastomotic leak are considered to be early (< 30 d) complications, whereas strictures, marginal ulcers, band erosions, and weight loss failure or weight recidivism are typically considered late (> 30 d) complications. Treatment of complications in the immediate post-operative period may require unique considerations. Endoluminal therapies serve as adjuncts to surgical and radiographic procedures. This review aims to summarize the spectrum and efficacy of endoscopic management of post-operative bariatric complications.

Key words: Bariatric surgery; Weight loss surgery; Bariatric complications; Endoscopy; Bariatrics

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There are minimal reviews in the literature discussing therapeutic options for endoscopic management of bariatric surgery complications. Treatment of bariatric complications in the post-operative period

may require unique considerations. Endoluminal therapies serve as adjuncts to surgical and radiographic procedures. This review aims to summarize the spectrum and efficacy of endoscopic management of post-operative bariatric complications.

Boules M, Chang J, Haskins IN, Sharma G, Froylich D, El-Hayek K, Rodriguez J, Kroh M. Endoscopic management of post-bariatric surgery complications. *World J Gastrointest Endosc* 2016; 8(17): 591-599 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i17/591.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i17.591>

INTRODUCTION

Obesity is an increasing health concern in the United States and worldwide. According to the World Health Organization, obesity has doubled since 1980. In 2014 alone, more than 1.9 billion adults were classified as overweight, of which 600 million were obese^[1]. Durable medical therapy for morbid obesity is limited. As an alternative, many studies have demonstrated the benefits of bariatric surgery in terms of excess weight loss and improvement or resolution of weight-related co-morbid diseases^[2-6]. As of 2013, the most commonly performed laparoscopic bariatric procedures worldwide are Roux-en-Y gastric bypass (RYGB) (45%), sleeve gastrectomy (SG) (37%) and adjustable gastric banding (AGB) (10%)^[7].

Peri-procedural complications have been reduced by the development and widespread use of laparoscopic techniques, improved training and credentialing, and establishment of comprehensive and dedicated bariatric surgery programs^[4,5,8]. Nevertheless, bariatric surgery related complications remain a clinical challenge. Traditional management of these complications has been performed using surgical and interventional radiology techniques. Recently, however, endoscopic therapies have been introduced as an alternative and minimally invasive approach to peri-procedural complications^[9].

Endoluminal treatment of peri-procedural complications following bariatric surgery may help to minimize patient morbidity. In order for endoscopic therapies to be successful, the treating endoscopist must be cognizant not only of the anatomical constructs of bariatric surgery but also of any newly constructed anastomosis or staple line^[9-11]. This review aims to summarize the spectrum and efficacy of endoscopic management of post-operative bariatric complications.

EARLY COMPLICATIONS (< 30 D POST-OPERATIVELY)

Gastrointestinal bleeding

Gastrointestinal (GI) bleeding usually presents in the immediate post-operative period secondary to technical complications. Most commonly, this occurs as intra-

luminal bleeding, but extra-luminal bleeding can occur. Bleeding primarily occurs from the submucosal vessels along the staple line at the gastro-jejunostomy, jejunogastro-jejunostomy, or along the staple lines of the gastric pouch.

Signs and symptoms of bleeding, including a drop in hemoglobin levels, hematemesis, hematochezia, or melena, should be considered an indication to undergo further evaluation. Endoscopy is often used as a first-line modality for investigation of the source of bleeding. However, when post-operative bleeding is severe and associated with hemodynamic instability, surgical re-exploration may be required.

As the incidence of RYGB increases worldwide, so too does the frequency of post-operative upper GI bleeding in this patient population^[12,13]. In the immediate 48 h after LRYGB, hemorrhage is reported to occur with an incidence between 1%-4%. Thirty to sixty-three percent of these occurrences require blood transfusion but are nonetheless self-limited^[11,14,15]. Endoscopy is considered in the early period when patients have proven bleeding and this is refractory to supportive therapy^[11]. Literature demonstrates therapeutic endoscopy interventions range between 6%-85% in these circumstances, and the culprit is often found at the G-J anastomosis^[11-14,16].

Various endoscopic treatments have been shown to be effective for the management of bleeding peptic ulcers. A meta-analysis of randomized controlled trials demonstrated efficacy with the use of several endoscopic therapies, including thermal therapies (heater probe, mono and bi-polar electrocoagulation, argon plasma coagulation, and laser therapy), injections with epinephrine and various sclerosants, clips, and fibrin or thrombin glues^[17]. We believe that the approaches described in this meta-analysis will be useful for the management of early post-operative bleeding in those patients undergoing bariatric surgery as the use of epinephrine injection with thermal coagulation, sclerosants, or clips, has previously been shown to be successful in the bariatric patient population^[14]. The most common endoscopic interventions performed for the management of acute bleeding in this patient population are described below.

Thermal therapy for bleeding: Electrocautery is a thermal heat therapy. It is delivered through the form of mono-, bi-, or multi-polar electrocautery. Coaptation is the process of applying mechanical pressure using the probe in combination with heat or electrical stimulation to coagulate a blood vessel. Argon plasma coagulation is considered a form of non-contact heat therapy that uses argon gas to deliver thermal energy with resultant hemostasis of superficial tissues. Laser therapy is not commonly used due to cost, need for specific training, and safety^[18].

Injection therapy for bleeding: The efficacy of injection therapy occurs by volume tamponade and fibrosis and vasoconstriction when used with epinephrine.

The volume of fluid injected results in mechanical tamponade of the bleeding vessel. This effect is coupled with fibrosis from an inflammatory response and vasoconstriction that is induced by an alpha-receptor mediated response to epinephrine which leads to platelet aggregation^[19].

The most important factor in the immediate control of bleeding is likely mechanical compression. Dual therapy with larger volumes of fluid combined with an epinephrine component result in better rates of hemostatic control, lower rates of re-bleeding, and decreased need for transfusion in patients with bleeding foregut ulcers^[19]. Several randomized trials have established the efficacy of achieving hemostasis with the use of epinephrine to treat active bleeding^[17]. In a recent study, single-therapy with epinephrine was shown to be less effective in the prevention of bleeding when compared to other single-therapy treatment modalities^[17,20]. These findings were also confirmed in a meta-analysis conducted by Marmo *et al*^[21] who found combination therapy to be a superior approach when compared to single agent epinephrine. A decreased rate of progression of the rate of bleeding was shown when epinephrine was used in combination with a second therapy such as bipolar electrocoagulation, injectable sclerosants, or clips^[17,22].

Clip therapy for bleeding: Endoscopic clips are composed of two stainless steel ribbons (with various lengths as needed), with a range of 90 to 135 degree angles. The opening distance of clips range from 6-12 mm, allowing for flexibility in securing the desired amount of tissue. Clips typically slough off after a period of 2-4 wk but have been reported to remain in place up to one year after placement^[23-27]. Advantages of clip placement for hemostasis include the ability to imbricate surrounding tissues for compression, the application of direct pressure to the targeted vessel, and ease of repeat clip placement^[25,28,29].

In a retrospective review of 742 patients that underwent LRYGB, post-operative bleeding was reported in 3.5% of the patients. Nineteen (2.6%) patients presented with early GI bleeding while 7 presented with late bleeding. A total of 5 patients with early GI bleeding were diagnosed by endoscopy and received a combination treatment with endoscopic clips and epinephrine injections. Similarly, a prospective study by Fernández-Esparrach *et al*^[30] reported results of 381 LRYGB patients. Twenty-two (5.8%) patients were determined to have upper GI bleeding. Sixteen were managed without procedural intervention. Six patients required intervention, all of whom were managed successfully with endoscopic intervention with epinephrine injections either as a single therapy or in combination with polidocanol^[30].

A retrospective study presented by Jamil *et al*^[14] identified 933 patients that underwent LRYGB during a 5-year study period. Thirty patients presented with signs of upper GI bleeding, 27 of whom required endoscopic intervention. All bleeding occurred at the G-J anastomosis. Endoscopic findings revealed active oozing in 13 (48%)

patients, a visible bleeding vessel in 7 (26%) patients, and an adherent clot in 7 (26%) patients. Twenty-three (85%) of these patients required endoscopic intervention, which included injection with epinephrine ($n = 3$, 13%), heat electrocautery ($n = 4$, 17%), dual therapy with epinephrine and heat electrocautery ($n = 14$, 61%), and clips ($n = 2$, 9%). Hemostasis was eventually achieved in all patients but 5 (17%) patients required repeat endoscopic management for re-bleeding^[14].

Anastomotic leak and fistulas

Anastomotic leaks following bariatric surgery are most commonly found along staple lines. Patients who undergo RYGB are most susceptible to anastomotic leak at the G-J anastomosis due to the single blood supply to the gastric pouch. Leak after SG is often at the EG junction and may be secondary to stenosis at the incisura. Leak after duodenal switch is typically at the duodenal-ileal staple line.

While the cause remains unclear, leaks are hypothesized to be due to technical factors including anastomotic tension, tissue ischemia, size of staple line, tissue thickness, and blood supply. Although rare, leaks are associated with significant morbidity and mortality. Overall incidence of anastomotic leak following bariatric surgery is reported to range from 1% to 6%. Specifically, LRYGB is associated with an incidence of 0.1% to 5.6% while SG is approximately 2.4%^[31,32].

Bariatric surgery can be challenging for the novice surgeon. As surgeon experience in this field increases, the risk of anastomotic leak is often shown to decrease. In a study by Schauer *et al*^[33], they defined the learning curve for laparoscopic bariatric surgery to be 100 cases, at which time there was a significant decrease in operative time and technical complications. In a prospective study by DeMaria *et al*^[34], 281 consecutive LRYGB operations were performed, with a decrease in the rate of anastomotic leak as surgeon experience with the laparoscopic approach increased.

In the early post-operative period, extra-luminal leaks may lead to a wide array of sequelae including abscess formation, peritonitis, sepsis, multi-organ failure, and death. Clinical signs of a leak, such as tachycardia, abdominal pain, or fever warrant prompt evaluation by the surgeon in order to minimize associated morbidity^[35]. The principles of managing these patients include infection control, nutritional support, and the appropriate therapeutic intervention. We recommend the use of non-surgical, endoscopic interventions for patients without hemodynamic instability in order to minimize the additional stress and risk of iatrogenic injury associated with reoperation. On the other hand, we recommend surgical re-exploration for all critically ill patients and for those patients who do not improve with endoscopic interventions. The types of endoscopic interventions for post-operative anastomotic leaks will be further discussed below.

Endoscopic stents: The use of endoscopic stents for

the management of post-operative anastomotic leaks is the most commonly used endoscopic modality in our experience. Self-expandable stents have gained popularity and can be a useful tool for management of leaks in the acute period (ref). There are several types of stents available, with fully covered and partially covered self-expanding metal stents (SEMS) being the most useful for management of bariatric complications. These stents work by means of omitting the site of leakage from esophago-gastric secretions, ultimately preventing further contamination and enhancing healing of the leak site. Patients may also resume oral liquid intake after the leak is excluded, which has been shown to lead to an improvement in the patient's nutritional status and therefore faster healing of the anastomotic or staple line leak^[35,36].

Authors of a small study reported successful endoscopic treatment of leaks in three patients and concluded that endoscopic treatment may serve as a less invasive and feasible alternative when compared to surgical management^[37]. A prospective study by Yimcharoen *et al*^[9] from the Cleveland Clinic evaluated the use of three different stents [silicone tube (prototype salivary), fully or partially covered expandable metal stents, or a silicone-coated polyester stent] for post-bariatric surgery complications in 18 patients. The study reported success in achieving symptom improvement in 17 (89%) patients and complete resolution of the anastomotic leak in 11 (85%) patients^[9]. Our group also presents results in a retrospective review of 47 patients that underwent endoscopic SEMS placement for anastomotic complication following upper GI surgery. Symptomatic improvement after stent placement was achieved in 70.9% ($n = 38$) of patients. Majority (68.1%, $n = 32$) of patients were able to initiate oral nutrition within 48 h of stent placement, with 57% of patients with anastomotic or staple-line leak and 89% of patient with strictures and stenosis able to initiate oral nutrition^[23]. A meta-analysis analyzing the use of SEMS in anastomotic leaks after bariatric surgery reports successful leak closure of 88%, with only 9% of patient's required further revisional surgical intervention for persistent anastomotic leak^[38].

The use of stents for the management of bariatric complications remains under investigation and is not without associated risks. The possibility of stent migration must be considered when deciding to proceed with stent insertion. Multiple techniques have been described in an effort to decrease migration of fully covered stents by means of clipping or suturing^[9,23]. Surgeons at our institute prefer the use of partially covered stents as these types of stents effectively exclude the leak while minimizing the risk of stent incorporation into the native tissues.

Clips: There is minimal data evaluating the role of endoscopic clips for management of anastomotic or staple line leaks. In a recent retrospective study by Keren *et al*^[39], the over-the-scope clip (OTSC) (Ovesco Endoscopy, TEndosco, Germany) was used in 26 patients that

developed leaks post-SG. The study concluded that 21 (80.7%) patients were successfully treated with the OTSC device^[39]. At our institute, clips are used to complement other management modalities, primarily stenting.

Suturing: The use of endoscopic suturing platforms has gained popularity for management of bariatric complications, including gastric pouch dilation and weight recidivism. This may be useful in both the acute and long-term setting. Current endoscopic suturing devices include the Apollo Overstitch (Apollo, Austin, TX) and the G-Prox (USGI Medical, San Capistrano, CA). Suturing via the Apollo Overstitch device allows for full thickness suturing for tissue approximation in the GI tract. This device has been implicated in the early use of marginal ulcers, stoma reduction after gastric bypass surgery, and closure of fistulas^[40,41]. The use of endoscopic plication will be further discussed under the management of long-term complications following bariatric surgery.

Fibrin glue: Fibrin glue or sealant is described in a brief review as a two-component hemostatic and sealant with tissue adhesive capabilities. Fibrin glue is composed of fibrinogen and thrombin^[42]. Once injected endoscopically at the site of leakage, the constituents promote occlusion at the site of defect, hindering the progression of the leak. Fibrin glue is rarely used a single modality but rather in combination with endoscopic stenting^[43-46]. Two endoscopic techniques have been described by several authors. Bolin and colleagues applied the fibrin glue under direct vision, through a double lumen catheter, leading to coagulation and the formation of a clot which plugged the defect^[47]. Victorzon *et al*^[48] described the process as a promotion in swelling and consolidation of the defect after endoscopic injection leading to a plug of the defect. Several studies in the literature indicate success in closure of gastrocutaneous fistulas using endoscopic injection of fibrin glue. Papavramidis *et al*^[49] reported success in two patients that received fibrin glue for high-output gastrocutaneous fistulas occurring post-vertical banded gastroplasty (VBG).

Late complications

Management of strictures: Endoscopic management of strictures continues to increase in an effort to avoid the higher morbidity of revisional procedures. The incidence of strictures varies according to the underlying bariatric operation^[50]. Strictures are more common post-LRYGB, with an estimated incidence rate ranging between 3%-28%^[51-53]. The cause of stricture development continues to remain unclear and is likely multifactorial. Tissue ischemia caused by the stapler, anastomotic tension, edema, and even foreign body reactions are believed to contribute to the development of anastomotic strictures^[51]. The development of stenosis maybe from the aforementioned factors, but some authors would agree the rate of stenosis may also be linked to the technique used for creation of the gastric reservoir

or anastomosis. Circular staplers have been implicated to have higher stricture rates vs hand-sewn or linear techniques. Common symptoms that should increase the index of suspicion for stricture development include nausea, vomiting, dysphagia, malnutrition, or significant weight loss over a short period of time.

Strictures can be diagnosed by several modalities, including endoscopy. Although other modalities may suffice, the ability to have direct, visual diagnostic and therapeutic capabilities gives endoscopy the upper hand^[54]. Endoscopic findings include the presence of a stenotic lumen, dilation of the gastric pouch, or non-digested food particles^[55].

Although less frequent, stricture development post-SG may present a greater management challenge. Incidence in patients undergoing SG is reported to be between 0.2% to 4%^[56]. Possible causes of post-SG stenosis development include the use of a small bougie. Post-SG strictures commonly occur at the proximal to mid stomach, incisura, or the gastro-esophageal junction. As in post-LRYGB, endoscopy plays a vital role in diagnosis and management of these strictures.

Endoscopic balloon dilation: Endoscopic balloon dilation has become first-line treatment and standard of care for the management of strictures post-LRYGB^[51]. There are many endoscopic balloons available for use, all of which are designed from polymers that have the ability to expand to the desired diameter. These balloons are geometrically designed to advance through the working channel (2.8 mm) of an endoscope with or without a guide wire.

The first step when performing endoscopic balloon dilatation is to identify the anatomy and properly estimate the size of the stricture. If the scope is unable to advance, a standard pediatric scope should be tried. The choice of balloon should then be decided based on the ability of the endoscope to traverse the stricture.

The balloon should be positioned at the site of maximum luminal narrowing. The balloon should be expanded slowly to its maximum diameter and held under tension for one minute. A prospective study conducted by Ahmad *et al*^[57], evaluating balloon dilation for strictures in patients that underwent LRYGB, concluded that balloon dilation is safe, effective and can be reproduced with minimal adverse effects. Additional studies have also shown that balloon dilation is a durable therapy for both the short- and long-term management of anastomotic strictures^[58,59].

Management of strictures post-SG includes observation, endoscopic dilation with or without stenting, seromyotomy, or ultimately converting to a LRYGB. It is important to differentiate true stenosis from sleeve rotation or torsion which may mimic obstructive symptoms. This may also be managed through endoscopic dilation, myotomy or surgical revision.

Stenting: Stenting may also be used in the management of strictures. In a prospective series presented

by Eubanks *et al*^[36], the authors report an 83% stent success rate in managing strictures in six patients that had been refractory to repeated balloon dilations. Nevertheless, a common concern of stent application is stent migration, which is reported to occur in 58% to 66% of stents placed^[9,60,61]. Controversies seem to exist regarding the rate of stent migration with the use of covered or partially covered stents. Some studies did not find a difference, while other studies reported a greater incidence of migration associated with fully covered stents. Covered stents are least likely to be incorporated by the native tissues which may lead to the higher rate of stent migration^[9].

Weight loss failure or weight recidivism: Weight loss failure is a broad term with no agreed upon definition amongst bariatric surgeons. As best we can tell, the incidence of weight recidivism is estimated to be 10%-20%^[62]. Technical failure may play a role in the development of initial weight loss failure post-bariatric surgery or recidivism after initial weight loss. Several other factors such as non-dietary compliance, large gastrojejunal anastomoses, dilation of the gastric pouch, and gastrogastic fistula development may contribute to weight loss failure or weight recidivism^[59,63]. Endoscopic therapies for weight regain continue to advance, providing a visible assessment of the anatomy as well as therapeutic intervention.

Endoscopy allows for the reduction in the stoma size of the gastrojejunal anastomosis by means of four quadrant endoscopic injection of sodium morrhuate into the seroma, which leads to scar formation, effectively reducing the stoma size^[59,63]. An alternative approach to the management of a dilated pouch is plication of the gastric pouch or stoma^[64]. This is an emerging technology and data on the long-term efficacy of this approach is not currently available. Nevertheless, in an effort to reduce pouch size, utilization of endoscopic suturing devices permit a non-surgical revision of the gastrojejunal anastomoses. Further studies demonstrating the durability and feasibility in the long-term are warranted^[65].

Marginal ulcer: Marginal ulcers occur at the gastrojejunal anastomosis with a reported incidence of 1% to 16% after RYGB. It typically occurs within the first several months post-operatively^[66-70]. Multiple factors have been identified in the development of ulcers, which include but are not limited to, ischemia, use of non-steroidal anti-inflammatory medications, disruption along the staple line, suture or staple erosion, gastrogastic fistula, increased gastric acidity, or tobacco use^[63,71]. The association of *Helicobacter pylori* (*H. pylori*) with the development of marginal ulcers remains unknown^[72]. Marginal ulcer may also be a cause of late bleeding post-bariatric surgery. Morbidity and mortality may be attributed to bleeding and perforation from marginal ulcers. Most common presenting symptoms include epigastric or abdominal pain, bleeding, nausea, vomiting, iron deficiency anemia, heme-positive stools, and in certain

instances patient may be asymptomatic.

In a study evaluating the incidence of marginal ulceration one month after gastric bypass, the ulcer rate was 4.1% after open RYGB and 12.3% after LRYGB patients. The study also noted that 28% of the ulcers were asymptomatic at the time of evaluation^[73]. Ulcers may be managed non-operatively by means of anti-acid, proton pump inhibitor medications and buffers such as sucralfate and discontinuation of the use of ulcer enhancing medications or lifestyles^[63]. Azagury *et al.*^[74] reported a 68% ulcer healing rate when combining medical therapies with eradication of possible risk factors.

The role of endoscopy in dealing with marginal ulcers is primarily to aid in establishing a diagnosis. In certain cases when eroded sutures are identified at the anastomosis, the sutures can be cut with endoscopic scissors and removed. If marginal ulcers are diagnosed during endoscopy, a meticulous examination for fistulas should be performed. If ulcers are refractory to medical treatment or are severe in nature, operative management may be required in an effort to prevent complications such as recurrent bleeding, perforation, and strictures^[75].

VBG: VBG was a popular procedure in the 1980s but has since been replaced by the AGB. VBG can be thought of as a combination of a SG with a non-AGB^[76]. In other words, this was a restrictive procedure that created a smaller stomach pouch with a non-adjustable band at the distal aspect of the pouch that controlled the rate at which nutrients reached the rest of the GI tract. The VBG procedure was ineffective at long-term weight loss and a majority of patients suffered from band erosion, outlet stricture, and gastro-gastric fistula causing weight regain^[76,77]. These complications can all be diagnosed on endoscopy but are best managed with surgical revision. Options for revision of VBG include RYGB or VBG reversal via gastrogastrostomy^[77].

Band erosion, migration and slippage: Since VBG and AGB were once the most commonly performed bariatric procedure, there is a large population at risk of their associated complications, including band erosion, migration, and slippage. The incidence of band erosions is reported to occur in 0.1% to 7.7% of all patients^[78-82]. This complication is commonly diagnosed endoscopically by the erosion of the band into the stomach lumen.

Upon discovery of erosion of a VBG, the band may be severed endoscopically just as long as the band has remained encapsulated^[63,83,84]. If uncertain about the state of capsulation, a computed tomography scan should be obtained for further evaluation prior to endoscopic intervention. On the other hand, patients who have undergone AGB may have diagnosis of band erosion on endoscopy but cannot undergo endoscopic intervention due to the presence of tubing that connects the band subcutaneously for adjustment.

Band slippage is a possible complication for both VBG and AGB but is more common with AGB. This is

typically diagnosed through an upper GI series but may be observed on endoscopy by visualization of a larger than expected stomach pouch with narrowing of the gastric lumen distally^[63,83,84]. Band slippage is a surgical emergency as it may lead to necrosis of the stomach.

CONCLUSION

Flexible endoscopy has become an essential tool in managing bariatric surgery patients. Endoscopy offers the benefit of providing both diagnostic and therapeutic applications. Endoscopy should be performed by an experienced endoscopist familiar with bariatric anatomies and with advanced skills in their therapeutic armamentarium. Endoscopic procedures in the post-bariatric surgery patient presents unique challenges unlike other endoscopic procedures because of altered anatomy, and specifically, access to the biliopancreatic limb, remnant stomach, and jejunojejunostomy. Common complications after bariatric surgery include: Bleeding, leaks/fistulas and strictures. Increasingly, endoscopist are gaining the experience to successfully diagnose and treat post-bariatric surgery patients and their complications.

REFERENCES

- 1 **World Health Organization.** Obesity and Overweight Fact Sheet [Internet]. 2015. Available from: URL: <http://www.who.int/mediacentre/factsheets/fs311/en/>
- 2 **Ramos AC,** Murakami A, Lanzarini EG, Neto MG, Galvão M. Achalasia and laparoscopic gastric bypass. *Surg Obes Relat Dis* 2009; **5**: 132-134 [PMID: 18722821 DOI: 10.1016/j.soard.2008.05.004]
- 3 **Corcelles R,** Boules M, Froylich D, Hag A, Daigle C, Aminian A, Brethauer SA, Burguera B, Schauer PR. Total Weight Loss as the Outcome Measure of Choice After Roux-en-Y Gastric Bypass. *Obes Surg* 2016; **26**: 1794-1798 [PMID: 26803753 DOI: 10.1007/s11695-015-2022-y]
- 4 **Sjöström CD,** Lissner L, Wedel H, Sjöström L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. *Obes Res* 1999; **7**: 477-484 [PMID: 10509605]
- 5 **Flum DR,** Belle SH, King WC, Wahed AS, Berk P, Chapman W, Pories W, Courcoulas A, McCloskey C, Mitchell J, Patterson E, Pomp A, Staten MA, Yanovski SZ, Thirlby R, Wolfe B. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009; **361**: 445-454 [PMID: 19641201 DOI: 10.1056/NEJMoa0901836]
- 6 **Adams TD,** Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; **357**: 753-761 [PMID: 17715409 DOI: 10.1056/NEJMoa066603]
- 7 **Angrisani L,** Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric Surgery Worldwide 2013. *Obes Surg* 2015; **25**: 1822-1832 [PMID: 25835983 DOI: 10.1007/s11695-015-1657-z]
- 8 **Adams TD,** Davidson LE, Litwin SE, Kolotkin RL, LaMonte MJ, Pendleton RC, Strong MB, Vinik R, Wanner NA, Hopkins PN, Gress RE, Walker JM, Cloward TV, Nuttall RT, Hammoud A, Greenwood JL, Crosby RD, McKinlay R, Simper SC, Smith SC, Hunt SC. Health benefits of gastric bypass surgery after 6 years. *JAMA* 2012; **308**: 1122-1131 [PMID: 22990271 DOI: 10.1001/2012.jama.11164]
- 9 **Yimcharoen P,** Heneghan HM, Tariq N, Brethauer SA, Kroh M, Chand B. Endoscopic stent management of leaks and anastomotic strictures after foregut surgery. *Surg Obes Relat Dis* 2011; **7**: 628-636 [PMID: 21798816 DOI: 10.1016/j.soard.2011.03.017]

- 10 **Nguyen NT**, Rivers R, Wolfe BM. Early gastrointestinal hemorrhage after laparoscopic gastric bypass. *Obes Surg* 2003; **13**: 62-65 [PMID: 12630615 DOI: 10.1381/096089203321136601]
- 11 **Ferreira LE**, Song LM, Baron TH. Management of acute postoperative hemorrhage in the bariatric patient. *Gastrointest Endosc Clin N Am* 2011; **21**: 287-294 [PMID: 21569980 DOI: 10.1016/j.giec.2011.02.002]
- 12 **Podnos YD**, Jimenez JC, Wilson SE, Stevens CM, Nguyen NT. Complications after laparoscopic gastric bypass: a review of 3464 cases. *Arch Surg* 2003; **138**: 957-961 [PMID: 12963651 DOI: 10.1001/archsurg.138.9.957]
- 13 **Eid JJ**, Radecke JM, Murr MM. Gastrointestinal bleeding from the excluded stomach: a proposed algorithmic approach to management. *Surg Obes Relat Dis* 2015; **11**: e11-e14 [PMID: 25449066 DOI: 10.1016/j.soard.2014.09.008]
- 14 **Jamil LH**, Krause KR, Chengelis DL, Jury RP, Jackson CM, Cannon ME, Duffy MC. Endoscopic management of early upper gastrointestinal hemorrhage following laparoscopic Roux-en-Y gastric bypass. *Am J Gastroenterol* 2008; **103**: 86-91 [PMID: 17941960 DOI: 10.1111/j.1572-0241.2007.01588.x]
- 15 **Rabl C**, Peeva S, Prado K, James AW, Rogers SJ, Posselt A, Campos GM. Early and late abdominal bleeding after Roux-en-Y gastric bypass: sources and tailored therapeutic strategies. *Obes Surg* 2011; **21**: 413-420 [PMID: 21240659 DOI: 10.1007/s11695-011-0354-9]
- 16 **Bakhos C**, Alkhoury F, Kyriakides T, Reinhold R, Nadzam G. Early postoperative hemorrhage after open and laparoscopic roux-en-y gastric bypass. *Obes Surg* 2009; **19**: 153-157 [PMID: 18629595 DOI: 10.1007/s11695-008-9580-1]
- 17 **Laine L**, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. *Clin Gastroenterol Hepatol* 2009; **7**: 33-47; quiz 1-2 [PMID: 18986845 DOI: 10.1016/j.cgh.2008.08.016]
- 18 **Buchwald H**, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004; **292**: 1724-1737 [PMID: 15479938 DOI: 10.1001/jama.292.14.1724]
- 19 **Lin HJ**, Hsieh YH, Tseng GY, Perng CL, Chang FY, Lee SD. A prospective, randomized trial of large- versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding. *Gastrointest Endosc* 2002; **55**: 615-619 [PMID: 11979239]
- 20 **Vergara M**, Calvet X, Gisbert JP. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. *Cochrane Database Syst Rev* 2007; **(2)**: CD005584 [PMID: 17443601 DOI: 10.1002/14651858.CD005584.pub2]
- 21 **Marmo R**, Rotondano G, Piscopo R, Bianco MA, D'Angella R, Cipolletta L. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *Am J Gastroenterol* 2007; **102**: 279-289; quiz 469 [PMID: 17311650 DOI: 10.1111/j.1572-0241.2006.01023.x]
- 22 **Laine L**, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012; **107**: 345-360; quiz 361 [PMID: 22310222 DOI: 10.1038/ajg.2011.480]
- 23 **Chang J**, Sharma G, Boules M, Brethauer S, Rodriguez J, Kroh M. Endoscopic stents in the management of anastomotic complications after foregut surgery: new applications and techniques. *Surg Obes Relat Dis* 2016; pii: S1550-7289(16)00087-3 [PMID: 27317605 DOI: 10.1016/j.soard.2016.02.041]
- 24 **Vanbiervliet G**, Filippi J, Karimjee BS, Venissac N, Iannelli A, Rahili A, Benizri E, Pop D, Staccini P, Tran A, Schneider S, Mouroux J, Gugenheim J, Benichmol D, Hébuterne X. The role of clips in preventing migration of fully covered metallic esophageal stents: a pilot comparative study. *Surg Endosc* 2012; **26**: 53-59 [PMID: 21792721 DOI: 10.1007/s00464-011-1827-6]
- 25 **Chuttani R**, Barkun A, Carpenter S, Chotiprasidhi P, Ginsberg GG, Hussain N, Liu J, Silverman W, Taitelbaum G, Petersen B. Endoscopic clip application devices. *Gastrointest Endosc* 2006; **63**: 746-750 [PMID: 16650531 DOI: 10.1016/j.gie.2006.02.042]
- 26 **Ginsberg GG**, Lipman TO, Fleischer DE. Endoscopic clip-assisted placement of enteral feeding tubes. *Gastrointest Endosc* 1994; **40**: 220-222 [PMID: 8013825]
- 27 **Hachisu T**, Miyazaki S, Hamaguchi K. Endoscopic clip-marking of lesions using the newly developed HX-3L clip. *Surg Endosc* 1989; **3**: 142-147 [PMID: 2814777]
- 28 **Tang SJ**, Rivas H, Tang L, Lara LF, Sreenarasimhaiah J, Rockey DC. Endoscopic hemostasis using endoclip in early gastrointestinal hemorrhage after gastric bypass surgery. *Obes Surg* 2007; **17**: 1261-1267 [PMID: 18074504]
- 29 **Jensen DM**, Machicado GA, Hirabayashi K. Randomized controlled study of 3 different types of hemoclips for hemostasis of bleeding canine acute gastric ulcers. *Gastrointest Endosc* 2006; **64**: 768-773 [PMID: 17055872 DOI: 10.1016/j.gie.2006.06.031]
- 30 **Fernández-Esparrach G**, Bordas JM, Pellisé M, Gimeno-García AZ, Lacy A, Delgado S, Cárdenas A, Ginès A, Sendino O, Momblán D, Zabalza M, Llach J. Endoscopic management of early GI hemorrhage after laparoscopic gastric bypass. *Gastrointest Endosc* 2008; **67**: 552-555 [PMID: 18294521 DOI: 10.1016/j.gie.2007.10.024]
- 31 **Morales MP**, Miedema BW, Scott JS, de la Torre RA. Management of postsurgical leaks in the bariatric patient. *Gastrointest Endosc Clin N Am* 2011; **21**: 295-304 [PMID: 21569981 DOI: 10.1016/j.giec.2011.02.008]
- 32 **Aurora AR**, Khaitan L, Saber AA. Sleeve gastrectomy and the risk of leak: a systematic analysis of 4,888 patients. *Surg Endosc* 2012; **26**: 1509-1515 [PMID: 22179470 DOI: 10.1007/s00464-011-2085-3]
- 33 **Schauer P**, Ikramuddin S, Hamad G, Gourash W. The learning curve for laparoscopic Roux-en-Y gastric bypass is 100 cases. *Surg Endosc* 2003; **17**: 212-215 [PMID: 12457218 DOI: 10.1007/s00464-002-8857-z]
- 34 **DeMaria EJ**, Sugerman HJ, Kellum JM, Meador JG, Wolfe LG. Results of 281 consecutive total laparoscopic Roux-en-Y gastric bypasses to treat morbid obesity. *Ann Surg* 2002; **235**: 640-645; discussion 645-647 [PMID: 11981209]
- 35 **Brethauer SA**. Sleeve gastrectomy. *Surg Clin North Am* 2011; **91**: 1265-1279, ix [PMID: 22054153 DOI: 10.1016/j.suc.2011.08.012]
- 36 **Eubanks S**, Edwards CA, Fearing NM, Ramaswamy A, de la Torre RA, Thaler KJ, Miedema BW, Scott JS. Use of endoscopic stents to treat anastomotic complications after bariatric surgery. *J Am Coll Surg* 2008; **206**: 935-938; discussion 938-939 [PMID: 18471727 DOI: 10.1016/j.jamcollsurg.2008.02.016]
- 37 **Merrifield BF**, Lautz D, Thompson CC. Endoscopic repair of gastric leaks after Roux-en-Y gastric bypass: a less invasive approach. *Gastrointest Endosc* 2006; **63**: 710-714 [PMID: 16564884 DOI: 10.1016/j.gie.2005.11.018]
- 38 **Puli SR**, Spofford IS, Thompson CC. Use of self-expandable stents in the treatment of bariatric surgery leaks: a systematic review and meta-analysis. *Gastrointest Endosc* 2012; **75**: 287-293 [PMID: 22047699 DOI: 10.1016/j.gie.2011.09.010]
- 39 **Keren D**, Eyal O, Sroka G, Rainis T, Raziel A, Sakran N, Goitein D, Matter I. Over-the-Scope Clip (OTSC) System for Sleeve Gastrectomy Leaks. *Obes Surg* 2015; **25**: 1358-1363 [PMID: 25511753 DOI: 10.1007/s11695-014-1540-3]
- 40 **Stavropoulos SN**, Modayil R, Friedel D. Current applications of endoscopic suturing. *World J Gastrointest Endosc* 2015; **7**: 777-789 [PMID: 26191342 DOI: 10.4253/wjge.v7.i8.777]
- 41 **Rieder E**, Dunst CM, Martinec DV, Cassera MA, Swanstrom LL. Endoscopic suture fixation of gastrointestinal stents: proof of biomechanical principles and early clinical experience. *Endoscopy* 2012; **44**: 1121-1126 [PMID: 23188662 DOI: 10.1055/s-0032-1325730]
- 42 **Spotnitz WD**. Fibrin sealant: past, present, and future: a brief review. *World J Surg* 2010; **34**: 632-634 [PMID: 19820991 DOI: 10.1007/s00268-009-0252-7]
- 43 **Bhayani NH**, Swanström LL. Endoscopic therapies for leaks and fistulas after bariatric surgery. *Surg Innov* 2014; **21**: 90-97 [PMID: 23980200 DOI: 10.1177/1553350613497270]
- 44 **Spyropoulos C**, Argentou MI, Petsas T, Thomopoulos K, Kehagias I, Kalfarentzos F. Management of gastrointestinal leaks after surgery for clinically severe obesity. *Surg Obes Relat Dis* 2012; **8**:

- 609-615 [PMID: 21616725 DOI: 10.1016/j.soard.2011.04.222]
- 45 **Bège T**, Emungania O, Vitton V, Ah-Soune P, Nocca D, Noël P, Bradjanian S, Berdah SV, Brunet C, Grimaud JC, Barthet M. An endoscopic strategy for management of anastomotic complications from bariatric surgery: a prospective study. *Gastrointest Endosc* 2011; **73**: 238-244 [PMID: 21295637 DOI: 10.1016/j.gie.2010.10.010]
- 46 **Schweitzer M**, Steele K, Mitchell M, Okolo P. Transoral endoscopic closure of gastric fistula. *Surg Obes Relat Dis* 2009; **5**: 283-284 [PMID: 19306823 DOI: 10.1016/j.soard.2008.11.014]
- 47 **Brolin RE**, Lin JM. Treatment of gastric leaks after Roux-en-Y gastric bypass: a paradigm shift. *Surg Obes Relat Dis* 2013; **9**: 229-233 [PMID: 22336493 DOI: 10.1016/j.soard.2012.01.006]
- 48 **Victorzon M**, Victorzon S, Peromaa-Haavisto P. Fibrin glue and stents in the treatment of gastrojejunal leaks after laparoscopic gastric bypass: a case series and review of the literature. *Obes Surg* 2013; **23**: 1692-1697 [PMID: 23912265 DOI: 10.1007/s11695-013-1048-2]
- 49 **Papavramidis ST**, Eleftheriadis EE, Apostolidis DN, Kotzampassi KE. Endoscopic fibrin sealing of high-output non-healing gastrocutaneous fistulas after vertical gastropasty in morbidly obese patients. *Obes Surg* 2001; **11**: 766-769 [PMID: 11775579 DOI: 10.1381/09608920160558759]
- 50 **Sharaiha RZ**, Kim KJ, Singh VK, Lennon AM, Amateau SK, Shin EJ, Canto MI, Kalloo AN, Khashab MA. Endoscopic stenting for benign upper gastrointestinal strictures and leaks. *Surg Endosc* 2014; **28**: 178-184 [PMID: 24013467 DOI: 10.1007/s00464-013-3150-x]
- 51 **Ukleja A**, Afonso BB, Pimentel R, Szomstein S, Rosenthal R. Outcome of endoscopic balloon dilation of strictures after laparoscopic gastric bypass. *Surg Endosc* 2008; **22**: 1746-1750 [PMID: 18347868 DOI: 10.1007/s00464-008-9788-0]
- 52 **Anderson MA**, Gan SI, Fanelli RD, Baron TH, Banerjee S, Cash BD, Dominitz JA, Harrison ME, Ikenberry SO, Jagannath SB, Lichtenstein DR, Shen B, Lee KK, Van Guilder T, Stewart LE. Role of endoscopy in the bariatric surgery patient. *Gastrointest Endosc* 2008; **68**: 1-10 [PMID: 18577471 DOI: 10.1016/j.gie.2008.01.028]
- 53 **Evans JA**, Muthusamy VR, Acosta RD, Bruining DH, Chandrasekhara V, Chathadi KV, Eloubeidi MA, Fanelli RD, Faulx AL, Fonkalsrud L, Khashab MA, Lightdale JR, Pasha SF, Saltzman JR, Shaukat A, Wang A, Stefanidis D, Richardson WS, Kothari SN, Cash BD. The role of endoscopy in the bariatric surgery patient. *Gastrointest Endosc* 2015; **81**: 1063-1072 [PMID: 25733126 DOI: 10.1016/j.gie.2014.09.044]
- 54 **Messmer JM**, Wolper JC, Sugerman HJ. Stomal disruption in gastric partition in morbid obesity (comparison of radiographic and endoscopic diagnosis). *Am J Gastroenterol* 1984; **79**: 603-605 [PMID: 6465108]
- 55 **Huang CS**, Farraye FA. Endoscopy in the bariatric surgical patient. *Gastroenterol Clin North Am* 2005; **34**: 151-166 [PMID: 15823445 DOI: 10.1016/j.gtc.2004.12.013]
- 56 **Parikh A**, Alley JB, Peterson RM, Harnisch MC, Pfluke JM, Tapper DM, Fenton SJ. Management options for symptomatic stenosis after laparoscopic vertical sleeve gastrectomy in the morbidly obese. *Surg Endosc* 2012; **26**: 738-746 [PMID: 22044967 DOI: 10.1007/s00464-011-1945-1]
- 57 **Ahmad J**, Martin J, Ikramuddin S, Schauer P, Slivka A. Endoscopic balloon dilation of gastroenteric anastomotic stricture after laparoscopic gastric bypass. *Endoscopy* 2003; **35**: 725-728 [PMID: 12929018 DOI: 10.1055/s-2003-41579]
- 58 **de Moura EG**, Orso IR, Aurélio EF, de Moura DT, Santo MA. Factors associated with complications or failure of endoscopic balloon dilation of anastomotic stricture secondary to Roux-en-Y gastric bypass surgery. *Surg Obes Relat Dis* 2016; **12**: 582-586 [PMID: 27174245 DOI: 10.1016/j.soard.2015.11.006]
- 59 **Catalano MF**, Chua TY, Rudic G. Endoscopic balloon dilation of stomal stenosis following gastric bypass. *Obes Surg* 2007; **17**: 298-303 [PMID: 17546835 DOI: 10.1007/s11695-007-9055-9]
- 60 **Babor R**, Talbot M, Tyndal A. Treatment of upper gastrointestinal leaks with a removable, covered, self-expanding metallic stent. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: e1-e4 [PMID: 19238047 DOI: 10.1097/SLE.0b013e318196c706]
- 61 **Edwards CA**, Bui TP, Astudillo JA, de la Torre RA, Miedema BW, Ramaswamy A, Fearing NM, Ramshaw BJ, Thaler K, Scott JS. Management of anastomotic leaks after Roux-en-Y bypass using self-expanding polyester stents. *Surg Obes Relat Dis* 2008; **4**: 594-599; discussion 599-600 [PMID: 18722820 DOI: 10.1016/j.soard.2008.05.009]
- 62 **Karmali S**, Brar B, Shi X, Sharma AM, de Gara C, Birch DW. Weight recidivism post-bariatric surgery: a systematic review. *Obes Surg* 2013; **23**: 1922-1933 [PMID: 23996349 DOI: 10.1007/s11695-013-1070-4]
- 63 **Schreiner MA**, Fennerty MB. Endoscopy in the obese patient. *Gastroenterol Clin North Am* 2010; **39**: 87-97 [PMID: 20202582 DOI: 10.1016/j.gtc.2009.12.009]
- 64 **Schweitzer M**. Endoscopic intraluminal suture plication of the gastric pouch and stoma in postoperative Roux-en-Y gastric bypass patients. *J Laparoendosc Adv Surg Tech A* 2004; **14**: 223-226 [PMID: 15345160 DOI: 10.1089/lap.2004.14.223]
- 65 **Thompson CC**, Slattey J, Bundga ME, Lautz DB. Peroral endoscopic reduction of dilated gastrojejunal anastomosis after Roux-en-Y gastric bypass: a possible new option for patients with weight regain. *Surg Endosc* 2006; **20**: 1744-1748 [PMID: 17024527 DOI: 10.1007/s00464-006-0045-0]
- 66 **Rasmussen JJ**, Fuller W, Ali MR. Marginal ulceration after laparoscopic gastric bypass: an analysis of predisposing factors in 260 patients. *Surg Endosc* 2007; **21**: 1090-1094 [PMID: 17514403 DOI: 10.1007/s00464-007-9285-x]
- 67 **MacLean LD**, Rhode BM, Nohr C, Katz S, McLean AP. Stomal ulcer after gastric bypass. *J Am Coll Surg* 1997; **185**: 1-7 [PMID: 9208953]
- 68 **Capella JF**, Capella RF. Gastro-gastric fistulas and marginal ulcers in gastric bypass procedures for weight reduction. *Obes Surg* 1999; **9**: 22-27; discussion 28 [PMID: 10065576 DOI: 10.1381/096089299765553674]
- 69 **Capella JF**, Capella RF. Staple Disruption and Marginal Ulceration in Gastric Bypass Procedures for Weight Reduction. *Obes Surg* 1996; **6**: 44-49 [PMID: 10731249 DOI: 10.1381/096089296765557259]
- 70 **Pope GD**, Goodney PP, Burchard KW, Proia RR, Olafsson A, Lacy BE, Burrows LJ. Peptic ulcer/stricture after gastric bypass: a comparison of technique and acid suppression variables. *Obes Surg* 2002; **12**: 30-33 [PMID: 11868294 DOI: 10.1381/096089202321144540]
- 71 **Gumbs AA**, Duffy AJ, Bell RL. Incidence and management of marginal ulceration after laparoscopic Roux-Y gastric bypass. *Surg Obes Relat Dis* 2006; **2**: 460-463 [PMID: 16925381 DOI: 10.1016/j.soard.2006.04.233]
- 72 **Rawlins L**, Rawlins MP, Brown CC, Schumacher DL. Sleeve gastrectomy: 5-year outcomes of a single institution. *Surg Obes Relat Dis* 2013; **9**: 21-25 [PMID: 23201209 DOI: 10.1016/j.soard.2012.08.014]
- 73 **Gill RS**, Whitlock KA, Mohamed R, Sarkhosh K, Birch DW, Karmali S. The role of upper gastrointestinal endoscopy in treating postoperative complications in bariatric surgery. *J Interv Gastroenterol* 2012; **2**: 37-41 [PMID: 22586549 DOI: 10.4161/jig.20133]
- 74 **Azagury DE**, Abu Dayyeh BK, Greenwalt IT, Thompson CC. Marginal ulceration after Roux-en-Y gastric bypass surgery: characteristics, risk factors, treatment, and outcomes. *Endoscopy* 2011; **43**: 950-954 [PMID: 21997722 DOI: 10.1055/s-0030-1256951]
- 75 **Bal B**, Koch TR, Finelli FC, Sarr MG. Managing medical and surgical disorders after divided Roux-en-Y gastric bypass surgery. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 320-334 [PMID: 20458335 DOI: 10.1038/nrgastro.2010.60]
- 76 **Brethauer SA**, Schauer PR. Perspective on Morbid Obesity and Its Surgical Treatment [Internet]. In: Zinner M, Ashley SW. *Maingot's Abdominal Operations*. New York: McGraw-Hill, 2013. Available from: URL: <http://accesssurgery.mhmedical.com/content.aspx?bookid=531&Sectionid=41808808>
- 77 **Tevis S**, Garren MJ, Gould JC. Revisional surgery for failed

- vertical-banded gastroplasty. *Obes Surg* 2011; **21**: 1220-1224 [PMID: 21234698 DOI: 10.1007/s11695-011-0358-5]
- 78 **Romy S**, Donadini A, Giusti V, Suter M. Roux-en-Y gastric bypass vs gastric banding for morbid obesity: a case-matched study of 442 patients. *Arch Surg* 2012; **147**: 460-466 [PMID: 22249850 DOI: 10.1001/archsurg.2011.1708]
- 79 **Eid I**, Birch DW, Sharma AM, Sherman V, Karmali S. Complications associated with adjustable gastric banding for morbid obesity: a surgeon's guides. *Can J Surg* 2011; **54**: 61-66 [PMID: 21251434]
- 80 **O'Brien PE**, Dixon JB. Weight loss and early and late complications--the international experience. *Am J Surg* 2002; **184**: 42S-45S [PMID: 12527350]
- 81 **Niville E**, Dams A, Vlasselaers J. Lap-Band erosion: incidence and treatment. *Obes Surg* 2001; **11**: 744-747 [PMID: 11775574]
- 82 **Msika S**. [Surgery for morbid obesity: 2. Complications. Results of a Technologic Evaluation by the ANAES]. *J Chir (Paris)* 2003; **140**: 4-21 [PMID: 12709648]
- 83 **Nocca D**, Frering V, Gallix B, de Seguin des Hons C, Noël P, Foulange MA, Millat B, Fabre JM. Migration of adjustable gastric banding from a cohort study of 4236 patients. *Surg Endosc* 2005; **19**: 947-950 [PMID: 15920690 DOI: 10.1007/s00464-004-2183-6]
- 84 **Stroh C**, Hohmann U, Will U, Flade-Kuthe R, Herbig B, Höhne S, Köhler H, Pick P, Horbach T, Weiner R, Wolff S, Lippert H, Wolf AM, Schmidt U, Meyer F, Manger T. Experiences of two centers of bariatric surgery in the treatment of intragastric band migration after gastric banding-the importance of the German multicenter observational study for quality assurance in obesity surgery 2005 and 2006. *Int J Colorectal Dis* 2008; **23**: 901-908 [PMID: 18535832 DOI: 10.1007/s00384-008-0495-z]

P- Reviewer: Akere A, Koch TR, Leitman M
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Li D



Review of small-bowel cleansing scales in capsule endoscopy: A panoply of choices

Ana Ponte, Rolando Pinho, Adélia Rodrigues, João Carvalho

Ana Ponte, Rolando Pinho, Adélia Rodrigues, João Carvalho, Department of Gastroenterology, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, 4434-502 Porto, Portugal

Author contributions: Ponte A designed the study, performed the research, analyzed the data and wrote the paper; Pinho R designed the study, performed the research, analyzed the data and wrote the paper; Rodrigues A performed the research and analyzed the data; Carvalho J performed the research and analyzed the data.

Conflict-of-interest statement: The authors declare no conflict of interest for this article, including commercial, personal, political, intellectual or religious interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Ana Ponte, MD, Department of Gastroenterology, Centro Hospitalar Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, Vila Nova de Gaia, 4434-502 Porto, Portugal. ana.ilponte@gmail.com
Telephone: +351-96-5651833
Fax: +351-22-7868369

Received: April 9, 2016
Peer-review started: April 10, 2016
First decision: June 6, 2016
Revised: June 17, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: September 16, 2016

Abstract

Evaluation of the quality of small-bowel cleansing is

required to assess the reliability of findings in capsule endoscopy (CE). Moreover, consensus regarding the need of intestinal preparation for CE remains to be achieved. The presence of multiple grading scales for small-bowel preparation in CE, which are time-consuming and complicated, adds difficulty to the comparison of different small-bowel cleansing regimens and their application in clinical practice. Nowadays, a validated scale universally accepted for grading small-bowel cleansing is lacking. In fact, there are numerous grading systems with very different technical characteristics, namely, the parameters and the portion of the CE video that are analyzed, the objectivity of the analysis, the lesser or greater dependency on the operator, and the validation of the score. The authors performed a review which aims to systematize and summarize currently available small-bowel grading scales in CE.

Key words: Capsule endoscopy; Small-bowel; Small-bowel Cleansing Scales; Enteroscopy; Grading

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Evaluation of the quality of small-bowel cleansing is required to assess the reliability of findings in capsule endoscopy (CE). Moreover, consensus regarding the need of intestinal preparation for CE remains to be achieved. Currently, there are numerous grading systems with very different technical characteristics, namely, the parameters and the portion of the CE video that are analyzed, the objectivity of the analysis, the lesser or greater dependency on the operator, and the validation of the score. The main purpose of this review is to gather and concise all small-bowel cleansing scales in CE available, as this has not been previously performed.

Ponte A, Pinho R, Rodrigues A, Carvalho J. Review of small-bowel cleansing scales in capsule endoscopy: A panoply of choices. *World J Gastrointest Endosc* 2016; 8(17): 600-609
Available from: URL: <http://www.wjgnet.com/1948-5190/full/>

INTRODUCTION

Capsule endoscopy (CE) was introduced into clinical practice in 2001, and since then it has assumed an important role in the study of numerous small-bowel disorders, namely obscure gastrointestinal bleeding, Crohn's disease, small-bowel tumors, polyposis syndromes and celiac disease^[1-4].

The diagnostic yield of CE and quality of mucosal visualization may be impaired by the presence of air bubbles, bile and intestinal debris. Moreover, evidence for the optimal approach for small-bowel preparation before CE is lacking. These research and clinical aspects emphasize the importance of a grading scale of small-bowel cleansing in CE, as the evaluation of the quality of small-bowel preparation is necessary to assess the accuracy of the findings in CE^[5,6] and the presence of a universal grading score would contribute to standardize CE protocols and to compare the results of different methods of small-bowel preparation^[6,7].

Nowadays, a validated scale universally accepted for grading small-bowel cleansing is lacking. In fact, there are numerous grading systems with very different technical characteristics, namely, the parameters and the portion of the CE video that are analysed, the objectivity of the analysis, the lesser or greater dependency on the operator, and the validation of the score.

This review aims to systematize and summarize available small-bowel grading scales in CE (Tables 1 and 2).

DISCUSSION

Computer dependent scales

In recent years, computer grading scales to evaluate small-bowel cleanliness have been developed and validated (Table 1)^[6,8]. These computed scores are based on objective measurements and may potentially overcome the disadvantages of human dependent scoring systems, namely the subjectivity, complexity and lengthiness. Furthermore, the incorporation of these scores into the CE reading software would result in a fully automated score^[6].

Van Weyenberg *et al*^[6] developed a computed assessment of cleansing (CAC) score, based on objective measurements of colour intensities in red and green channels of the tissue colour bar of the Rapid Reader[®] in the PillCam CE[®] system. The authors assumed that if the tissue colour bar, which comprises the summary of all CE images, was converted to the red-green-blue mode (RGB), the relation between the mean intensity of the red and green channels could be used as a measure of small-bowel cleanliness. Therefore, areas of adequate mucosal visibility could be associated with high values of red intensity and low values of green intensity. Conversely, areas with high amount of intestinal debris

could be associated with low values of red intensity and high values of green intensity. The mean intensity values of the green and red channels of the small-bowel segment of the tissue colour bar were determined using the histogram function of a photo-editing software. The final score was obtained by applying the formula $[(\text{Mean intensity of the red channel})/(\text{Mean intensity of the green channel}) - 1] \times 10$. The CAC score was further compared with three validated grading scales^[5]. In this study, the authors concluded that the CAC score had a very good reproducibility and could be used to assess the overall and segmental quality of small-bowel cleanliness. Moreover, CAC score achieved a strong agreement with previously validated subjective scales^[5].

Due to the potential advantage of a computed score of small-bowel cleansing in CE, other studies were developed to adapt the CAC score to the OMOM and MiroCam CE systems^[9,10]. Ponte *et al*^[10] aimed to adapt the CAC score to the MiroCam system and to evaluate its reliability with the MiroCam[®] CE system. The MiroCam reading software (Miroview Client[®]) has a function named "Map View" which displays a bar containing a representation of all images recorded by the CE. Although this bar can be zoomed, without zoom the bar is similar to the tissue colour bar of the Rapid Reader[®] in the PillCam[®] CE system. Applying the same methodology as used by Van Weyenberg *et al*^[6], the mean intensities of the red and green channels of the small-bowel segment of the "Map View" bar of Miroview Client[®] were determined using the histogram option of two photo-editing softwares. The authors concluded that the reproducibility of the CAC score was excellent as the results of the two different photo-editing softwares were identical, resulting in an intra-test reliability of 1.0 ($P < 0.001$). CAC score achieved a moderate agreement with previously validated subjective scales^[5]. The results were slightly inferior to those of Van Weyenberg *et al*^[6] but still significant and reinforce the feasibility of the CAC score in the assessment of the intestinal preparation in CE systems other than the PillCam[®].

More recently, Klein *et al*^[8] designed and validated a computer algorithm based on the pixels in the tissue colour bar of the CE PillCam[®] system. To develop this algorithm, multiple points on the colour bar corresponding to a spectrum of inadequately or adequately segments were marked and defined as "adequate" or "inadequate" criteria. These criteria were defined based on the pixel color and hue derived from the pixel RGB values. A computer algorithm based on the pixels in each of the marked areas was then created, and applied to the entire tissue colour bar. Each pixel of the tissue colour bar was independently compared to the predefined criteria "adequate"/"inadequate". The computer algorithm then calculated and summarized the total number of "inadequate" pixels, their locations, the "adequate" to "inadequate" pixel ratio and the longest duration of consecutive "inadequate" pixels in the colour bar. Based on the image analysis results, the algorithm quantified

Table 1 Computer dependent scales

Ref.	Computer or human dependent	Capsule endoscopy system	Type of preparation	Qualitative/ quantitative scale	Reproducibility	Parameters evaluated	Entire video, segments of video or consecutive single frames	Time-consuming	Easy to perform ¹	Global assessment ²
Van Weyenberg <i>et al</i> ^[6]	Computer dependent	PillCam	2 L of PEG	Quantitative	$r = 1.0$	Mean intensity values of the green and red channels of the small-bowel segment of the tissue colour bar	Tissue colour bar	No	ΔΔΔΔΔ	ΔΔΔΔ
Ponte <i>et al</i> ^[10]	Computer dependent	MiroCam	Clear liquid diet and overnight fast	Quantitative	$r = 1.0$	Mean intensity values of the green and red channels of the small-bowel segment of the tissue colour bar	Map view bar	No	ΔΔΔΔΔ	ΔΔΔΔ
Klein <i>et al</i> ^[8]	Computer dependent	PillCam	Clear liquid diet and overnight fast	Quantitative	Kappa = 0.9	Pixels of the small-bowel segment of the tissue colour bar	Tissue colour bar	No	ΔΔΔΔΔ	ΔΔΔΔ

¹Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to easier scales; ²Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to better scales. PEG: Polyethylene glycol.

the level of bowel preparation and a final result based on predetermined criteria was produced. Computer analysis restricted to adequate and inadequate cases yielded accurate classification of bowel preparation when compared to the subjective opinion of the authors with a sensitivity of 95%, specificity 82%, total accuracy 90%, and kappa 0.79.

OPERATOR DEPENDENT SCALES

The numerous operator dependent scales which have been developed are summarized in Table 2. Throughout this revision, the authors classified the scales taking into consideration the type of parameters that were used: Quantitative and/or qualitative.

Quantitative parameters

Park *et al*^[11,12] developed and validated an operator dependent grading score which consists of the assessment of two parameters in the PillCam® CE, in patients who received 4 L of polyethylene glycol (PEG). The first parameter corresponds to the percentage of mucosa visualized which is classified from 0 to 3: Score 3, ≥ 75%; score 2, 50%-75%; score 1, 25%-50%; score 0, ≤ 25%. The second parameter refers to the degree of obscuration by bubbles, debris, and bile which is also classified from 0 to 3: score 3 (no obscuration), < 5%; score 2 (mild obscuration), 5%-25%; score 1 (moderate obscuration), 25%-50%; score 0 (severe obscuration), ≥ 50%. The two parameters of the Park's score were evaluated in images from the entire small bowel selected at 5-min intervals (1 frame/5 min). Mean scores of each parameter were obtained by summing the scores of all selected images and dividing them by the number of frames examined. The final score was then calculated by the overall average of the two mean scores. This scale showed an excellent inter-observer, intra-patient and intra-observer agreement. Moreover, the authors proposed a cut-off value of 2.25 for an adequate small-bowel preparation. The main limitation of this grading scale is the use of only 1 frame at 5 min intervals in the analysis of small bowel cleansing, which leaves the great majority of available frames unanalysed.

Brotz *et al*^[5] developed and validated three grading systems in CE PillCam®, namely a quantitative index (QI), a qualitative evaluation (QE) and an overall adequacy assessment (OAA). As the QE and OAA are based on qualitative parameters, these scores are described in the corresponding section. In their study, patients received a clear liquid diet the day before the exam and an overnight fast. The QI was obtained by assessment of 5 elements [(1) Mucosal visualization; (2) Fluid and debris; (3) Bubbles; (4) Bile/chyme staining, and (5) Brightness], according to a 3-point scale (0 = severe impairment, 1 = moderate impairment, 2 = minimal impairment), leading to a total score ranging from 0 to 10, with higher scores corresponding to better cleansing. QI obtained a moderate interobserver agreement. As opposed to Park's score,

Table 2 Human dependent scales

Ref.	Computer or human dependent	Capsule endoscopy system	Type of preparation	Qualitative/quantitative scale	Correlation coefficient	Parameters evaluated	Entire video, segments of video or consecutive single frames	Time-consuming	Easy to perform ¹	Global assessment ²
Park <i>et al</i> ^[11]	Human dependent	PillCam	4 L of PEG	Quantitative	ICC = 0.80	Proportion of visualized mucosa and degree of obscuration by bubbles, debris, and bile	Consecutive single frames	Yes	ΔΔ	ΔΔΔ
QI - Brotz <i>et al</i> ^[5]	Human dependent	PillCam	Clear liquid diet and overnight fast	Quantitative	ICC = 0.47	QI based on percentage of mucosa visualized, fluid and debris, bubbles, bile/chyme staining, and brightness	Entire video	No	ΔΔΔΔ	ΔΔΔΔΔ
Spada <i>et al</i> ^[13]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 2 L of PEG and simethicone	Quantitative	Kappa = 0.75-0.9	Proportion of mucosa visualized	Entire video	Yes	Δ	ΔΔΔ
Oliva <i>et al</i> ^[14]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 25 or 50 mL/kg of PEG, and/or 20 mL of simethicone	Quantitative	Kappa = 0.89	Proportion of mucosa visualized	Consecutive single frames	Yes	ΔΔ	ΔΔΔ
van Tuyl <i>et al</i> ^[15]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 1 L of PEG, or 2 L of PEG	Quantitative	Kappa = 0.78	Proportion of mucosa visualized	Segments of video	No	ΔΔ	ΔΔΔ
Caddy <i>et al</i> ^[16]	Human dependent	-	250 mL sodium picosulphate plus 500 mL PEG with or without erythromycin	Quantitative	Kappa = 0.3	Proportion of visualized mucosa	Entire video	No	ΔΔΔΔΔ	ΔΔ
Viazis <i>et al</i> ^[19]	Human dependent	PillCam	Clear liquid diet and overnight fast or 2 L PEG	Quantitative	-	Proportion of unclean mucosa due to intestinal debris	Entire video	Yes	ΔΔΔ	ΔΔ
Kantianis <i>et al</i> ^[22]	Human dependent	PillCam	2 and 4 L of PEG	Quantitative	-	Proportion of mucosa visualized	Consecutive single frames	Yes	Δ	Δ
Chen <i>et al</i> ^[23]	Human dependent	OMOM	Clear liquid diet and overnight fast, or 250 mL mannitol with or without simethicone	Quantitative	-	Proportion of mucosa visualized	Consecutive single frames	Yes	Δ	Δ
Rosa <i>et al</i> ^[25]	Human dependent	PillCam	Clear liquid diet and overnight fast, or 2 L of PEG with or without simethicone	Quantitative	-	Proportion of visualized mucosa	Entire video	Yes	ΔΔ	ΔΔ
Niv <i>et al</i> ^[26]	Human dependent	PillCam	Clear liquid diet and overnight fast, or NaP	Quantitative	-	Proportion of SBT with invisible mucosa	Entire video	No	ΔΔΔ	ΔΔΔ
OAA - Brotz <i>et al</i> ^[5]	Human dependent	PillCam	Clear liquid diet and overnight fast	Qualitative	Kappa = 0.41	Overall assessment of small-bowel cleansing	Entire video	No	ΔΔΔΔΔ	ΔΔΔ
QE - Brotz <i>et al</i> ^[5]	Human dependent	PillCam	Clear liquid diet and overnight fast	Qualitative	Kappa = 0.20	QE based on percentage of mucosa visualized, fluid and debris, bubbles, bile/chyme staining, and brightness	Entire video	No	ΔΔΔΔΔ	ΔΔΔ
Albert <i>et al</i> ^[28]	Human dependent	PillCam	Overnight fast or simethicone	Qualitative	$r = 0.89$ (segment A)	Mucosal invisibility due to intraluminal bubbles	Segments of video	No	ΔΔΔ	ΔΔΔ

Pons Beltrán <i>et al</i> ^[29]	Human dependent	PillCam	Clear liquid diet, or 90 mL NaP, or 4 L of PEG	Qualitative	and $r = 0.79$ (segment B) Kappa = 0.38	Amounts of enteric residues	Entire video	No	ΔΔΔΔ	ΔΔΔ
Ninomiya <i>et al</i> ^[30]	Human dependent	PillCam	Clear liquid diet and overnight fast, or citrate magnesium	Qualitative	-	Bubbles, food residues and intestinal juice color	Consecutive single frames	Yes	ΔΔ	ΔΔ
Esaki <i>et al</i> ^[31]	Human dependent	PillCam	Simethicone or magnesium citrate	Quantitative and Qualitative	$r = 0.77-0.88$	Fluid transparency and proportion of non-visualized mucosa	Entire video	Yes	ΔΔΔ	ΔΔΔΔ
Dai <i>et al</i> ^[32]	Human dependent	PillCam	4 L of PEG or overnight fast	Quantitative and qualitative	Kappa = 0.56	Proportion of visualized mucosa and overall visibility	Segments of video	Yes	ΔΔ	ΔΔΔ
Lapalus <i>et al</i> ^[33]	Human dependent	PillCam	Clear liquid diet and overnight fast, or NaP	Quantitative and qualitative	$r = 0.55-0.8$	Proportion of visualized mucosa and amounts of enteric liquid and bubbles	Segments of video	No	ΔΔΔ	ΔΔΔ
Hooks <i>et al</i> ^[34]	Human dependent	PillCam	Clear liquid diet and overnight fast, with or without lubiprostone	Quantitative and qualitative	-	Proportion of mucosa visualized and amounts of enteric debris	Entire video and segments of video	No	ΔΔΔ	ΔΔΔΔ

¹Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to easier scales; ²Graduation from Δ to ΔΔΔΔΔ, with higher classifications corresponding to better scales. PEG: Polyethylene glycol; QI: Quantitative index; QE: Qualitative evaluation; OAA: Overall adequacy assessment; ICC: Intraclass correlation coefficient.

the QI uses all available frames in the evaluation of small bowel cleansing.

Spada *et al*^[13] developed an operator dependent small-bowel scale in PillCam[®] CE to evaluate different regimens of intestinal preparation. It consisted of a classification in "complete", "incomplete" and "insufficient" if visualization of the mucosa was equal to 100%, between 50%-100%, or less than 50%, respectively. This assessment was evaluated minute by minute and the overall small-bowel cleansing score was then calculated by determining the percentage of each classification. If different grades of cleansing level were present in each minute, the overall preparation level per minute was synthesized as follows: "complete", if the entire small-bowel wall was assessable for 35 s or more, with no more than 5 s of "insufficient" cleansing; "insufficient" if less than 50% of the small bowel wall was visible for 20 s or more; and "incomplete" in all the other cases. The authors achieved a good-to-excellent inter-observer agreement, with a kappa = 0.9 for completely clean and insufficiently clean small-bowel and a kappa = 0.75 for incompletely clean small bowel. The main limitation is that this scale is very cumbersome to perform and time-consuming.

In a study in paediatric patients using PillCam[®] CE, Oliva *et al*^[14] applied a method of evaluation of small-bowel cleanliness similar to the score of Park *et al*^[11]. The small-bowel transit time (SBTT) was divided into five equal segments and in each segment an image was picked at 5-min intervals. Every single image was evaluated according to the percentage of visualized mucosal surface area as follows: (1) < 25%; (2) 25%-49%; (3) 50%-74%; (4) 75%-89%; and (5) > 90%. Mean scores for each segment were obtained by summing the scores of all selected images and dividing the sum by the number of images. The total score for each patient was obtained by adding the five segmental scores. The authors achieved an excellent interobserver agreement (kappa 0.89) with this scale. This scale has, however, the same sampling limitations as the Park's scale.

In order to compare different small-bowel preparations for PillCam[®] CE, van Tuyl *et al*^[15], developed a grading scale which analysed the amount of mucosa visualized. For each CE, the SBTT was divided in four quartiles and the first ten minutes of each quartile was classified according to the percentage of mucosa visualized. Moreover, the last ten minutes of the small intestine were also analysed. The visualization of the mucosa was graded into 6 categories: less than 5%, 5%-24%, 25%-49%, 50%-74%, 75%-95%, or more than 95%. Mucosal visibility was considered good if more than 75% of the mucosa was observed, otherwise it was graded as poor. Interobserver agreement for mucosal visualization was high with a kappa of 0.78. Although this scale is easier to perform than Park's and Oliva's scales, the level of cleanliness of significant portions of the CE video remain unexamined.

Caddy *et al.*^[16] developed a 4-graded scale which was further adopted in other studies^[17,18], to analyse the effect of erythromycin in the completion rate of CE to the cecum. The scale consisted of the percentage of mucosa visualized which was graded as excellent, good, fair or poor if $\geq 95\%$, 75%-94%, 50%-74%, and $< 50\%$ of the mucosa was visualized, respectively. The authors reported a poor inter-observer agreement with kappa 0.3. Nevertheless, if the parameters excellent and good were aggregated, a good level of agreement was achieved with a kappa of 0.7. Although this scale is easy and fast to implement, its low reproducibility limits its utilization.

In order to analyse the difference in small-bowel cleansing in patients receiving 2 L of a PEG and electrolyte lavage solution or ingesting a clear liquid diet during the entire day before PillCam[®] CE, Viazis *et al.*^[19] developed a classification which was subsequently adopted by other authors^[20,21]. The enteric mucosa was classified as clean if less than 25% of it was covered by debris or intestinal contents. This small-bowel cleansing score consisted of recording the exact period of time during which the mucosa was considered unclean. If the total period was inferior to 10% of the SBTT the cleansing was classified as "adequate". Conversely, it was classified as "inadequate" if the period of time of unclean mucosa exceeded 10% of the SBTT. Despite the authors recognized the simplicity of use of this classification, this scale lacks validity and is cumbersome to implement.

In the study developed by Kantianis *et al.*^[22] to compare small-bowel cleansing using 2 L or 4 L of PEG, a 3-scale scoring system according to the visibility of the small-bowel mucosa in consecutive single frames captured every 3 min of the SBTT was adopted. Three points were given when 60%-100% of the mucosa was visible, 2 points when visibility of the mucosa ranged from 30% to 60% and 1 point if less than 30% of the mucosa was visible. The final score was obtained by dividing the sum of scores of each frame by (the total number of frames \times 3), thus leading to a cleansing coefficient range between 0.33 (indicating the worst preparation) and 1.00 (indicating the ideal preparation). Although simple, the same limitations as other scales like Park's that use sampling frames remains.

In another study to evaluate different small-bowel regimens with mannitol and simethicone, Chen *et al.*^[23] created a method of evaluation of small-bowel cleansing using consecutive single frames of the small-bowel video selected at 3 min intervals. In each frame, the area of visible mucosa was outlined and calculated, as well as the area of the entire image. The ratio of both areas was graded as excellent (3 points), good (2 points), fair (1 point) and poor (0 point) if the ratio was 76%-100%, 51%-75%, 26%-50%, and 0%-25%, respectively. For overall assessment, small bowel cleansing for proximal and distal small bowel was separately graded, and considered adequate if the percentage of single frames assessed that was graded as good or excellent was $\geq 85\%$, and inadequate otherwise. In a subsequent study^[9], the same group of authors compared this scale, which

they designated as assessment of cleansing score (AAC) with the CAC developed by Van Weyenberg *et al.*^[6]. The authors concluded that the assessment of interobserver reliability of these two scores showed a high intraclass correlation coefficient (ICC) and no significant difference between them was found using the kappa statistic. For AAC, the ICC was 0.791.

Similar to other studies^[19,21,24], a 4-point scale based on the proportion of enteric mucosa visualized without any liquid, bubbles or debris was adopted by Rosa *et al.*^[25] in order to assess the difference in small-bowel cleansing using a liquid diet and an overnight fast or 2 L of PEG with or without simethicone. The authors recorded with the time counter of the Rapid Reader[®] software the exact time period during which the mucosa was not clean, due to contamination with fluid or debris. The presence of bubbles was evaluated separately. Small-bowel cleansing was graded in excellent in cases of perfect visualization in every small-bowel segments, in good where $> 75\%$ of the mucosa was in perfect conditions, with some fluid or debris remaining not interfering with the examination, in fair if 50%-75% of the mucosa was clean, with presence of enough fluid, bubbles or debris to prevent completely reliable examination and in poor if $< 50\%$ of the mucosa was clean with the presence of significant amounts of fluid or debris. The authors considered an adequate small-bowel preparation if $> 75\%$ of the mucosa was clean, corresponding to the "excellent" and "good" scores.

Niv *et al.*^[26] developed a cleansing scale taking into account the proportion of the SBTT which was filled with intraluminal fluid preventing visualization of the mucosa. The proportion of non-ideal visualization was determined, dividing the time duration of non-ideal visualization recorded with the time counter of the Rapid Reader[®] software by the SBTT. The degree of cleanliness was graded as good if this ratio is $< 20\%$, moderate when between 21%-35% and poor if $> 35\%$.

Qualitative parameters

As previously detailed, Brotz *et al.*^[5] developed and validated three grading systems in PillCam[®] CE system, namely a QI, a QE and an OAA. The QE was categorized in poor, fair, good and excellent according to the percentage of enteric mucosa visualized, the amounts of debris, bubbles, bile and level of brightness (Table 3). The OAA consisted of global assessment of small-bowel cleansing and rated as "adequate" or "inadequate". The authors concluded that the QI had the greatest reliability, the reliability for the OAA was in the moderate range, while the QE performed more poorly. Quantitative scales provide parameters more uniformly assessed thus reducing the subjective interpretation and providing a better evaluation of the small-bowel preparation level. These scales were adopted in other studies^[27].

Albert *et al.*^[28] adopted a 4-grade system based on qualitative parameters to assess bowel preparation using the PillCam[®] CE system. Two segments of 1-h duration were selected, with the first segment (segment A) starting immediately after passage of CE through the

Table 3 Qualitative evaluation of small-bowel cleanliness developed by Brotz *et al.*^[51]

Qualitative evaluation
Excellent: Visualization of $\geq 90\%$ of mucosa; no or minimal, fluid and debris, bubbles, and bile/chyme staining; no or minimal, reduction of brightness
Good: Visualization of $\geq 90\%$ of mucosa; mild fluid and debris, bubbles, and bile/chyme staining; mildly reduced brightness
Fair: Visualization of $< 90\%$ of mucosa; moderate fluid and debris, bubbles, and bile/chyme staining; moderately reduced brightness
Poor: Visualization of $< 80\%$ of mucosa; excessive fluid and debris, bubbles, and bile/chyme staining; severely reduced brightness

pylorus and the other segment (segment B) finishing before the passage through the ileocecal valve. In each segment, the impairment of visibility of the mucosa due to intraluminal gas bubbles was evaluated and graded as (0) if there was no intraluminal gas; (1) if only a few gas bubbles not limiting the interpretation were seen; (2) if there was an increased amount of intraluminal gas bubbles which moderately impaired visibility; and (3) if a large amount of gas bubbles which severely limited the interpretation of mucosal surface were found. Of note, the amount of food residue or small-bowel secretions was not analysed. This grading scale obtained a good interobserver agreement, with a Spearman correlation of $r = 0.89$ in segment A ($P < 0.001$) and $r = 0.79$ ($P < 0.001$) in segment B. This scale also suffers from sampling error limitations, as only two segments with 1-h duration from the entire CE video are analysed.

Pons Beltrán *et al.*^[29] proposed a 4-point subjective score of "poor", if there was intestinal content impeding evaluation, "fair", if there was liquid or solid intestinal content allowing evaluation, "good", if there was no intestinal content or some content in the terminal ileum and/or cecum and "excellent", if there was no intestinal content in any part of the small-bowel or the cecum. Differently from QE, the enteric level of cleanliness in PillCam® CE was judged according to the amount of intestinal content throughout the small-bowel and cecum. Due to the subjectivity of the assessed parameter, the interobserver agreement was fair, with a kappa = 0.38.

In a study to assess the effect of magnesium citrate in small-bowel cleansing in PillCam® CE, Ninomiya *et al.*^[30] classified from 0 to 4, each of three parameters, namely food residue, intestinal juice clarity and bubbles (Table 4). After dividing the SBTT into three segments, images from each segment were recorded and classified according to the three parameters.

Quantitative and qualitative parameters

Esaki *et al.*^[31] developed a grading scale using the PillCam® CE system to assess the differences in small bowel preparation with magnesium citrate or simethicone. After determining the terciles of the SBTT, the authors evaluated the fluid transparency and mucosal invisibility in each segment, according to Table 5. The grade of fluid transparency was determined according to the

Table 4 Grading scale of intestinal cleansing proposed by Ninomiya *et al.*^[30]

Residue elimination effect	
4 points	No food residue at all, clear views
3 points	Some food residue present, not interfering with observations
2 points	Quite a lot of food residue, slightly hindering observations
1 points	Large amount of food residue, hindering observations
Intestinal juice clarity	
4 points	Intestinal juice is clear, clear views
3 points	Intestinal juice is light colored and does not interfere with observations
2 points	Intestinal juice is light dark colored, slightly hindering observation
1 points	Intestinal juice is dark colored and interferes with observations
Froth reduction effect	
4 points	No froth, clear views
3 points	Froth present, not interfering with observations
2 points	Quite a lot of froth, slightly hindering observations
1 points	Large amount of froth, hindering observations

predominant grade in each segment. The grade of mucosal invisibility was determined in each video segment by the proportion of duration in which air bubbles or food residues disturbed more than 50% of its visualization and interpretation. The overall score for each parameter corresponded to the sum of the grades obtained in each segment, ranging from 3 to 12. The authors achieved an excellent interobserver agreement in each segment analysed, with the results showing a strong correlation ($r = 0.88$, $P < 0.0001$ in the first tercile; $r = 0.77$, $P < 0.0001$ in the second tercile; $r = 0.81$, $P < 0.0001$ in the third tercile). Conversely, this grading system was applied by other authors who obtained a moderate intra-observer agreement (kappa = 0.52) and a poor interobserver agreement (kappa = 0.29 for fluid transparency and kappa = 0.42 for mucosal invisibility)^[7].

Dai *et al.*^[32] studied the effect of bowel preparation with 4 L of PEG in small-bowel cleanliness. To assess the enteric cleanliness, the authors used an overall assessment of quality based on a 4-step scale: (1) large volume of residual ingested food or fecal material; (2) moderate volume of residual ingested food; (3) small volume of residual ingested food; and (4) clear or colored liquid. They also determined the proportion of the enteric wall visualized using 10-min video segments at 1-h intervals: (1) less than 25%; (2) 25% to 49%; (3) 50% to 75%; and (4) greater than 75%. The authors concluded that the score was subjective, as reflected by the fair interobserver agreement achieved with a kappa = 0.56.

Lapalus *et al.*^[33] created a small-bowel cleansing score in PillCam® to evaluate the effect of oral sodium phosphate in small-bowel preparation. The preparation was evaluated in five segments of 5 min, with the first segment starting at 5 min after passage of the CE

Table 5 Small-bowel cleansing scale of Esaki *et al*^[31]

Fluid transparency	
Grade 1	Clear fluid without obscuring vision
Grade 2	Slightly dark fluid minimally obscuring vision
Grade 3	Opaque fluid partly obscuring vision
Grade 4	Turbid fluid severely obscuring vision
Mucosal invisibility ¹	
Grade 1	< 5% in duration of > 50% bubbles or residues
Grade 2	5%-15%
Grade 3	15%-25%
Grade 4	> 25%
Overall image quality ²	
Grade A	3-5
Grade B	6-8
Grade C	9-12

¹The percentage indicates the proportion of length of time of video image in which air bubbles or food residues disturbed more than 50% of visualization and interpretation; ²The number indicates the sum of grades in each small intestinal segment.

through the pylorus, and the last segment corresponding to the 5 min before passage through the ileocecal valve. The remaining segments started at one fourth, one half, and three fourths of the SBTT. Each segment was graded in a 4-point scale according to the bowel cleanliness (1) no liquid and no bubbles (excellent); (2) clear liquid (good); (3) dark liquid and/or air bubbles (fair); and (4) food residue (poor) and the proportion of mucosa visualized [(1) \geq to 75% of the mucosa visualized; (2) 50% to 74% of the mucosa visualized; (3) 25% to 49% of the mucosal visualized; and (4) \leq to 24% of the mucosa visualized]. The interobserver agreement for the score of cleansing varied between 0.55 and 0.69 and for the score of visibility varied between 0.55 and 0.8.

Similarly to the previous grading scale, Hooks *et al*^[34] developed a grading scale with quantitative and qualitative parameters using PillCam[®] CE to evaluate the effect of lubiprostone in the gastric and small-bowel transit time and in the enteric preparation. This last parameter was analysed with a 4-point scale considering the overall preparation in the proximal, middle and distal small bowel and the amount of mucosa visualized in 10-min segments at one-hour intervals, as described in Table 6.

In summary, various grading scales to assess the cleanliness of small-bowel in CE have been proposed, and a consensus regarding which scale is better remains to be achieved. Computer grading scales are based on objective measurements and may potentially overcome the disadvantages of human dependent scoring systems, namely the subjectivity, complexity and lengthiness. Current results of computer grading scales are encouraging and the future may encompass the incorporation of a fully automated cleansing score in the software of CE. Nevertheless, more research is warranted to ameliorate and achieve an optimal computed score completely independent of human action.

In human dependent grading scales, the authors consider that those which include the entire video have more advantages as the operator may score the small-

Table 6 Small-bowel cleansing scale of Hooks *et al*^[34]

Overall preparation	
Excellent	Small bits of adherent solid material with clear or colored liquid
Good	Few liquids, small amounts of solid material, or dark fluid that did not interfere with the examination
Fair	Enough solid material or dark liquid to prevent a reliable examination
Poor	Large volume of residual food or fecal material precluding a complete examination
Proportion of mucosa visualized	
4 points	> 75%
3 points	50%-75%
2 points	25%-49%
1 point	< 25%

bowel cleanliness during CE analysis, thus reducing the time of the procedure as the re-evaluation of single frames or segments of video is avoided. Moreover, sample bias is avoided as the overall video will be evaluated. The authors also conclude that operator dependent scales based on quantitative parameters may reduce subjective interpretation and provide a better evaluation of the small-bowel preparation level. Despite the heterogeneity of the methodology adopted by the developers of each small-bowel grading system in CE, which limit the comparison between the operator dependent grading scales, the authors suggest that the QI grading scale of Brotz *et al*^[5] may aggregate the best characteristics for evaluation of small-bowel cleanliness in CE.

CONCLUSION

Numerous small-bowel grading scales to assess the cleanliness in CE have been developed, and a consensus regarding a universally accepted scale is lacking.

Computer grading scales are based on objective measurements and may potentially overcome the disadvantages of human dependent scoring systems, namely the subjectivity, complexity and lengthiness. Concerning human dependent grading scales, only few are validated and there is a huge heterogeneity regarding the methodology of each scale, namely the parameters and portion of the CE analysed and the objectivity of the analysis. Finally, human dependent scales which are based in quantitative assessments are more uniformly assessed thus reducing the subjective interpretation and providing a better evaluation of the small-bowel preparation.

REFERENCES

- 1 Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy

- (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: 25826168 DOI: 10.1055/s-0034-1391855]
- 2 **Ladas SD**, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; **42**: 220-227 [PMID: 20195992 DOI: 10.1055/s-0029-1243968]
- 3 **Pinho R**, Mascarenhas-Saraiva M, Mão-de-Ferro S, Ferreira S, Almeida N, Figueiredo P, Rodrigues A, Cardoso H, Marques M, Rosa B, Cotter J, Vilas-Boas G, Cardoso C, Salgado M, Marcos-Pinto R. Multicenter survey on the use of device-assisted enteroscopy in Portugal. *United European Gastroenterol J* 2016; **4**: 264-274 [PMID: 27087956 DOI: 10.1177/2050640615604775]
- 4 **Pinho R**, Ponte A, Rodrigues A, Pinto-Pais T, Fernandes C, Ribeiro I, Silva J, Rodrigues J, Mascarenhas-Saraiva M, Carvalho J. Long-term rebleeding risk following endoscopic therapy of small-bowel vascular lesions with device-assisted enteroscopy. *Eur J Gastroenterol Hepatol* 2016; **28**: 479-485 [PMID: 26808473 DOI: 10.1097/MEG.0000000000000552]
- 5 **Brotz C**, Nandi N, Conn M, Daskalakis C, DiMarino M, Infantolino A, Katz LC, Schroeder T, Kastenbergs D. A validation study of 3 grading systems to evaluate small-bowel cleansing for wireless capsule endoscopy: a quantitative index, a qualitative evaluation, and an overall adequacy assessment. *Gastrointest Endosc* 2009; **69**: 262-270, 270.e1 [PMID: 18851851 DOI: 10.1016/j.gie.2008.04.016]
- 6 **Van Weyenberg SJ**, De Leest HT, Mulder CJ. Description of a novel grading system to assess the quality of bowel preparation in video capsule endoscopy. *Endoscopy* 2011; **43**: 406-411 [PMID: 21425039 DOI: 10.1055/s-0030-1256228]
- 7 **Goyal J**, Goel A, McGwin G, Weber F. Analysis of a grading system to assess the quality of small-bowel preparation for capsule endoscopy: in search of the Holy Grail. *Endosc Int Open* 2014; **2**: E183-E186 [PMID: 26134966 DOI: 10.1055/s-0034-1377521]
- 8 **Klein A**, Gizbar M, Bourke M, Ahlenstiel G. A validated computerized cleansing score for Video Capsule Endoscopy. *Dig Endosc* 2015; **28**: 564-569 [PMID: 26716407 DOI: 10.1111/den.12599]
- 9 **Hong-Bin C**, Yue H, Su-Yu C, Chun H, Lan-Hua G, Dong-Ying D, Xiao-Juan L, Song H, Xiao-Lin L. Evaluation of visualized area percentage assessment of cleansing score and computed assessment of cleansing score for capsule endoscopy. *Saudi J Gastroenterol* 2013; **19**: 160-164 [PMID: 23828745 DOI: 10.4103/1319-3767.114512]
- 10 **Ponte A**, Pinho R, Rodrigues A, Silva S, Rodrigues J, Carvalho J. Validation of the Computed Assessment of Cleansing score with the Mirocam® system. *Rev Esp Enferm Dig* 2016; In press
- 11 **Park SC**, Keum B, Hyun JJ, Seo YS, Kim YS, Jeon YT, Chun HJ, Um SH, Kim CD, Ryu HS. A novel cleansing score system for capsule endoscopy. *World J Gastroenterol* 2010; **16**: 875-880 [PMID: 20143467]
- 12 **Park SC**, Keum B, Seo YS, Kim YS, Jeon YT, Chun HJ, Um SH, Kim CD, Ryu HS. Effect of bowel preparation with polyethylene glycol on quality of capsule endoscopy. *Dig Dis Sci* 2011; **56**: 1769-1775 [PMID: 21161380 DOI: 10.1007/s10620-010-1500-2]
- 13 **Spada C**, Riccioni ME, Familiari P, Spera G, Pirozzi GA, Marchese M, Bizzotto A, Ingrosso M, Costamagna G. Polyethylene glycol plus simethicone in small-bowel preparation for capsule endoscopy. *Dig Liver Dis* 2010; **42**: 365-370 [PMID: 19736051 DOI: 10.1016/j.dld.2009.07.017]
- 14 **Oliva S**, Cucchiara S, Spada C, Hassan C, Ferrari F, Civitelli F, Pagliaro G, Di Nardo G. Small bowel cleansing for capsule endoscopy in paediatric patients: a prospective randomized single-blind study. *Dig Liver Dis* 2014; **46**: 51-55 [PMID: 24041737 DOI: 10.1016/j.dld.2013.08.130]
- 15 **van Tuyt SA**, den Ouden H, Stolk MF, Kuipers EJ. Optimal preparation for video capsule endoscopy: a prospective, randomized, single-blind study. *Endoscopy* 2007; **39**: 1037-1040 [PMID: 18072052]
- 16 **Caddy GR**, Moran L, Chong AK, Miller AM, Taylor AC, Desmond PV. The effect of erythromycin on video capsule endoscopy intestinal-transit time. *Gastrointest Endosc* 2006; **63**: 262-266 [PMID: 16427932]
- 17 **Endo H**, Kondo Y, Inamori M, Ohya TR, Yanagawa T, Asayama M, Hisatomi K, Teratani T, Yoneda M, Nakajima A, Matsuhashi N. Ingesting 500 ml of polyethylene glycol solution during capsule endoscopy improves the image quality and completion rate to the cecum. *Dig Dis Sci* 2008; **53**: 3201-3205 [PMID: 18465241 DOI: 10.1007/s10620-008-0292-0]
- 18 **Ito T**, Ohata K, Ono A, Chiba H, Tsuji Y, Sato H, Matsuhashi N. Prospective controlled study on the effects of polyethylene glycol in capsule endoscopy. *World J Gastroenterol* 2012; **18**: 1789-1792 [PMID: 22553403 DOI: 10.3748/wjg.v18.i15.1789]
- 19 **Viazis N**, Sgouros S, Papaxoinis K, Vlachogiannakos J, Bergele C, Sklavos P, Panani A, Avgerinos A. Bowel preparation increases the diagnostic yield of capsule endoscopy: a prospective, randomized, controlled study. *Gastrointest Endosc* 2004; **60**: 534-538 [PMID: 15472674]
- 20 **Wei W**, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. Purgative bowel cleansing combined with simethicone improves capsule endoscopy imaging. *Am J Gastroenterol* 2008; **103**: 77-82 [PMID: 18005366]
- 21 **Wi JH**, Moon JS, Choi MG, Kim JO, Do JH, Ryu JK, Shim KN, Lee KJ, Jang BI, Chun HJ. Bowel preparation for capsule endoscopy: a prospective randomized multicenter study. *Gut Liver* 2009; **3**: 180-185 [PMID: 20431743 DOI: 10.5009/gnl.2009.3.3.180]
- 22 **Kantianis A**, Karagiannis S, Liatos C, Galanis P, Psilopoulos D, Tenta R, Kalantzis N, Mavrogiannis C. Comparison of two schemes of small bowel preparation for capsule endoscopy with polyethylene glycol: a prospective, randomized single-blind study. *Eur J Gastroenterol Hepatol* 2009; **21**: 1140-1144 [PMID: 19757514]
- 23 **Chen HB**, Huang Y, Chen SY, Song HW, Li XL, Dai DL, Xie JT, He S, Zhao YY, Huang C, Zhang SJ, Yang LN. Small bowel preparations for capsule endoscopy with mannitol and simethicone: a prospective, randomized, clinical trial. *J Clin Gastroenterol* 2011; **45**: 337-341 [PMID: 20871410 DOI: 10.1097/MCG.0b013e3181f0f3a3]
- 24 **Pons Beltrán V**, Carretero C, Gonzalez-Suárez B, Fernandez-Urrien I, Muñoz-Navas M. Intestinal preparation prior to capsule endoscopy administration. *World J Gastroenterol* 2008; **14**: 5773-5775 [PMID: 18837100]
- 25 **Rosa BJ**, Barbosa M, Magalhães J, Rebelo A, Moreira MJ, Cotter J. Oral purgative and simethicone before small bowel capsule endoscopy. *World J Gastrointest Endosc* 2013; **5**: 67-73 [PMID: 23424190 DOI: 10.4253/wjge.v5.i2.67]
- 26 **Niv Y**, Niv G. Capsule endoscopy: role of bowel preparation in successful visualization. *Scand J Gastroenterol* 2004; **39**: 1005-1009 [PMID: 15513342]
- 27 **Magalhães-Costa P**, Carmo J, Bispo M, Santos S, Chagas C. Superiority of the Split-dose PEG Regimen for Small-Bowel Capsule Endoscopy: A Randomized Controlled Trial. *J Clin Gastroenterol* 2015; **50**: e65-e70 [PMID: 26646803 DOI: 10.1097/MCG.0000000000000460]
- 28 **Albert J**, Göbel CM, Lesske J, Lotterer E, Nietsch H, Fleig WE. Simethicone for small bowel preparation for capsule endoscopy: a systematic, single-blinded, controlled study. *Gastrointest Endosc* 2004; **59**: 487-491 [PMID: 15044883]
- 29 **Pons Beltrán V**, González Suárez B, González Asanza C, Pérez-Cuadrado E, Fernández Díez S, Fernández-Urrien I, Mata Bilbao A, Espinós Pérez JC, Pérez Grueso MJ, Argüello Viudez L, Valle Muñoz J, Carballo Álvarez F, Muñoz-Navas M, Llach Vila J, Ramírez Armengol JA, Balanzó Tintoré J, Sala Felis T, Menchen Fernández-Pacheco P. Evaluation of different bowel preparations for small bowel capsule endoscopy: a prospective, randomized, controlled study. *Dig Dis Sci* 2011; **56**: 2900-2905 [PMID: 21479818 DOI: 10.1007/s10620-011-1693-z]
- 30 **Ninomiya K**, Yao K, Matsui T, Sato Y, Kishi M, Karashima Y, Ishihara H, Hirai F. Effectiveness of magnesium citrate as preparation for capsule endoscopy: a randomized, prospective, open-label, inter-group trial. *Digestion* 2012; **86**: 27-33 [PMID: 22710397 DOI: 10.1159/000337937]

- 31 **Esaki M**, Matsumoto T, Kudo T, Yanaru-Fujisawa R, Nakamura S, Iida M. Bowel preparations for capsule endoscopy: a comparison between simethicone and magnesium citrate. *Gastrointest Endosc* 2009; **69**: 94-101 [PMID: 18710720 DOI: 10.1016/j.gie.2008.04.054]
- 32 **Dai N**, Gubler C, Hengstler P, Meyenberger C, Bauerfeind P. Improved capsule endoscopy after bowel preparation. *Gastrointest Endosc* 2005; **61**: 28-31 [PMID: 15672052]
- 33 **Lapalus MG**, Ben Soussan E, Saurin JC, Favre O, D'Halluin PN, Coumaros D, Gaudric M, Fumex F, Antonietti M, Gaudin JL, Jacob P, Heresbach D, Pilichos C, Fan R, Mozer M, Heyries L, Dumortier J, Ponchon T. Capsule endoscopy and bowel preparation with oral sodium phosphate: a prospective randomized controlled trial. *Gastrointest Endosc* 2008; **67**: 1091-1096 [PMID: 18513551 DOI: 10.1016/j.gie.2007.11.053]
- 34 **Hooks SB**, Rutland TJ, Di Palma JA. Lubiprostone neither decreases gastric and small-bowel transit time nor improves visualization of small bowel for capsule endoscopy: a double-blind, placebo-controlled study. *Gastrointest Endosc* 2009; **70**: 942-946 [PMID: 19577749 DOI: 10.1016/j.gie.2009.04.045]

P- Reviewer: Christodoulou DK, Stanciu C, Sakin YS

S- Editor: Qi Y **L- Editor:** A **E- Editor:** Li D



Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges

Dong Zheng, Chen-Song Huang, Shao-Bin Huang, Chao-Xu Zheng

Dong Zheng, Department of Hematology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

Chen-Song Huang, Shao-Bin Huang, Chao-Xu Zheng, Department of Pancreato-biliary Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

Author contributions: All authors contributed equally to this paper with conception and design of the study, literature review and analysis, drafting, critical revision and editing, and final approval of the final version.

Supported by Science and Technique Project of Guangdong Province, No. 2012B031800284.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Chao-Xu Zheng, MD, PhD, Professor of Surgery, Department of Pancreato-biliary Surgery, the First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan 2 Road, Guangzhou 510080, Guangdong Province, China. zhengchaoxu@yahoo.com
Telephone: +86-20-87755766-6214
Fax: +86-20-87750632

Received: March 27, 2016

Peer-review started: March 28, 2016

First decision: May 17, 2016

Revised: June 2, 2016

Accepted: June 27, 2016

Article in press: June 29, 2016

Published online: September 16, 2016

Abstract

Primary immune thrombocytopenia (ITP) is an immune-mediated disorder affecting both adults and children, characterised by bleeding complications and low platelet counts. Corticosteroids are the first-line therapy for ITP, but only 20%-40% of cases achieve a stable response. Splenectomy is the main therapy for patients failing to respond to corticosteroids for decades, and about two-thirds of patients achieve a long-lasting response. Although some new drugs are developed to treat ITP as second-line therapies in recent years, splenectomy is still the better choice with less cost and more efficiency. Laparoscopic splenectomy (LS) for ITP proves to be a safe technique associated with lower morbidity and faster recovery and similar hematological response when compared to traditional open splenectomy. Based on the unified hematological outcome criteria by current international consensus, the response rate of splenectomy should be reassessed. So far, there are not widely accepted preoperative clinical indicators predicting favorable response to LS. Since the patients undergoing surgery take the risk of complications and poor hematological outcome, the great challenge facing the doctors is to identify a reliable biomarker for predicting long-term outcome of splenectomy which can help make the decision of operation.

Key words: Laparoscopic splenectomy; Corticosteroids; Open splenectomy; Hematological outcome; Predictor; Biomarker; Immune thrombocytopenia

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Despite the new drugs developed to treat primary immune thrombocytopenia, splenectomy is still

the main therapy for patients who fail corticosteroid treatment. Laparoscopic splenectomy proves to be a preferable technique compared to open splenectomy. The response rate to splenectomy should be reassessed based on the unified outcome criteria by current international consensus. So far, there are not widely accepted preoperative indicators predicting response to laparoscopic splenectomy. The challenge facing the doctors is to identify a reliable predictor of long-term outcome of splenectomy which can help make the decision of operation.

Zheng D, Huang CS, Huang SB, Zheng CX. Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges. *World J Gastrointest Endosc* 2016; 8(17): 610-615 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i17/610.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i17.610>

INTRODUCTION

Primary immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura or primary immune thrombocytopenic purpura, is an immune-mediated disease characterized by bleeding complications and low platelet counts in both children and adults^[1]. ITP occurs at an annual rate of 1.9 to 6.4 per 100000 children and 3.3 per 100000 adults^[2]. Bleeding symptoms are highly variable in primary ITP. According to a newly published systematic review that enrolled all prospective ITP studies with 20 or more patients, weighted proportion for intracerebral hemorrhage (ICH) was 0.4% for children and 1.4% for adults, and severe (non-ICH) bleeding rate was 20.2% for children and 9.6% for adults^[3]. The term "purpura" was inappropriate because bleeding symptoms are absent or minimal in a large proportion of cases^[4,5]. Therefore, an International Working Group (IWG) of recognized experts suggested to replace the original term "idiopathic thrombocytopenic purpura" or "immune thrombocytopenic purpura" with the term "immune thrombocytopenia"^[1]. The new term was soon accepted by the American Society of Hematology (ASH) and the new ASH guidelines^[6].

Corticosteroids were introduced in the 1950s to treat ITP^[7]. Until now, corticosteroids are still recommended as the first-line therapy in primary ITP by current international consensus^[8]. However, only 20%-40% of patients can achieve a stable response with steroid treatment^[9,10]. Splenectomy is recommended as the main second-line method for patients who do not respond to steroid or relapse for a long time^[1]. Since the first laparoscopic splenectomy (LS) was reported by Delaitre *et al.*^[11] in 1991, this technique has gradually replaced traditional open splenectomy (OS) in surgical treatment of ITP. The following is our review of the current status and challenges of LS for ITP.

OVERVIEW OF PATHOPHYSIOLOGY OF ITP

Understanding of the immunopathogenesis of ITP is very important for treatment of this disease. The mechanisms which cause the accelerated platelet destruction and the inhibited platelet production are very complicated and intricate, for several abnormalities are involved in its immunopathogenesis. In terms of humoral immune dysregulation, the increased expression of B cell-activated factor and cyclophilin ligand interactor can prolong the survival and enhance the proliferation of B cells^[12], and B cells can produce substantial antiplatelet autoantibodies against GP II b/IIIa and GP I b/IX^[13]. Macrophages in the spleen and liver can destroy those autoantibody-combined platelets, causing the accelerated platelet destruction. Besides that, autoantibodies can also inhibit megakaryocyte production and maturation and platelet release, thus leading to the decreased platelet production^[14]. As for cellular immune dysregulation, multiple cell types are involved in the development of ITP. CD4⁺CD25⁺ regulatory T cells (Treg cells) which can depress T cell responses are found quantitatively and functionally impaired^[15]. In patients with ITP, the considerably high Th1/Th2 ratio^[16], the increase of Th17 and Th22 cells^[17], and the augment of CD3⁺ cytotoxic T cells have been found^[18]. Dysfunctions of macrophages and dendritic cells also take part in the immune disequilibrium of ITP patients^[19].

THE STATUS OF SPLENECTOMY IN THE ERA OF NEW SECOND-LINE THERAPIES

Both intravenous anti-D immunoglobulin (IV anti-D) and intravenous immunoglobulin (IVIg) are recommended as first-line therapies for ITP in the international consensus report of IWG^[1]. Either IV anti-D or IVIg produces short-term responses within 24-48 h in 60%-80% of patients. However, the responses are rarely durable beyond 4 wk^[20,21]. In the past few decades, splenectomy is considered the first choice for ITP after failure treatment of corticosteroids. In recent years, some new drugs are developed to treat ITP and recommended as second-line therapies. These drugs include the monoclonal anti-CD20 antibody rituximab, recombinant human thrombopoietin molecule (rhTPO), and thrombopoietin receptor agonists (TPO-RAs). Some promising results have been reported in the treatment of ITP with these drugs. Thus whether continuing to regard splenectomy as the main second-line therapy has evoked much controversy. Rituximab has a depleting effect on B lymphocytes. However, its long-term effect is modest, for no significant differences in treatment failure rate within 78 wk between rituximab and placebo had been found [32 (58%) of 55 vs 37 (69%) of 54]^[22]. RhTPO and TPO-RAs (Eltrombopag and Romiplostim) can considerably promote the platelet production, but ITP patients should rely on these medica-

Table 1 Case series reporting 50 or more patients undergoing splenectomy for immune thrombocytopenia that contain platelet count response

Publication date	Accrual years	Ref.	Country	No. patients	Operation method	CR rate	R rate	NR rate	Relapse
2006 ¹	1993-2003	Balagué <i>et al</i> ^[34]	Spain	103	LS	NA	NA	4.9%	6.1%
2007 ²	1988-2006	Sampath <i>et al</i> ^[29]	Canada	105	LS, OS	NA	NA	NA	21.6%
2007 ¹	1994-2004	Kang <i>et al</i> ^[35]	South Korea	59	LS	47.5%	40.7%	11.9%	15.2%
2011 ³	2005-2010	Chen <i>et al</i> ^[36]	China	81	LS	88.9%	8.6%	2.5%	NA
2011 ⁴	1999-2006	Zheng <i>et al</i> ^[37]	China	127	LS	79.5%	9.5%	11%	9.7%
2013 ³	1982-2011	Gonzalez-Porras <i>et al</i> ^[38]	Spain	218	LS, OS	80.7%	8.3%	11.0%	36.1%
2014 ³	1995-2012	Montalvo <i>et al</i> ^[39]	Mexico	150	LS	88.7%	2.7%	8.6%	NA
2014 ³	2001-2009	Rijcken <i>et al</i> ^[40]	Germany	72	LS	77.8%	9.7%	12.5%	30.2%
2014 ³	2010-2012	Cai <i>et al</i> ^[41]	China	88	LS	77.3%	19.3%	3.4%	NA
2015 ³	1992-2013	Navez <i>et al</i> ^[42]	Belgium	82	LS	72.0%	24.4%	3.6%	NA

¹Remission was defined as CR when platelet count increased to $> 150 \times 10^9/L$, and as R when it was $50-150 \times 10^9/L$; ²The criterion of ITP remission was not mentioned in the study; ³Remission was defined as CR when platelet count increased to $> 100 \times 10^9/L$, and as R when it was $30-100 \times 10^9/L$; ⁴Remission was defined as CR when platelet count increased to $> 100 \times 10^9/L$, and as R when it was $50-100 \times 10^9/L$. OS: Open splenectomy; LS: Laparoscopic splenectomy; CR: Complete response; R: Response; NR: No response; ITP: Immune thrombocytopenia.

tions, since these drugs only have short-term therapeutic effects^[6,23]. Eltrombopag and Romiplostim were approved by the Food and Drug Administration for clinical use. While in many countries, these two drugs are unavailable. Splenectomy is also the second-line therapy for ITP patients who do not respond to first-line therapy. About 80% of ITP patients respond to splenectomy and about two-thirds achieve a lasting response with no additional therapy for at least 5 years^[8]. A systematic review of 23 articles and 1223 patients showed that by the resection of the site of platelet destruction and antiplatelet antibody production, laparoscopic splenectomy can cure 72% of ITP patients with long-term response^[24]. Compared with expensive therapies with these drugs, splenectomy is less costly and more efficient^[25]. Therefore, splenectomy is the better choice of the second-line therapy for ITP patients, especially in the developing countries.

TECHNIQUE ASPECTS OF LS

The comparison of the long-term outcomes and safety between LS and OS is always an issue. One systematic review^[26] published in 2004 and some case series^[27-29] in the past decade suggested that the hematologic efficacy of LS is the same as that of OS, while LS had fewer complications and mortality than OS. The systematic review^[26] including 47 case series reported that mortality was 1.0% with OS and 0.2% with LS. Complication rates were 12.9% with OS and 9.6% with LS. The common complications of splenectomy include bleeding, thrombosis, pancreatic leakage, infection, prolonged hospitalization, requirement for additional intervention and readmission to the hospital; however, all the studies were retrospective. Randomized studies are needed to confirm this conclusion. LS has other advantages such as less postoperative pain, shorter hospital stays and better cosmetic outcomes^[27,30]. Therefore, LS is preferred over OS for ITP by more and more surgeons.

In recent years, there are some case reports about the application of single-incision LS^[31-33]. This technique emphasizes the concept of operation through one small

transabdominal incision rather than the traditional multiple trocar sites, in order to show benefits of less pain and better cosmetics. However, because of the limited number of included patients in these studies, no obvious advantages of this technique could be showed when compared with traditional LS^[31].

HEMATOLOGICAL OUTCOME CRITERIA

The response rate to splenectomy for ITP in different studies differs from each other. Case series^[29,34-42] reporting 50 or more patients undergoing splenectomy for ITP that contain platelet count response are listed in Table 1. All these data were published in recent ten years and searched from PubMed database. One of the main reason for the discrepancies of hematological outcomes is the different definitions and clinical criteria which were used in different studies^[9,43,44]. Fortunately, the standard terminology, definitions and outcome criteria for ITP have been unified^[1,6]. In the new guidelines updated by ASH^[6], a platelet count $< 100 \times 10^9/L$ was diagnosed as thrombocytopenia and a platelet count $> 100 \times 10^9/L$ or $30 \times 10^9/L$ was diagnosed as complete response or partial response after splenectomy. The recommendations for using $100 \times 10^9/L$ as an upper-threshold were based on three reasons: Over 10 years of follow-up, only 6.9% of patients with a platelet count between 100 and $150 \times 10^9/L$ may develop a persistent platelet count $< 100 \times 10^9/L$ ^[45]. In some non-Western healthy individuals, platelet count values may be between 100 and $150 \times 10^9/L$ ^[46-48]. Using $100 \times 10^9/L$ as a threshold would reduce inclusion of most women with pregnancy-related thrombocytopenia^[49]. The new guidelines will provide the evidence-based guidance for the diagnosis and therapy of ITP, as well as unified criteria for evaluating treatment outcome.

PREDICTORS OF SPLENECTOMY

Splenectomy is benefit for most of the patients, but there are still some patients who have a poor long-term

response. They should also take the risk of surgery, in the worst case, even death. So the choice of surgery is a deliberate decision. Many studies have attempted to determine reliable predictors of hematological response to splenectomy. Some factors including younger age^[50,51], preoperative platelet count after using steroids and immunoglobulins^[40,42], response to preoperative steroids^[52,53], shorter disease duration (from diagnosis to splenectomy)^[51], and splenic sequestration^[54,55] have been reported as successful predictors of splenectomy for ITP. But all the above conclusions cannot be verified in other studies. So far, there have been not widely accepted preoperative clinical indicators predicting response to splenectomy. Identifying a preoperative biological or immunological marker to predict long-term results of LS for patients with primary ITP will be the focus of future research. Our team has made preliminary progress toward this goal^[56]. In our study, we showed that preoperative heptoglobin in serum may be a favourable predictor for the long-term response to splenectomy in ITP. Further studies with long-term follow-up and larger sample size are needed to confirm this finding. With the efforts of hematologists and surgeons, identifying biomarkers for favorable hematological outcome of ITP patients undergoing splenectomy and therefore avoiding invalid operation may come true in the future.

In summary, although some new drugs are developed as second-line therapies for primary ITP, splenectomy is still recommended as the first choice for patients who fail corticosteroid therapy. LS is a good alternative to OS for treatment of ITP. The great challenge facing the doctors is to identify a reliable predictor of long-term outcome of splenectomy which can help make the decision of operation.

REFERENCES

- Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B, Lechner K, Mazzucconi MG, McMillan R, Sanz MA, Imbach P, Blanchette V, Kühne T, Ruggeri M, George JN. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; **113**: 2386-2393 [PMID: 19005182 DOI: 10.1182/blood-2008-07-162503]
- Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. *Am J Hematol* 2010; **85**: 174-180 [PMID: 20131303 DOI: 10.1002/ajh.21616]
- Neunert C, Noroozi N, Norman G, Buchanan GR, Goy J, Nazi I, Kelton JG, Arnold DM. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. *J Thromb Haemost* 2015; **13**: 457-464 [PMID: 25495497 DOI: 10.1111/jth.12813]
- Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. *Blood* 1999; **94**: 909-913 [PMID: 10419881]
- Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br J Haematol* 2003; **122**: 966-974 [PMID: 12956768 DOI: 10.1046/j.1365-2141.2003.04547.x]
- Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; **117**: 4190-4207 [PMID: 21325604 DOI: 10.1182/blood-2010-08-302984]
- Bethell FH, Meyers MC, Miller S, Bullock WH. Effects of ACTH and cortisone on idiopathic thrombocytopenic purpura. *Trans Assoc Am Physicians* 1951; **64**: 199-203 [PMID: 14884250]
- Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; **115**: 168-186 [PMID: 19846889 DOI: 10.1182/blood-2009-06-225565]
- British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 2003; **120**: 574-596 [PMID: 12588344]
- Rodeghiero F. Idiopathic thrombocytopenic purpura: an old disease revisited in the era of evidence-based medicine. *Haematologica* 2003; **88**: 1081-1087 [PMID: 14555300]
- Delaitre B, Maignien B. [Splenectomy by the laparoscopic approach. Report of a case]. *Presse Med* 1991; **20**: 2263 [PMID: 1838167]
- Min YN, Wang CY, Li XX, Hou Y, Qiu JH, Ma J, Shao LL, Zhang X, Wang YW, Peng J, Hou M, Shi Y. Participation of B-cell-activating factor receptors in the pathogenesis of immune thrombocytopenia. *J Thromb Haemost* 2016; **14**: 559-571 [PMID: 26749059 DOI: 10.1111/jth.13246]
- McMillan R, Tani P, Millard F, Berchtold P, Renshaw L, Woods VL. Platelet-associated and plasma anti-glycoprotein autoantibodies in chronic ITP. *Blood* 1987; **70**: 1040-1045 [PMID: 3651598]
- McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood* 2004; **103**: 1364-1369 [PMID: 14576051 DOI: 10.1182/blood-2003-08-2672]
- Liu B, Zhao H, Poon MC, Han Z, Gu D, Xu M, Jia H, Yang R, Han ZC. Abnormality of CD4(+)CD25(+) regulatory T cells in idiopathic thrombocytopenic purpura. *Eur J Haematol* 2007; **78**: 139-143 [PMID: 17328716]
- Panitsas FP, Theodoropoulou M, Kouraklis A, Karakantza M, Theodorou GL, Zoumbos NC, Maniatis A, Mouzaki A. Adult chronic idiopathic thrombocytopenic purpura (ITP) is the manifestation of a type-1 polarized immune response. *Blood* 2004; **103**: 2645-2647 [PMID: 14670926]
- Hu Y, Li H, Zhang L, Shan B, Xu X, Li H, Liu X, Xu S, Yu S, Ma D, Peng J, Hou M. Elevated profiles of Th22 cells and correlations with Th17 cells in patients with immune thrombocytopenia. *Hum Immunol* 2012; **73**: 629-635 [PMID: 22537755 DOI: 10.1016/j.humimm.2012.04.015]
- Olsson B, Andersson PO, Jernäs M, Jacobsson S, Carlsson B, Carlsson LM, Wadenvik H. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat Med* 2003; **9**: 1123-1124 [PMID: 12937414]
- Zhang XL, Ma J, Xu M, Meng F, Qu M, Sun J, Qin P, Wang L, Hou Y, Song Q, Peng J, Hou M. Imbalance between CD205 and CD80/CD86 in dendritic cells in patients with immune thrombocytopenia. *Thromb Res* 2015; **135**: 352-361 [PMID: 25554498 DOI: 10.1016/j.thromres.2014.11.042]
- Cooper N. Intravenous immunoglobulin and anti-RhD therapy in the management of immune thrombocytopenia. *Hematol Oncol Clin North Am* 2009; **23**: 1317-1327 [PMID: 19932436 DOI: 10.1061/j.hoc.2009.09.002]
- Despotovic JM, Lambert MP, Herman JH, Gernsheimer TB, McCrae KR, Tarantino MD, Bussel JB. RhIG for the treatment of immune thrombocytopenia: consensus and controversy (CME). *Transfusion* 2012; **52**: 1126-1136; quiz 1125 [PMID: 21981825 DOI: 10.1111/j.1537-2995.2011.03384.x]
- Ghanima W, Khelif A, Waage A, Michel M, Tjønnfjord GE,

- Romdhan NB, Kahrs J, Darne B, Holme PA. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; **385**: 1653-1661 [PMID: 25662413 DOI: 10.1016/S0140-6736(14)61495-1]
- 23 **Rodeghiero F**, Ruggeri M. Chronic immune thrombocytopenic purpura. New agents. *Hamostaseologie* 2009; **29**: 76-79 [PMID: 19151853]
 - 24 **Mikhael J**, Northridge K, Lindquist K, Kessler C, Deuson R, Danese M. Short-term and long-term failure of laparoscopic splenectomy in adult immune thrombocytopenic purpura patients: a systematic review. *Am J Hematol* 2009; **84**: 743-748 [PMID: 19714591 DOI: 10.1002/ajh.21501]
 - 25 **Ghanima W**, Godeau B, Cines DB, Bussel JB. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. *Blood* 2012; **120**: 960-969 [PMID: 22740443 DOI: 10.1182/blood-2011-12-309153]
 - 26 **Kojouri K**, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood* 2004; **104**: 2623-2634 [PMID: 15217831 DOI: 10.1182/blood-2004-03-1168]
 - 27 **Qu Y**, Xu J, Jiao C, Cheng Z, Ren S. Long-term outcomes of laparoscopic splenectomy versus open splenectomy for idiopathic thrombocytopenic purpura. *Int Surg* 2014; **99**: 286-290 [PMID: 24833154 DOI: 10.9738/INTSURG-D-13-00175.1]
 - 28 **Vecchio R**, Marchese S, Intagliata E, Swehli E, Ferla F, Cacciola E. Long-term results after splenectomy in adult idiopathic thrombocytopenic purpura: comparison between open and laparoscopic procedures. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 192-198 [PMID: 23231471 DOI: 10.1089/lap.2012.0146]
 - 29 **Sampath S**, Meneghetti AT, MacFarlane JK, Nguyen NH, Benny WB, Panton ON. An 18-year review of open and laparoscopic splenectomy for idiopathic thrombocytopenic purpura. *Am J Surg* 2007; **193**: 580-583; discussion 583-584 [PMID: 17434359]
 - 30 **Cordera F**, Long KH, Nagorney DM, McMurtry EK, Schleck C, Ilstrup D, Donohue JH. Open versus laparoscopic splenectomy for idiopathic thrombocytopenic purpura: clinical and economic analysis. *Surgery* 2003; **134**: 45-52 [PMID: 12874582 DOI: 10.1067/msy.2003.204]
 - 31 **Gkegkes ID**, Mourtarakos S, Iavazzo C. Single-incision laparoscopic splenectomy. *JSLs* 2014; **18**: e2014 [PMID: 25392670 DOI: 10.4293/JSLs.2014.00350]
 - 32 **Liang ZW**, Cheng Y, Jiang ZS, Liu HY, Gao Y, Pan MX. Transumbilical single-incision endoscopic splenectomy: report of ten cases. *World J Gastroenterol* 2014; **20**: 258-263 [PMID: 24415880 DOI: 10.3748/wjg.v20.i1.258]
 - 33 **Monclova JL**, Targarona EM, Vidal P, Peraza Y, Garcia F, Otero CR, Pallares L, Balague C, Trias M. Single incision versus reduced port splenectomy--searching for the best alternative to conventional laparoscopic splenectomy. *Surg Endosc* 2013; **27**: 895-902 [PMID: 23052510 DOI: 10.1007/s00464-012-2530-y]
 - 34 **Balagué C**, Vela S, Targarona EM, Gich IJ, Muñoz E, D'Ambra A, Pey A, Monllau V, Ascaso E, Martinez C, Garriga J, Trias M. Predictive factors for successful laparoscopic splenectomy in immune thrombocytopenic purpura: study of clinical and laboratory data. *Surg Endosc* 2006; **20**: 1208-1213 [PMID: 16865623 DOI: 10.1007/s00464-005-0445-6]
 - 35 **Kang CM**, Lee JG, Kim KS, Choi JS, Lee WJ, Kim BR, Ko YW, Han JS, Min YH. Long-term follow-up of laparoscopic splenectomy in patients with immune thrombocytopenic purpura. *J Korean Med Sci* 2007; **22**: 420-424 [PMID: 17596647 DOI: 10.3346/jkms.2007.22.3.420]
 - 36 **Chen X**, Peng B, Cai Y, Zhou J, Wang Y, Wu Z, Chen S. Laparoscopic splenectomy for patients with immune thrombocytopenia and very low platelet count: is platelet transfusion necessary? *J Surg Res* 2011; **170**: e225-e232 [PMID: 21816423 DOI: 10.1016/j.jss.2011.06.031]
 - 37 **Zheng CX**, Zheng D, Chen LH, Yu JF, Wu ZM. Laparoscopic splenectomy for immune thrombocytopenic purpura at a teaching institution. *Chin Med J (Engl)* 2011; **124**: 1175-1180 [PMID: 21542991]
 - 38 **Gonzalez-Porras JR**, Escalante F, Pardal E, Sierra M, Garcia-Frade LJ, Redondo S, Arefi M, Aguilar C, Ortega F, de Cabo E, Fisac RM, Sanz O, Esteban C, Alberca I, Sanchez-Barba M, Santos MT, Fernandez A, Gonzalez-Lopez TJ. Safety and efficacy of splenectomy in over 65-yrs-old patients with immune thrombocytopenia. *Eur J Haematol* 2013; **91**: 236-241 [PMID: 23679653 DOI: 10.1111/ejh.12146]
 - 39 **Montalvo J**, Velazquez D, Pantoja JP, Sierra M, López-Karpovitch X, Herrera MF. Laparoscopic splenectomy for primary immune thrombocytopenia: clinical outcome and prognostic factors. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 466-470 [PMID: 24905792 DOI: 10.1089/lap.2013.0267]
 - 40 **Rijcken E**, Mees ST, Bisping G, Krueger K, Bruewer M, Senninger N, Mennigen R. Laparoscopic splenectomy for medically refractory immune thrombocytopenia (ITP): a retrospective cohort study on longtime response predicting factors based on consensus criteria. *Int J Surg* 2014; **12**: 1428-1433 [PMID: 25448666 DOI: 10.1016/j.ijsu.2014.10.012]
 - 41 **Cai Y**, Liu X, Peng B. Should we routinely transfuse platelet for immune thrombocytopenia patients with platelet count less than $10 \times 10^9/L$ who underwent laparoscopic splenectomy? *World J Surg* 2014; **38**: 2267-2272 [PMID: 24722866 DOI: 10.1007/s00268-014-2560-9]
 - 42 **Navez J**, Hubert C, Gigot JF, Navez B, Lambert C, Jamar F, Danse E, Lannoy V, Jabbour N. Does the site of platelet sequestration predict the response to splenectomy in adult patients with immune thrombocytopenic purpura? *Platelets* 2015; **26**: 573-576 [PMID: 25275667 DOI: 10.3109/09537104.2014.959915]
 - 43 **Cines DB**, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood* 2005; **106**: 2244-2251 [PMID: 15941913 DOI: 10.1182/blood-2004-12-4598]
 - 44 **George JN**, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, Warrier I. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; **88**: 3-40 [PMID: 8704187]
 - 45 **Stasi R**, Amadori S, Osborn J, Newland AC, Provan D. Long-term outcome of otherwise healthy individuals with incidentally discovered borderline thrombocytopenia. *PLoS Med* 2006; **3**: e24 [PMID: 16401142]
 - 46 **Bain BJ**. Ethnic and sex differences in the total and differential white cell count and platelet count. *J Clin Pathol* 1996; **49**: 664-666 [PMID: 8881919]
 - 47 **Lugada ES**, Mermin J, Kaharuzza F, Ulvestad E, Were W, Langeland N, Asjo B, Malamba S, Downing R. Population-based hematologic and immunologic reference values for a healthy Ugandan population. *Clin Diagn Lab Immunol* 2004; **11**: 29-34 [PMID: 14715541]
 - 48 **Adibi P**, Faghih Imani E, Talaei M, Ghanei M. Population-based platelet reference values for an Iranian population. *Int J Lab Hematol* 2007; **29**: 195-199 [PMID: 17474897]
 - 49 **Burrows RF**, Kelton JG. Incidentally detected thrombocytopenia in healthy mothers and their infants. *N Engl J Med* 1988; **319**: 142-145 [PMID: 3386694 DOI: 10.1056/NEJM198807213190304]
 - 50 **Vianelli N**, Galli M, de Vivo A, Intermesoli T, Giannini B, Mazzucconi MG, Barbui T, Tura S, Baccaranion M. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. *Haematologica* 2005; **90**: 72-77 [PMID: 15642672]
 - 51 **Shojaieard A**, Mousavi SA, Faghihi SH, Abdollahzade S. Prediction of response to splenectomy in patients with idiopathic thrombocytopenic purpura. *World J Surg* 2008; **32**: 488-493 [PMID: 18196318 DOI: 10.1007/s00268-007-9399-2]
 - 52 **Radaelli F**, Faccini P, Goldaniga M, Guggiari E, Pozzoli E, Maiolo AT, Ciani A, Pogliani EM. Factors predicting response to splenectomy in adult patients with idiopathic thrombocytopenic purpura. *Haematologica* 2000; **85**: 1040-1044 [PMID: 11025594]
 - 53 **Kwon HC**, Moon CH, Cho YR, Kim MC, Kim KH, Han JY,

- Lee YH, Oh SY, Kim SH, Kim JS, Kim HJ. Prognostic factors of response to laparoscopic splenectomy in patients with idiopathic thrombocytopenic purpura. *J Korean Med Sci* 2005; **20**: 417-420 [PMID: 15953862]
- 54 **Palandri F**, Polverelli N, Catani L, Sollazzo D, Romano M, Levorato M, Vianelli N. The choice of second-line therapy in steroid-resistant immune thrombocytopenia: role of platelet kinetics in a single-centre long-term study. *Am J Hematol* 2014; **89**: 1047-1050 [PMID: 25103500 DOI: 10.1002/ajh.23823]
- 55 **Sarpawari A**, Provan D, Erqou S, Sobnack R, David Tai FW, Newland AC. Autologous 111 In-labelled platelet sequestration studies in patients with primary immune thrombocytopenia (ITP) prior to splenectomy: a report from the United Kingdom ITP Registry. *Br J Haematol* 2010; **151**: 477-487 [PMID: 20950403 DOI: 10.1111/j.1365-2141.2010.08377.x]
- 56 **Zheng CX**, Ji ZQ, Zhang LJ, Wen Q, Chen LH, Yu JF, Zheng D. Proteomics-based identification of haptoglobin as a favourable serum biomarker for predicting long-term response to splenectomy in patients with primary immune thrombocytopenia. *J Transl Med* 2012; **10**: 208 [PMID: 23039040 DOI: 10.1186/1479-5876-10-208]

P- Reviewer: Dina I, Erginel B, Enomoto H

S- Editor: Qi Y **L- Editor:** Wang TQ **E- Editor:** Li D



Retrospective Study

Predictors of suboptimal bowel preparation in asymptomatic patients undergoing average-risk screening colonoscopy

Shail M Govani, Eric E Elliott, Stacy B Menees, Stephanie L Judd, Sameer D Saini, Constantinos P Anastassiades, Annette L Urganus, Suzanna J Boyce, Philip S Schoenfeld

Shail M Govani, Eric E Elliott, Stacy B Menees, Sameer D Saini, Annette L Urganus, Philip S Schoenfeld, Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109, United States

Shail M Govani, Stacy B Menees, VA Ann Arbor Healthcare System, Ann Arbor, MI 48109, United States

Eric E Elliott, Sameer D Saini, Annette L Urganus, Philip S Schoenfeld, Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI 48109, United States

Stephanie L Judd, Department of Internal Medicine, Wayne State University, Detroit, MI 48202, United States

Constantinos P Anastassiades, Division of Gastroenterology, Case Western Reserve University Hospital, Cleveland, OH 44106, United States

Suzanna J Boyce, Department of Internal Medicine, Duke University, Durham, NC 27708, United States

Author contributions: Govani SM and Elliott EE drafted the paper; Govani SM, Elliott EE and Menees SB analyzed the data; Govani SM, Elliott EE, Menees SB, Judd SL, Saini SD, Anastassiades CP, Urganus AL and Boyce SJ performed chart review; Schoenfeld PS conceived and designed the study; all authors approved the final paper.

Institutional review board statement: The study was reviewed and approved for publication by our institutional reviewer.

Informed consent statement: Waiver of informed consent was obtained from our institutional review board.

Conflict-of-interest statement: Dr. Schoenfeld has worked as a consultant and advisory board member for Salix Pharmaceuticals, Inc, which is the manufacturer of MoviPrep®. Other authors have no conflicts of interest.

Data sharing statement: These analyses were performed using raw data that are available only within the US Department of

Veterans Affairs firewall in a secure research environment, the VA Informatics and Computing Infrastructure (VINCI). In order to comply with VA privacy and data security policies and regulatory constraints, only aggregate summary statistics and results of our analyses are permitted to be removed from the data warehouse for publication. The authors have provided detailed results of the analyses in the paper. These restrictions are in place in order to maintain patient privacy and confidentiality. Access to these data can be granted to persons who are not employees of the VA; however, there is an official protocol that must be followed for doing so. Those wishing to access the raw data that were used for this analysis may contact Shail Govani (shailg@umich.edu) to discuss the details of the VA data access approval process. The authors also confirm that an interested researcher would be able to obtain a de-identified, raw dataset upon request pending ethical approval.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Shail M Govani, MD, MSc, Department of Internal Medicine, University of Michigan, 2215 Fuller Road, Room 111D, Ann Arbor, MI 48109, United States. shailg@umich.edu
Telephone: +1-734-8455865
Fax: +1-734-2322302

Received: March 20, 2016
Peer-review started: March 22, 2016
First decision: May 17, 2016
Revised: June 15, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016

Published online: September 16, 2016

Abstract

AIM

To identify risk factors for a suboptimal preparation among a population undergoing screening or surveillance colonoscopy.

METHODS

Retrospective review of the University of Michigan and Veteran's Administration (VA) Hospital records from 2009 to identify patients age 50 and older who underwent screening or surveillance procedure and had resection of polyps less than 1 cm in size and no more than 2 polyps. Patients with inflammatory bowel disease or a family history of colorectal cancer were excluded. Suboptimal procedures were defined as procedure preparations categorized as fair, poor or inadequate by the endoscopist. Multivariable logistic regression was used to identify predictors of suboptimal preparation.

RESULTS

Of 4427 colonoscopies reviewed, 2401 met our inclusion criteria and were analyzed. Of our population, 16% had a suboptimal preparation. African Americans were 70% more likely to have a suboptimal preparation (95%CI: 1.2-2.4). Univariable analysis revealed that narcotic and tricyclic antidepressants (TCA) use, diabetes, prep type, site (VA vs non-VA), and presence of a gastroenterology (GI) fellow were associated with suboptimal prep quality. In a multivariable model controlling for gender, age, ethnicity, procedure site and presence of a GI fellow, diabetes [odds ratio (OR) = 2.3; 95%CI: 1.6-3.2], TCA use (OR = 2.5; 95%CI: 1.3-4.9), narcotic use (OR = 1.7; 95%CI: 1.2-2.5) and Miralax-Gatorade prep vs 4L polyethylene glycol 3350 (OR = 0.6; 95%CI: 0.4-0.9) were associated with a suboptimal prep quality.

CONCLUSION

Diabetes, narcotics use and TCA use were identified as predictors of poor preparation in screening colonoscopies while Miralax-Gatorade preps were associated with better bowel preparation.

Key words: Preparation; Quality; Narcotics; Diabetes; Colonoscopy

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Suboptimal preparation quality affects the ability of endoscopists to identify polyps during colonoscopy, leading to repeated procedures or missed lesions. In this large retrospective review of screening and surveillance procedures, we found that suboptimal preparation affected 16% of the procedures. Diabetes, narcotics

use and tricyclic antidepressants use were identified as predictors of poor preparation in multivariable analysis. More aggressive preparations should be considered with patients with these risk factors.

Govani SM, Elliott EE, Menees SB, Judd SL, Saini SD, Anastassiades CP, Urganus AL, Boyce SJ, Schoenfeld PS. Predictors of suboptimal bowel preparation in asymptomatic patients undergoing average-risk screening colonoscopy. *World J Gastrointest Endosc* 2016; 8(17): 616-622 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i17/616.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i17.616>

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer mortality in the United States, with an estimated 50830 deaths in 2013 alone^[1]. Colonoscopy has been shown to be effective at detection and removal of pre-cancerous lesions^[2]. However, bowel wall mucosa that is obscured due to inadequate bowel preparation cleansing is a significant problem, affecting 17.5%-28.2% of colonoscopies^[3-5]. The importance of bowel cleanliness was highlighted in a study by Froehlich *et al*^[6]. While preparation quality did not affect cancer detection rates, the study demonstrated that patients with good and excellent bowel preparations were 1.7x and 1.5x, respectively, as likely to have a polyp detected and removed compared to poor bowel preparation quality.

Suboptimal bowel preparation inhibits the endoscopist's ability to visualize the mucosal lining for polyps and cancers; this lack of visualization influences recommended follow-up intervals for repeat screening or surveillance colonoscopy^[7,8]. Data presented by Karasek *et al*^[9] demonstrated that among all colonoscopies in a Veteran population, when the bowel preparation quality was inadequate the interval follow-up was 17.1 mo shorter than the average recommendation of 58.7 mo. Similarly in an Israeli study of seventy-eight gastroenterologists^[7], they found shorter follow-up intervals when bowel preparation became increasing worse.

Regardless of indication for colonoscopy, numerous risk factors for inadequate preparation have been identified: Increasing age, male gender, diabetics, obesity, hypertension, cirrhosis, inpatient status, history of constipation, use of narcotics and tricyclic antidepressants (TCA), time of colonoscopy procedure, and patient comprehension of bowel preparation agent instructions^[4,10,11].

To the best of our knowledge no previous study has identified predictors of inadequate bowel preparation within a strictly asymptomatic outpatient screening population. Thus, the aim of this study was to estimate the impact of predictors on suboptimal bowel preparation among patients undergoing average-risk screening colonoscopy in the outpatient setting.

MATERIALS AND METHODS

Study design

This was a retrospective analysis of patient electronic medical records and colonoscopy reports from the Veterans Affairs Ann Arbor Medical Center (VA), and the University of Michigan in-hospital (Ann Arbor, MI, United States) medical procedures unit and two satellite ambulatory surgery medical procedures units (Ann Arbor, MI and Livonia, MI, United States). All colonoscopies were performed by board-certified gastroenterology staff or gastroenterology fellows under direct supervision of staff gastroenterologists.

Study population

All individuals 50 years or older undergoing average-risk screening colonoscopy in the outpatient setting between January 1st and December 31st, 2009 were reviewed for study eligibility. Subject exclusions included any listed concurrent gastrointestinal symptoms (*i.e.*, overt or occult GI bleeding, change in bowel habits, iron deficiency anemia or unexplained weight loss); family history of CRC; personal history of colon polyps, CRC, hereditary CRC syndromes (*i.e.*, hereditary non-polyposis colorectal cancer or familial adenomatous polyposis), and inflammatory bowel disease; any finding of large polyps (diameter ≥ 10 mm), or three or more polyps. Inpatient procedures or incomplete colonoscopies (determined by visualization of cecum and appendiceal orifice) resulted in study exclusion. Colonoscopy reports that lacked a preparation quality (adequate/inadequate or excellent/good/fair/poor) were also excluded.

Bowel preparation quality

The University of Michigan Healthcare System and VA Ann Arbor Medical Center use the Provation[®] Medical system (v5.0 and v4.2, respectively) to record endoscopic data. Physicians report bowel cleansing as "Quality" (excellent, good, fair, or poor), and/or "Adequacy" (Adequate or Inadequate/Unsatisfactory). For this analysis, bowel preparation quality was organized into a three-category variable: (1) Excellent and good and/or adequate; (2) Fair (defined as fair or fair-adequate); and (3) Poor (defined as poor and/or inadequate/unsatisfactory); and as a dichotomous variable: Optimal (excellent, good, adequate) and Suboptimal (fair, poor/inadequate).

Predictors of bowel preparation quality

Demographic and clinical factors were extracted from the patient's medical records. Demographic data included the patient's age at colonoscopy, gender, and race/ethnicity. Clinical factors included narcotic and TCA usage, diabetic status, body mass index (BMI): kg/m², endoscopy site, bowel preparation agent (GoLytely[®], Miralax[®]-Gatorade[®], *etc.*), number of polyps detected, and if a gastroenterology (GI) fellow was present during the procedure.

Statistical analysis

Descriptive statistics for continuous variables were cal-

culated as means and standard errors, and categorical variables were characterized as proportions. Continuous variables (patient age and BMI) were categorized for the analysis. Logistic regression was used to estimate relative risks as odds ratios (ORs) with 95% CIs.

The primary objective was to identify predictors of fair and poor bowel preparation quality. Age was categorized into 50-59 years, 60-69 year, and ≥ 70 year; BMI was categorized into < 30 kg/m² and ≥ 30 kg/m². Bowel preparation types were categorized as 8L polyethylene glycol (PEG)-3350, 4L PEG-3350, Miralax[®]-Gatorade[®], and other; bowel preparation effect estimates were referenced to 4L PEG-3350. All categorical variables were referenced to their lowest category, and effect estimates were adjusted for the site of colonoscopy and GI fellow presence. To measure the impact of risk factors on bowel preparation quality, a multivariable logistic regression model including all variables was fit.

All study database management and all statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, United States) and $P < 0.05$ was considered statistically significant. IRB approval was obtained from the University of Michigan and Veterans Affairs Ann Arbor Medical Complex prior to commencement of the data collection.

RESULTS

We reviewed 4427 average-risk screening colonoscopies performed between 1/1/2009 and 12/31/2009; 2026 (45.8%) subjects were excluded. The most frequent exclusionary criteria was polyp diameter ≥ 10 mm and/or three or more polyps, $n = 709$ (15.9%). Ninety-two (2.1%) subjects were excluded due missing bowel preparation quality data. The analysis included 2401 subjects: 1507 (62.8%) from the University of Michigan satellite outpatient ambulatory surgery centers, 407 (16.9%) from the University of Michigan in-hospital endoscopy unit, and 487 (20.3%) from the Ann Arbor VA endoscopy unit.

The study population had a mean age of 56.9 (± 7.1) and mean BMI of 28.6 (± 5.9). Males made up 55.3% of the population, and a majority (78.3%) of the population was Caucasian (Table 1). Fair bowel preparation was significantly greater amongst male subjects (12.9% vs 9.9%, $P = 0.02$), procedures performed in the presence of a GI fellow (16.0% vs 10.6%, $P < 0.01$), and procedures completed at the University of Michigan in-hospital and VA endoscopy units (11.8% and 17.1% vs 9.7%, respectively, $P < 0.01$). African-American individuals more frequently received fair and poor preparations ratings. Narcotics and tri-cyclic antidepressant users, and diabetics more frequently received fair and poor bowel preparations. Miralax/Gatorade bowel preparation users had the lowest occurrence of fair or poor bowel quality. No trends existed in the distribution of bowel cleansing quality by increasing age or number of polyps detected.

Table 2 provides adjusted effect magnitudes of predictors of suboptimal bowel cleansing after adjust-

Table 1 Frequency distribution of subject characteristics across level of bowel preparation quality

Characteristics	Bowel preparation quality ¹				
	Excellent or good		Fair	Poor or inadequate	
	<i>n</i> (%)	<i>n</i> (%)	<i>P</i> value ²	<i>n</i> (%)	<i>P</i> value ²
Demographics					
Age (yr)					
50-59	1385 (84.8)	177 (10.8)	0.21	71 (4.4)	0.20
60-69	502 (82.0)	78 (12.8)		32 (5.2)	
≥ 70	130 (83.3)	23 (14.7)		3 (1.9)	
Gender					
Female	916 (85.3)	106 (9.9)	0.02	52 (4.8)	0.46
Male	1101 (83.0)	172 (13.0)		54 (4.1)	
Race/ethnicity					
White	1596 (84.9)	210 (11.2)	0.16	73 (3.9)	< 0.01
Black	134 (75.3)	27 (15.2)		17 (9.6)	
Other ³	150 (82.8)	21 (11.6)		10 (5.5)	
Body mass index, (kg/m ²)					
< 25	523 (85.9)	59 (9.7)	0.05	27 (4.4)	0.79
≤ 25 to < 30	744 (85.1)	96 (11.0)		34 (3.9)	
≤ 30 to < 35	403 (81.3)	73 (14.7)		20 (4.0)	
≥ 35	238 (81.5)	39 (13.4)		15 (5.1)	
Clinical					
Narcotics use ⁴					
Yes	159 (74.0)	37 (17.2)	< 0.01	19 (8.8)	< 0.01
No	1842 (85.0)	239 (11.0)		86 (4.0)	
TCA use ⁴					
Yes	36 (69.2)	10 (19.2)	0.04	6 (11.5)	0.01
No	1965 (84.3)	266 (11.4)		99 (4.3)	
Prior diagnosis of diabetes					
Yes	204 (70.3)	61 (21.0)	< 0.01	25 (8.6)	< 0.01
No	1798 (85.9)	215 (10.3)		80 (3.8)	
GI fellow present					
Yes	344 (78.7)	70 (16.0)	< 0.01	23 (5.3)	0.22
No	1673 (85.2)	208 (10.6)		83 (4.2)	
No. of polyps ⁵ detected					
None	1232 (83.2)	179 (12.1)	0.57	69 (4.7)	0.65
1	537 (85.4)	68 (10.8)		24 (3.8)	
2	248 (84.9)	31 (10.6)		13 (4.5)	
Bowel prep type					
8L PEG-3350	334 (79.9)	70 (16.8)	< 0.01	14 (3.4)	0.01
4L PEG-3350	843 (81.8)	125 (12.1)		62 (6.0)	
MiraLAX®/Gatorade®	466 (90.0)	39 (7.5)		13 (2.5)	
Other ⁶	306 (85.7)	35 (9.8)		16 (4.5)	
Endoscopy site					
UMich Satellite Outpatient Units ⁷	1302 (86.4)	146 (9.7)	< 0.01	59 (3.9)	0.11
UMich in-Hospital Outpatient Unit	334 (82.1)	48 (11.8)		25 (6.1)	
Veterans Affairs Unit	381 (78.2)	84 (17.3)		22 (4.5)	
Total	2017 (84.0)	278 (11.6)		106 (4.4)	

¹Values may not sum to "All Subjects" due to missing data; ²Association relative to "Excellent or Good"; ³Other includes Asian, Hispanic, Native American, and those self-reported bi- or multi-racial; ⁴Defined as usage at time of colonoscopy procedure; ⁵Defined as polyps < 10 mm in diameter, and without villous histology; ⁶Includes Osmoprep®, Half-Lytely®, and MoviPrep®; ⁷Includes data from two satellite endoscopy units from the academic hospital. TCA: Tricyclic antidepressants; GI: Gastroenterology; PEG: Polyethylene glycol.

ment for site of endoscopy and GI fellow presence during the procedure. Diabetic status (OR = 2.3, 95%CI: 1.7-3.1), TCA use (OR = 2.5, 95%CI: 1.4-4.6), and narcotics use (OR = 1.8, 95%CI: 1.3-2.5) were associated with suboptimal bowel preparation. Compared to Caucasians, African-Americans were 70% (95%CI: 1.2-2.4) more likely to have suboptimal bowel cleansing. Relative to the 4L PEG-3350 preparations, 8L PEG-3350 and MiraLAX®/Gatorade® bowel preparation agents were associated with decreased odds of suboptimal bowel cleansing (OR = 0.52, 95%CI: 0.30-0.91 and OR = 0.55, 95%CI: 0.39-0.76), respectively. Patients with BMI ≥

30 trended towards increased frequency of suboptimal bowel cleansing (relative to those with a BMI < 30).

After adjustment for all variables (Table 3), the University of Michigan in-hospital endoscopy unit patients were 10% more likely to have suboptimal bowel preparations, relative to those at the satellite ambulatory surgery centers. However, the Veteran population was at a 2.2-fold increased risk of suboptimal bowel preparation relative to the same population. All other previously noted associations remained statistically significant after fitting the saturated multivariable logistic regression model.

Table 2 Adjusted estimates [odds ratio (95%CI)] of predictors of suboptimal bowel preparation

Suboptimal bowel prep Predictors	OR (95%CI) ¹
Age (yr)	
50-59	1.0
60-69	1.1 (0.84-1.4)
≥ 70	1.0 (0.67-1.6)
Male gender	0.99 (0.77-1.3)
Race	
White	1.0
Black	1.7 (1.2-2.4)
Other	1.2 (0.80-1.8)
Body mass index (kg/m ²)	
< 30	1.0
≥ 30	1.3 (0.99-1.6)
Clinical	
Narcotics use	1.8 (1.3-2.5)
TCA use	2.5 (1.4-4.6)
Diagnosis of diabetes	2.3 (1.7-3.1)
GI fellow present	1.1 (0.82-1.6)
Polyps detected	0.85 (0.68-1.1)
Bowel prep type	
4L PEG 3350	1.0
8L PEG 3350	0.52 (0.30-0.91)
MiraLAX®/Gatorade®	0.55 (0.39-0.76)
Other	0.76 (0.54-1.1)
Endoscopy site	
UMich Satellite Outpatient Units	1.0
UMich in-Hospital Outpatient Unit	1.3 (0.94-1.8)
Veterans Affairs in-Hospital Unit	1.6 (1.2-2.3)

¹Effect adjusted for endoscopy site and GI fellow presence. TCA: Tricyclic antidepressants; GI: Gastroenterology; PEG: Polyethylene glycol; OR: Odds ratio.

The distribution of bowel cleansing ratings between the University of Michigan in-hospital and VA endoscopy units varied depending on whether a GI fellow was present during the colonoscopy (Table 4). In the absence of GI fellows, endoscopists at the University of Michigan were more likely to issue bowel quality rates of poor, compared to those at the VA endoscopy unit (7.4% vs 3.1%, $P = 0.05$). However, when GI fellows were present during the procedure, VA endoscopists were more likely (18.9% vs 11.7%, $P = 0.04$) to rate bowel preparations as fair.

DISCUSSION

This retrospective study is the first to focus on identifying predictors of bowel preparation quality among patients undergoing average-risk screening colonoscopy. In addition to reduced adenoma detection rates and increased risk of procedural complications, suboptimal preparation leads to increased healthcare costs by increasing the likelihood that a patient receives a shorter interval recommendation for repeat endoscopy^[7,9]. Repeat colonoscopy procedures due to suboptimal bowel preparation have significant implications on the increasing cost of medical care in the United States, especially within the average-risk screening population that accounts for approximately two million colonoscopies

Table 3 Multivariable estimates [odds ratio (95%CI)] of predictors of suboptimal bowel preparation

Factor	Suboptimal prep, OR (95%CI)
Endoscopy site	
Academic in-Hospital Unit	1.1 (0.76-1.6)
Veterans Affairs Hospital	2.2 (1.1-4.3)
African-American	1.5 (1.0-2.2)
Diabetic	2.3 (1.6-3.2)
TCA use	2.5 (1.3-4.9)
Narcotics use	1.7 (1.2-2.5)
Bowel prep type	
8L PEG-3350	0.46 (0.24-0.87)
MiraLAX®/Gatorade®	0.61 (0.43-0.86)

TCA: Tricyclic antidepressants; OR: Odds ratio; PEG: Polyethylene glycol.

performed annually^[12,13]. With an aging population the increased need for screening colonoscopy is greater than ever. However, predictions show no significant increase in the number of practicing gastroenterologists, thus reducing the percentage of endoscopies with suboptimal preparations is critical to utilization sustainability.

The findings of our study within an asymptomatic average-risk population are similar to those which included other indications for CRC screening. Amongst average-risk screening individuals, we identified that diabetes along with narcotics and TCA use was associated with approximately a two-fold increase in the risk of suboptimal bowel preparation. Though not statistically significant, our study showed that individuals with a BMI ≥ 30 trended towards suboptimal bowel preparations compared those with a BMI < 30 . Our study also identified that African-American patients were less likely to have optimal bowel cleansing relative to Caucasians. African-Americans have been found to have both more advanced disease at diagnosis and poorer outcomes than other groups^[14]. However, unlike previous studies, we did not find that patient age or gender were predictors of suboptimal preparation quality.

Our study is novel in that it compared average-risk screening patients amongst an academic in-hospital and satellite ambulatory endoscopy centers, and a Veterans Affairs endoscopy suite. Relative to the study population at the outpatient ambulatory academic satellite surgery centers, the Veteran population was twice as likely to produce a suboptimal bowel preparation. The 2010 Veterans Health Administration Health Report^[15] indicated that in the fiscal year 2009, 214955 colonoscopies were performed for all indications; our study found that 22.2% of the screening colonoscopies amongst Veterans had suboptimal bowel preparations. This has significant implications on the already scarce availability of colonoscopy for repeat procedures especially as the VHA continues to increase the rate of colorectal screening amongst Veterans.

A number of studies have compared the results of different bowel preparation types on colonoscopy preparation quality^[16,17]. The finding of the MiraLAX®-Gatorade® bowel preparation producing superior bowel preparation quality is in contrast to published literature.

Table 4 Distribution of bowel preparation quality and endoscopy site, across level of gastroenterology fellow presence during colonoscopy

GI fellow presence	Bowel preparation quality				
	Excellent/good	Fair		Poor	
	<i>n</i> (%)	<i>n</i> (%)	<i>P</i> value ¹	<i>n</i> (%)	<i>P</i> value ¹
Not present					
UMich in-Hospital Endoscopy Unit	186 (80.9)	27 (11.7)	0.34	17 (7.4)	0.05
Veterans Affairs Endoscopy Unit	185 (81.5)	35 (15.4)		7 (3.1)	
Present					
UMich in-Hospital Endoscopy Unit	148 (83.6)	21 (11.9)	0.04	8 (4.5)	0.44
Veterans Affairs Endoscopy Unit	196 (75.4)	49 (18.9)		15 (5.8)	
Total	715 (80.0)	132 (14.8)		47 (5.2)	

¹Relative to excellent/good. GI: Gastroenterology.

Two recently published randomized controlled trials comparing MiraLAX[®] to Golytely[®] have shown Golytely[®] to produce superior preparation quality^[18,19]. The study by Enestvedt *et al*^[18] focused on screening colonoscopies, but excluded patients with a history of constipation; whereas, Hjelkrem *et al*^[19] did not exclude patients with risk factors of suboptimal preparation (except prior surgery). Though our study did not directly compare GoLytely[®] to MiraLAX[®], it did demonstrate that compared to all 4L PEG-3350 solutions, MiraLAX[®]-Gatorade[®] produced superior bowel preparation qualities. Noting the retrospective nature of the study design, our study consisted of a large population and allowed for statistical adjustment of known risk factors such as narcotics and TCA use, and diabetic status. Given these conflicting findings, further research on the efficacy of MiraLAX[®] as a colonoscopy preparation agent is warranted.

We are aware that our study has several limitations due to its design. The first limitation is the retrospective nature of medical records relies on patient self-report and documentation by nursing and physician personnel. Between January 1 and December 31, 2009, there were forty-eight practicing gastroenterologists. Some physicians only performed colonoscopy at a single endoscopy center, while others at performed at multiple sites; similarly not all physicians performed colonoscopy in the presence of a GI fellow. We attempted to control for this through our statistical modeling with adjustments for endoscopy site and GI fellow presence. Secondly, our measured outcome was not a standardized scale system such as the Boston Bowel Preparation Scale or the Ottawa scale, but rather subjective determination by our endoscopists using the Aronchick scale (*i.e.*, excellent, good, fair, and poor). Third, data were not collected on previously identified predictors of suboptimal prep such as patient comprehension of bowel preparation instructions, concurrent comorbidities (*i.e.*, dementia, cirrhosis, and stroke), or previous gastrointestinal and/or genitourinary surgeries. The analysis of preparation types is limited by the lack of data on the amount of prep consumed. It is possible that patients may have found the MiraLAX[®]/Gatorade preparation more tolerable and consumed more of this than the PEG-3350 preparations. Lastly, due the tertiary nature of our hospital system,

our results may not be generalizable to the community setting.

In conclusion, our study identified that average-risk patients using narcotics or TCAs prior to colonoscopy, as well as, diabetics are at increased risk for suboptimal bowel preparation quality when undergoing screening colonoscopy. Similarly, our study noted a strong disparity between bowel preparation outcomes amongst Veterans and African-Americans. Further studies aimed at improving bowel preparation outcomes of colonoscopic preparations within these populations are warranted.

COMMENTS

Background

Suboptimal bowel preparation affects approximately 20% of colonoscopies. Suboptimal preparation leads to reduced polyp detection and leads endoscopist to recommend shorter interval follow-up.

Research frontiers

Identifying predictors of suboptimal preparation may allow endoscopists to risk-stratify patients into high and low risk groups and prescribe a more aggressive preparation type for those in the high risk group.

Innovations and breakthroughs

Diabetes, narcotics and tricyclic antidepressant use predict suboptimal preparation.

Applications

Suboptimal preparation affected 1 out of every 6 colonoscopies in this population. Prescription of more aggressive preparation types for patients with diabetes or those who use narcotics or tricyclic antidepressants may reduce the incidence of suboptimal preparations.

Terminology

Suboptimal preparation occurs when the endoscopist characterizes the preparation as fair, poor or inadequate. Screening or surveillance colonoscopies are done to identify polyps and with the aim of preventing subsequent colorectal cancer.

Peer-review

The manuscript by Govani *et al* deals with clinically important question how to improve bowel cleansing before colonoscopy. Given the incidence of colon cancer, the implications of missed lesions due to suboptimal preparation and the costs of performing repeated procedures due to suboptimal preparation, this topic is of immense clinical importance.

REFERENCES

- 1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 2335087 DOI: 10.3322/caac.21166]
- 2 Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology* 2003; **124**: 544-560 [PMID: 12557158 DOI: 10.1053/gast.2003.50044]
- 3 Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003; **58**: 76-79 [PMID: 12838225 DOI: 10.1067/mge.2003.294]
- 4 Chung YW, Han DS, Park KH, Kim KO, Park CH, Hahn T, Yoo KS, Park SH, Kim JH, Park CK. Patient factors predictive of inadequate bowel preparation using polyethylene glycol: a prospective study in Korea. *J Clin Gastroenterol* 2009; **43**: 448-452 [PMID: 18978506 DOI: 10.1097/MCG.0b013e3181662442]
- 5 Sanaka MR, Shah N, Mullen KD, Ferguson DR, Thomas C, McCullough AJ. Afternoon colonoscopies have higher failure rates than morning colonoscopies. *Am J Gastroenterol* 2006; **101**: 2726-2730 [PMID: 17227519 DOI: 10.1111/j.1572-0241.2006.00887.x]
- 6 Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005; **61**: 378-384 [PMID: 15758907]
- 7 Ben-Horin S, Bar-Meir S, Avidan B. The impact of colon cleanliness assessment on endoscopists' recommendations for follow-up colonoscopy. *Am J Gastroenterol* 2007; **102**: 2680-2685 [PMID: 17714555 DOI: 10.1111/j.1572-0241.2007.01486.x]
- 8 Rex DK, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and cost of colonoscopy. *Am J Gastroenterol* 2002; **97**: 1696-1700 [PMID: 12135020 DOI: 10.1111/j.1572-0241.2002.05827.x]
- 9 Karasek V, Gerkin R, Ramirez F, Gilani N, Hayden CT. How Does the Adequacy of Bowel Preparation Affect Endoscopists' Recommendations of Follow-up Colonoscopy Interval? *Am J Gastroenterol* 2009; **104**: S171 [DOI: 10.1038/ajg.2009.492_6]
- 10 Ness RM, Manam R, Hoen H, Chalasani N. Predictors of inadequate bowel preparation for colonoscopy. *Am J Gastroenterol* 2001; **96**: 1797-1802 [PMID: 11419832 DOI: 10.1111/j.1572-0241.2001.03874.x]
- 11 Borg BB, Gupta NK, Zuckerman GR, Banerjee B, Gyawali CP. Impact of obesity on bowel preparation for colonoscopy. *Clin Gastroenterol Hepatol* 2009; **7**: 670-675 [PMID: 19245852 DOI: 10.1016/j.cgh.2009.02.014]
- 12 Seeff LC, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS, Dong FB, Wings LD, McKenna MT. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastroenterology* 2004; **127**: 1670-1677 [PMID: 15578503 DOI: 10.1053/j.gastro.2004.09.051]
- 13 Lieberman DA, Holub J, Eisen G, Kraemer D, Morris CD. Utilization of colonoscopy in the United States: results from a national consortium. *Gastrointest Endosc* 2005; **62**: 875-883 [PMID: 16301030 DOI: 10.1016/j.gie.2005.06.037]
- 14 Marcella S, Miller JE. Racial differences in colorectal cancer mortality. The importance of stage and socioeconomic status. *J Clin Epidemiol* 2001; **54**: 359-366 [PMID: 11297886 DOI: 10.1016/S0895-4356(00)00316-4]
- 15 Performance OoQa. Measure master report for national quarter 2 FY2009: Veteran's Health Administration. 2009
- 16 Tepeš B, Mlakar DN, Metličar T. Bowel preparation for colonoscopy with magnesium sulphate and low-volume polyethylene glycol. *Eur J Gastroenterol Hepatol* 2014; **26**: 616-620 [PMID: 24694759 DOI: 10.1097/MEG.000000000000093]
- 17 Huynh L, Yermakov S, Davis M, Campbell R, Cleveland M, Farraye FA, Yenikomshian M. Cost-analysis model of colonoscopy preparation using split-dose reduced-volume oral sulfate solution (OSS) and polyethylene glycol with electrolytes solution (PEG-ELS). *J Med Econ* 2016; **19**: 356-363 [PMID: 26610148 DOI: 10.3111/13696998.2015.1125907]
- 18 Enestvedt BK, Fennerty MB, Eisen GM. Randomised clinical trial: MiraLAX vs. Golytely - a controlled study of efficacy and patient tolerability in bowel preparation for colonoscopy. *Aliment Pharmacol Ther* 2011; **33**: 33-40 [PMID: 21083586 DOI: 10.1111/j.1365-2036.2010.04493.x]
- 19 Hjelkrem M, Stengel J, Liu M, Jones DP, Harrison SA. MiraLAX is not as effective as GoLyteLy in bowel cleansing before screening colonoscopies. *Clin Gastroenterol Hepatol* 2011; **9**: 326-332.e1 [PMID: 21115134 DOI: 10.1016/j.cgh.2010.11.007]

P- Reviewer: Tepes B S- Editor: Gong ZM

L- Editor: A E- Editor: Li D



Retrospective Study

Transanal endoscopic microsurgery as optimal option in treatment of rare rectal lesions: A single centre experience

Monica Ortenzi, Roberto Ghiselli, Maria Michela Cappelletti Trombettoni, Luca Cardinali, Mario Guerrieri

Monica Ortenzi, Roberto Ghiselli, Maria Michela Cappelletti Trombettoni, Luca Cardinali, Mario Guerrieri, Department of General Surgery, Università Politecnica delle Marche, 60126 Ancona, Italy

Author contributions: Ortenzi M and Ghiselli R designed the study; Ortenzi M, Cappelletti Trombettoni MM and Cardinali L contributed to acquisition of data and drafting the article; Guerrieri M approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ospedali Riuniti Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No financial support or incentive has been provided for this manuscript. All authors have no conflicts of interest or financial ties to disclose.

Data sharing statement: Technical appendix, original data, and statistical code of manuscript NO 26052 submitted to World Journal of Gastrointestinal Endoscopy are available from the corresponding author at monica.ortenzi@gmail.com. Participants gave informed consent for data sharing.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Monica Ortenzi, Department of General Surgery, Università Politecnica delle Marche, Via Tronto 10/a, 60126 Ancona, Italy. monica.ortenzi@gmail.com
Telephone: +39-71-5963648
Fax: +39-71-5963326

Received: March 28, 2016

Peer-review started: March 29, 2016

First decision: May 17, 2016

Revised: June 2, 2016

Accepted: July 11, 2016

Article in press: July 13, 2016

Published online: September 16, 2016

Abstract

AIM

To analyze the outcomes of transanal endoscopic microsurgery (TEM) in the treatment of rare rectal condition like mesenchymal tumors, condylomas, endometriosis and melanoma.

METHODS

We retrospectively reviewed a twenty-three years database. Fifty-two patients were enrolled in this study. The lesions were considered suitable for TEM if they were within 20 cm from the anus. All of them underwent an accurate preoperative workup consisting in clinical examination, total colonoscopy with biopsies, endoscopic ultrasonography, and pelvic computerized tomography or pelvic magnetic resonance imaging. Operative time, intraoperative complications, rate of conversion, tumor size, postoperative morbidity, mortality, the length of hospital stay, local and distant recurrence were analyzed.

RESULTS

Among the 1328 patients treated by TEM in our department, the 52 patients with rectal abnormalities other than adenoma or adenocarcinoma represented 4.4%. There were 30 males (57.7%) and 22 females (42.3%). Mean age was 55 years (median = 60, range = 24-78). This series included 14 (26.9%) gastrointestinal stromal tumors, 21 neuroendocrine tumors (40.4%), 1 ganglioneuroma (1.9%), 2 solitary ulcers in the rectum (3.8%), 6 cases of rectal endometriosis (11.5%), 6

cases of rectal condylomatosis (11.5%) and 2 rectal melanomas (3.8%). Mean lesion diameter was 2.7 cm (median: 4, range: 0.4-8). Mean distance from the anal verge was 9.5 cm (median: 10, range: 4-15). One patient operated for rectal melanoma developed distant metastases and died two years after the operation. We experienced 2 local recurrences (3.8%) with an overall survival equal to 97.6% (95%CI: 95%-99%) at the end of follow-up and a disease free survival of 98% (95%CI: 96%-99%).

CONCLUSION

We could conclude that TEM is an important therapeutic option for rectal rare conditions.

Key words: Transanal endoscopic microsurgery; Rare rectal conditions; Full-thickness excision; Minimally invasive surgery; Retrospective study

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This paper is about the management of rare rectal lesions by transanal endoscopic microsurgery (TEM). The rarity of these conditions and the lack of big reports about this topic make this work important. We focused our attention on operative data and post-operative long-term outcomes. Our results suggested that TEM is a safe, minimally invasive procedure that can be adopted for the treatment of these conditions with excellent results.

Ortenzi M, Ghiselli R, Cappelletti Trombettoni MM, Cardinali L, Guerrieri M. Transanal endoscopic microsurgery as optimal option in treatment of rare rectal lesions: A single centre experience. *World J Gastrointest Endosc* 2016; 8(17): 623-627 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i17/623.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i17.623>

INTRODUCTION

Adenocarcinoma is the most frequent malignancy of the rectum, but the distal part of the bowel can host several other rare lesions which together represent an important part of rectal tumors^[1]. This heterogeneous group comprehends mesenchymal tumors like gastrointestinal stromal tumors (GISTs), neuroendocrine tumors (NETs) and ganglioneuromas. Other abnormalities can involve the rectal wall, and surgery is the only curative option, as is also the case for condyloma, endometriosis and melanoma. The aim of this study was to analyze the results of transanal endoscopic microsurgery (TEM) in the treatment of these rare rectal conditions.

MATERIALS AND METHODS

A retrospective accurate analysis of a twenty-two-year-old database built from 1992 to 2015 identified

52 patients eligible for the study. Indications for TEM were determined on the basis of the anatomical criteria assessed by rigid preoperative rectoscopy in order to locate the lesions and to measure its distance from the anal verge.

All patients were properly informed about the operation and give their consensus to surgery. The lesions were considered suitable for TEM if they were within 20 cm from the anus. Preoperative workup included clinical examination, total colonoscopy with biopsies, endoscopic ultrasonography, and pelvic computerized tomography or pelvic magnetic resonance imaging. Patients' characteristics such as age and gender were considered. All patients received similar pre-operative management with an oral intake of an osmotic solution the day before surgery and a short term intravenous antibiotics prophylaxis to provide coverage for the normal bowel flora, aerobic and anaerobic species.

Procedures were performed by the Wolf TEM equipment (Knittlingen, Germany) consisting of a rigid 12 or 20 cm long rectoscope, an endosurgical unit steadily controlling rectal endoluminal pressure, and curved instruments. In all cases, a full-thickness excision was performed, and the rectal defect was closed by a running suture secured with silver clips at the extremities.

The operative data examined included operative time, intraoperative complications and conversion to abdominal surgery. Tumor size was measured macroscopically and reported as the maximum diameter. Pathological examination included histopathological definition, degree of differentiation, macroscopical measurement, and the examination of radial margins of excision. A urinary catheter was placed in all the patients at the time of surgery, which was removed 24 h after the operation. In the post-operative period, we analyzed postoperative morbidity, mortality and the length of hospital stay. Long-term outcomes included local and distant recurrence. We considered as local recurrence any recurrence diagnosed endoscopically and confirmed by biopsy. Follow-up included digital examination, rigid rectoscopy and endorectal ultrasound every 6 mo for the first year from the time of operation and subsequently every year.

Quantitative variables are shown as the mean value with median and range in brackets. Recurrence-free survival was considered as a continuous variable. The probability of overall survival at the end of follow-up and the probability of disease-free survival were estimated using the Kaplan-Meier method. All analyses were performed using the R statistical package.

RESULTS

Among the 1328 patients treated by TEM in our department, the 52 patients with rectal abnormalities other than adenoma or adenocarcinoma represented 4.4%. There were 30 males (57.7%) and 22 females (42.3%). Mean age was 55 years (median = 60, range = 24-78). We excised, by TEM, 14 (26.9%) GISTs, 21 NETs (40.4%), 1 ganglioneuroma (1.9%) and 2 solitary

Table 1 Population characteristics *n* (%)

Variables	
Sex	
Male	30 (67.7)
Female	22 (42.3)
Neuroendocrine tumors	21 (40.4)
Gastrointestinal stromal tumors	14 (26.9)
Ganglioneuroma	1 (1.9)
Solitary ulcers	2 (3.8)
Endometriosis	6 (11.5)
Condylomas	6 (11.5)
Melanomas	2 (3.8)
Diameter (cm), [mean (median, range)]	2.7 (4, 0.4-8)

ulcers in the rectum (3.8%). We used TEM to treat 6 cases of rectal endometriosis (11.5%), 6 cases of rectal condilomatosis (11.5%) and 2 rectal melanomas (3.8%).

Preoperative symptoms ranged from rectal bleeding (9/52, 17.3%), urgency (3/52, 5.8%) and alteration in bowel habit (7/52, 13.5%). Thirty-two (61.5%) patients were asymptomatic and the lesions were discovered incidentally. Mean lesion diameter was 2.7 cm (median: 4, range: 0.4-8). Mean distance from the anal verge was 9.5 cm (median: 10, range: 4-15) (Table 1).

GISTs had a mean diameter of 1.4 cm (median = 1, range = 0.4-5). Two of them received neoadjuvant Imatinib resulting in reduction in tumor size. Six GISTs were defined as medium risk GISTs and 4 as high risk.

As for NETs, the mean lesion diameter was 2.7 cm (median = 2, range = 0.5-5). Except for one, all of them were G1 well differentiated NETs. There was only one ganglioneuroma which extended circumferentially on the rectal wall and had a diameter of 10 cm. The condyloma had a mean diameter of 2.7 cm (median: 3, range: 2-3). The 2 solitary ulcers had a diameter of 3 and 4 cm respectively and were completely excised.

Complete resection with disease-free margins was achieved in all the cases except for one case in which the pathologist was unable to assess the margin due to thermal damage. Mean operative time was 41 min (median: 45, range: 20-55). There was no conversion to abdominal surgery. We observed one intraoperative minor complication (1.9%) consisting in rectal bleeding controlled by TEM.

We observed a postoperative morbidity rate of 3.8% (2/50), consisting of one case of acute urinary retention and one case of mild incontinence to gas resolved within two months from the operation by means of physiotherapy. Mean hospital stay was 3 d (median: 4, range: 2-7).

All the patients completed the follow-up protocol, including clinical and instrumental assessment. Two patients (3.8%) died from unrelated causes. One patient with rectal NET showed local recurrence within a year after operation. One patient operated for rectal melanoma developed distant metastases and died two years after the operation (Table 2). We observed an overall survival equal to 97.6% (95%CI: 95%-99%) at the end of follow-up and a disease free survival of 98% (95%CI: 96%-99%) (Figure 1).

Table 2 Operative and post-operative data *n* (%)

Variables	
Operative time-min [mean (median, range)]	41 (45, 20-55)
Intraoperative complications	1 (1.9)
Hospital stay (d) [mean (median, range)]	3 (4, 2-7)
Post-operative complications	2 (3.8)
Recurrence	1 (1.9)
Follow-up (yr) [mean (median, range)]	11 (13, 23-1)
Death at the end of follow-up	2 (3.8)

DISCUSSION

Rectal lesions different from adenomas-carcinomas represent a small but important group in terms of oncological and functional implications. Surgery is the main choice in the treatment of these conditions, but debate regarding the best method for their management exists^[1-3]. Their localization in the rectum may represent a therapeutical challenge. Most authors opt for anterior resection or even abdominal perineal resection, but traditional surgery may represent an overtreatment^[1,2,4].

NETs represent the largest group in our series. This kind of tumors are being diagnosed increasingly frequently, and current European Neuroendocrine Tumor Society guidelines recommend endoscopic resection for G1 rectal NET < 10 mm with a low risk of metastatic disease^[5]. The current methods of endoscopic removal are polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and TEM. Since complete surgical resection for a localized lesion was demonstrated as the only effective option, several studies have proved the superiority of TEM over the other endoscopic techniques in the treatment of rectal NET. EMR and ESD achieve a complete microscopic resection in 46.3% to 65.5% and in 75% to 82.6% of cases, respectively^[6-11]. TEM allows us to achieve a 100% rate of free resection margins, as observed in other reports^[9,10]. We did not observe cases of incomplete resection nor recurrence in our experience. Most tumors (80%) were ≤ 10 mm in diameter, and the risk of metastases has been estimated at less than 3% for rectal NETs within 1 cm in diameter^[9]. In our series, all the lesions were G1 well-differentiated rectal NET without lymphovascular invasion except for one patient with a G3 poorly differentiated NET with lymphatic and vascular invasion, who relapsed within a year from operation and was treated by means of an abdominal perineal resection.

As for GISTs, according to Miettinen *et al.*^[12], the rectum is the third most common site of onset, comprising approximately 5%-10% of all GISTs. Neither radiation therapy nor chemotherapy has any proven efficacy as adjuvant therapy. Rectal GIST exhibits two specific features which may significantly affect surgical management: Metastases are extremely rare in loco-regional lymphnodes, and GISTs typically show a tendency to grow away from the intestinal lumen. These characteristics may make these tumors eligible for TEM^[13-16]. In our series, all GISTs were completely resected by TEM. TEM excision is considered to be an interesting alternative

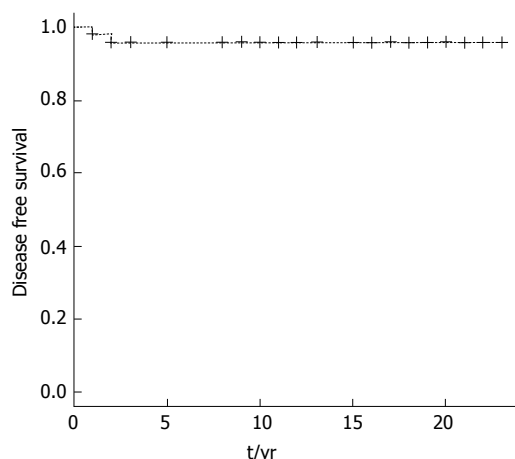


Figure 1 Disease free survival after transanal endoscopic microsurgery for rare rectal lesions.

for small GISTs located within the rectal wall, which are usually incidental findings during endoscopy. This approach, however, is considered not indicated for larger (> 5 cm) tumors growing away from the rectal lumen. In our series, only one GIST had a 5 cm diameter, but it was completely excised, and we did not observe recurrence.

Condyloma mainly affects the anorectal region, and rare reports have described condylomata involving the rectal wall which have often been incidentally discovered by endoscopy^[17-19].

Standard therapy such as laser, fulguration, freezing or microwaves can be difficult to apply inside the rectum^[18]. Surgical resection by TEM can offer a good local disease control, and none of the patients treated by TEM experienced recurrence.

Rectum can also be the site of extrapelvic endometriosis^[2,4,8,20]. Open or laparoscopic surgery is the primary mode of treatment in most of the infiltrating diseases. Surgical treatment is effective in relieving painful defecation, pelvic pain and dyspareunia^[20]. We registered a positive resection margin in one patient affected by endometriosis, but no recurrence was observed in this case. Probably, the margin presented to the pathologist as elettro coagulated. Primary anorectal malignant melanoma is an extremely rare malignancy that is believed to arise from melanocytes in the mucosa around the anorectal junction. Surgery resection is the only curative option, but this malignancy is associated with poor prognosis^[21,22]. We treated only two patients with rectal melanoma by TEM who were incidentally diagnosed during endoscopy. Both cases had an early stage of melanoma confirmed by the pathologist. Both patients received adjuvant chemotherapy. One of them developed local recurrence at 1 year from surgery and was treated with laparoscopic anterior resection.

TEM has demonstrated to be feasible in the treatment of different conditions different from adenomas and carcinomas which may affect the rectum. TEM allows us to reach lesions located up to 20 cm from the anal verge. The magnified tridimensional vision offered by TEM is

crucial to reach the complete rate of complete resection. The possibility to perform a full thickness excision of the rectal wall makes TEM appropriate for tumors like GISTs arising from submucosal layers.

In this series, we did not experience long term morbidity. We registered only one patient with mild gas incontinence which was resolved within two months from surgery by means of physiotherapy.

We could conclude that TEM is an important therapeutic option for rectal rare diseases. Other studies with more numerous series will be necessary to understand the real role of minimally invasive transanal techniques in the treatment of these lesions.

COMMENTS

Background

The rectum can be the site of origin of different lesion far more rare than adenocarcinoma but that have surgery as the only curative option. The full thickness excision reached by transanal endoscopic microsurgery (TEM) offers the possibility to achieve a complete resection with very low morbidity.

Research frontiers

TEM has several advantages compared with traditional approach. It allows to perform a complete transanal full thickness excision of the lesions, with an accurate individuation of free margins due to a magnified stereoscopic view. The morbidity related to this approach is low compared to other surgical techniques.

Innovations and breakthroughs

The exact role of TEM in the treatment of rare rectal lesions is hard to define mainly due to the lack of large series. The retrospective analysis of the authors' experience allowed them to built one of the largest series now available on this topic.

Applications

This retrospective analysis of the authors' experience suggest TEM can be considered safe and feasible in the treatment of these lesions.

Peer-review

This is a large retrospective analysis on the treatment of rare rectal lesions by TEM. The paper is overall well written. The results are well reported.

REFERENCES

- 1 **Jakob J**, Mussi C, Ronellenfitch U, Wardelmann E, Negri T, Gronchi A, Hohenberger P. Gastrointestinal stromal tumor of the rectum: results of surgical and multimodality therapy in the era of imatinib. *Ann Surg Oncol* 2013; **20**: 586-592 [PMID: 22965573 DOI: 10.1245/s10434-012-2647-1]
- 2 **Roman H**, Tuech JJ, Resch B, Leroi AM, Marpeau L, Michot F. Letter re: "Complete surgery for low rectal endometriosis: long-term results of a 100-case prospective study". *Ann Surg* 2013; **257**: e18-e19 [PMID: 23665974 DOI: 10.1097/SLA.0b013e31828d6ff2]
- 3 **Caplin M**, Sundin A, Nillson O, Baum RP, Klose KJ, Kelestimur F, Plöckinger U, Papotti M, Salazar R, Pascher A. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. *Neuroendocrinology* 2012; **95**: 88-97 [PMID: 22261972 DOI: 10.1159/000335594]
- 4 **Haggag H**, Solomayer E, Juhasz-Böss I. The treatment of rectal endometriosis and the role of laparoscopic surgery. *Curr Opin Obstet Gynecol* 2011; **23**: 278-282 [PMID: 21666468 DOI: 10.1097/GCO.0b013e328348a25b]
- 5 **Ramage JK**, De Herder WW, Delle Fave G, Ferolla P, Ferone D, Ito T, Ruszniewski P, Sundin A, Weber W, Zheng-Pei Z, Taal B, Pascher A. ENETS Consensus Guidelines Update for Colorectal

- Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; **103**: 139-143 [PMID: 26730835 DOI: 10.1159/000443166]
- 6 **Jeon SM**, Lee JH, Hong SP, Kim TI, Kim WH, Cheon JH. Feasibility of salvage endoscopic mucosal resection by using a cap for remnant rectal carcinoids after primary EMR. *Gastrointest Endosc* 2011; **73**: 1009-1014 [PMID: 21316666 DOI: 10.1016/j.gie.2010.12.029]
 - 7 **Lee SH**, Park SJ, Kim HH, Ok KS, Kim JH, Jee SR, Seol SY, Kim BM. Retraction notice to "endoscopic resection for rectal carcinoid tumors: comparison of polypectomy and endoscopic submucosal resection with band ligation". *Clin Endosc* 2015; **48**: 87 [PMID: 25674848 DOI: 10.5946/ce.2015.48.1.87]
 - 8 **Sung HY**, Kim SW, Kang WK, Kim SY, Jung CK, Cho YK, Park JM, Lee IS, Choi MG, Chung IS. Long-term prognosis of an endoscopically treated rectal neuroendocrine tumor: 10-year experience in a single institution. *Eur J Gastroenterol Hepatol* 2012; **24**: 978-983 [PMID: 22647741 DOI: 10.1097/MEG.0b013e3283551e0b]
 - 9 **Jeon JH**, Cheung DY, Lee SJ, Kim HJ, Kim HK, Cho HJ, Lee IK, Kim JI, Park SH, Kim JK. Endoscopic resection yields reliable outcomes for small rectal neuroendocrine tumors. *Dig Endosc* 2014; **26**: 556-563 [PMID: 24447261 DOI: 10.1111/den.12232]
 - 10 **Chen WJ**, Wu N, Zhou JL, Lin GL, Qiu HZ. Full-thickness excision using transanal endoscopic microsurgery for treatment of rectal neuroendocrine tumors. *World J Gastroenterol* 2015; **21**: 9142-9149 [PMID: 26290641 DOI: 10.3748/wjg.v21.i30.9142]
 - 11 **Sekiguchi M**, Sekine S, Sakamoto T, Otake Y, Nakajima T, Matsuda T, Taniguchi H, Kushima R, Ohe Y, Saito Y. Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion. *J Gastroenterol* 2015; **50**: 1184-1189 [PMID: 25936647 DOI: 10.1007/s00535-015-1079-7]
 - 12 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1466-1478 [PMID: 17090188]
 - 13 **Hassan I**, You YN, Dozois EJ, Shayyan R, Smyrk TC, Okuno SH, Donohue JH. Clinical, pathologic, and immunohistochemical characteristics of gastrointestinal stromal tumors of the colon and rectum: implications for surgical management and adjuvant therapies. *Dis Colon Rectum* 2006; **49**: 609-615 [PMID: 16552495 DOI: 10.1007/s10350-006-0503-8]
 - 14 **Khalifa AA**, Bong WL, Rao VK, Williams MJ. Leiomyosarcoma of the rectum. Report of a case and review of the literature. *Dis Colon Rectum* 1986; **29**: 427-432 [PMID: 3709322 DOI: 10.1007/BF02555068]
 - 15 **Changchien CR**, Wu MC, Tasi WS, Tang R, Chiang JM, Chen JS, Huang SF, Wang JY, Yeh CY. Evaluation of prognosis for malignant rectal gastrointestinal stromal tumor by clinical parameters and immunohistochemical staining. *Dis Colon Rectum* 2004; **47**: 1922-1929 [PMID: 15622586]
 - 16 **Helewa RM**, Rajaei AN, Raiche I, Williams L, Paquin-Gobeil M, Boushey RP, Moloo H. The implementation of a transanal endoscopic microsurgery programme: initial experience with surgical performance. *Colorectal Dis* 2016; Epub ahead of print [PMID: 26990716 DOI: 10.1111/codi.13333]
 - 17 **Musquer N**, Bossard C, Coron E. An uncommon combination of polyps. *Gastroenterology* 2014; **147**: e1-e2 [PMID: 25064549 DOI: 10.1053/j.gastro.2014.03.037]
 - 18 **Remorgida V**, Ferrero S, Fulcheri E, Ragni N, Martin DC. Bowel endometriosis: presentation, diagnosis, and treatment. *Obstet Gynecol Surv* 2007; **62**: 461-470 [PMID: 17572918]
 - 19 **Ye Y**, Sun XZ, Feng JS. Woman with rectal condyloma acuminatum: a case report. *Int J Clin Exp Med* 2015; **8**: 6365-6368 [PMID: 26131258]
 - 20 **Darwish B**, Roman H. Surgical treatment of deep infiltrating rectal endometriosis: in favor of less aggressive surgery. *Am J Obstet Gynecol* 2016; Epub ahead of print [PMID: 26851598 DOI: 10.1016/j.ajog.2016.01.189]
 - 21 **Matsuda A**, Miyashita M, Matsumoto S, Takahashi G, Matsutani T, Yamada T, Kishi T, Uchida E. Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma: a systematic review. *Ann Surg* 2015; **261**: 670-677 [PMID: 25119122 DOI: 10.1097/SLA.0000000000000862]
 - 22 **Ballo MT**, Gershenwald JE, Zagars GK, Lee JE, Mansfield PF, Strom EA, Bedikian AY, Kim KB, Papadopoulos NE, Prieto VG, Ross MI. Sphincter-sparing local excision and adjuvant radiation for anal-rectal melanoma. *J Clin Oncol* 2002; **20**: 4555-4558 [PMID: 12454112]

P- Reviewer: McSorley ST, Samardzic S, Santoro GA, Sterpetti AV
S- Editor: Gong ZM **L- Editor:** A **E- Editor:** Li D



Observational Study

Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection

Vitor Arantes, Noriya Uedo, Moises Salgado Pedrosa, Yasuhiko Tomita

Vitor Arantes, Endoscopy Unit, Alfa Institute of Gastroenterology, School of Medicine, Federal University of Minas Gerais, Hospital Mater Dei Contorno, Belo Horizonte 30130-100, Brazil

Noriya Uedo, Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan

Moises Salgado Pedrosa, Laboratory CEAP, Department of Pathology, School of Medicine, Federal University of Minas Gerais, Belo Horizonte 30130-090, Brazil

Yasuhiko Tomita, Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan

Author contributions: Arantes V and Uedo N designed the study and contributed equally to data acquisition, analysis, interpretation of the data, writing the article, critical revision and final approval of the manuscript; Pedrosa MS and Tomita Y contributed equally to the histopathological analysis and interpretation of histological findings and study results.

Institutional review board statement: The data was extracted retrospectively from the endoscopy database. Our Ethics and Research Committee does not require IRB submission for such kind of study. Patients signed a consent form for the procedure and the study was conducted according to Helsinki Declaration.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No data were created so no data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this

work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Vitor Arantes, MD, MSc, PhD, Endoscopy Unit, Alfa Institute of Gastroenterology, School of Medicine, Federal University of Minas Gerais, Hospital Mater Dei Contorno, Rua Florália 18, apt. 1201, Anchieta, Belo Horizonte 30130-100, Brazil. arantesvitor@ufmg.br
Telephone: +55-319-96173441

Received: March 21, 2016

Peer-review started: March 23, 2016

First decision: April 20, 2016

Revised: April 26, 2016

Accepted: July 11, 2016

Article in press: July 13, 2016

Published online: September 16, 2016

Abstract

AIM

To describe a series of patients with aberrant polypoid nodule scar developed after gastric endoscopic submucosal dissection (ESD), and to discuss its pathogenesis and clinical management.

METHODS

We reviewed retrospectively the endoscopic database of two academic institutions located in Brazil and Japan and searched for all patients that underwent ESD to manage gastric neoplasms from 2003 to 2015. The criteria for admission in the study were: (1) successful *en bloc* ESD procedure with R0 and curative resection confirmed histologically; (2) postoperative endoscopic examination with identification of a polypoid nodule scar (PNS) at ESD scar; (3) biopsies of the PNS with

hyperplastic or regenerative tissue, reviewed by two independent experienced gastrointestinal pathologists, one from each Institution. Data were examined for patient demographics, *Helicobacter pylori* status, precise neoplastic lesion location in the stomach, tumor size, histopathological assessment of the ESD specimen, and postoperative information including medical management, endoscopic and histological findings, and clinical outcome.

RESULTS

A total of 14 patients (10 men/4 women) fulfilled the inclusion criteria and were enrolled in this study. One center contributed with 8 cases out of 60 patients (13.3%) from 2008 to 2015. The second center contributed with 6 cases (1.7%) out of 343 patients from 2003 to 2015. Postoperative endoscopic follow-up revealed similar findings in all patients: A protruded polypoid appearing nodule situated in the center of the ESD scar surrounded by convergence of folds. Biopsies samples were taken from PNS, and histological assessment revealed in all cases regenerative and hyperplastic tissue, without recurrent tumor or dysplasia. Primary neoplastic lesions were located in the antrum in 13 patients and in the angle in one patient. PNS did not develop in any patient after ESD undertaken for tumors located in the corpus, fundus or cardia. All patients have been followed systematically on an annual basis and no malignant recurrence in the ESD scar has been identified (mean follow-up period: 45 mo).

CONCLUSION

PNS may occur after ESD for antral lesions and endoscopically look concerning, especially for the patient or the family doctor. However, as long as curative R0 resection was successfully achieved and histology demonstrates only regenerative and hyperplastic tissue, PNS should be viewed as a benign alteration that does not require any type of intervention, other than endoscopic surveillance.

Key words: Endoscopic submucosal dissection; Early gastric cancer; Endoscopic treatment; Healing; Scar

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic submucosal dissection is the treatment of choice for superficial gastric neoplasms. After curative endoscopic submucosal dissection (ESD), postoperative scar is expected to look consolidated and homogeneous. We describe a series of 14 patients that underwent curative gastric ESD with R0 resection and surprisingly developed an aberrant polypoid nodule at the ESD scar. We denominated this new entity as polypoid nodule scar (PNS). It is noteworthy that PNS occurred only after ESD undertaken for tumors located in the antrum. We reviewed the hypothesis and pathogenic factors that could explain the occurrence of this unusual phenomenon, and discuss propositions about patient's postoperative clinical management.

Arantes V, Uedo N, Pedrosa MS, Tomita Y. Clinical relevance of aberrant polypoid nodule scar after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016; 8(17): 628-634 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i17/628.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i17.628>

INTRODUCTION

Endoscopic submucosal dissection (ESD) is considered by current guidelines as the treatment of choice for patients with superficial gastric neoplasms with little or no risk of lymph nodes metastasis^[1-3]. It permits *en bloc* resection of tumors and reliable histological assessment of the resected specimen to determine the potential curability of the endoscopic resection. Particularly for lesions situated in the antrum, ESD is technically easier and highly effective to proportionate cure of intramucosal cancers removed with free margins. Postoperative endoscopic examination is recommended to all patients after curative ESD with two main purposes: (1) inspection of the scar to rule out residual tumor or recurrence; and (2) surveillance for metachronous neoplastic lesions.

After a curative ESD, postoperative scar usually looks consolidated and homogeneous without residual tumor, infiltration or polypoid formation. Interestingly, we have been observing that a subset of patients after curative ESD, particularly for lesions located in the antrum, may develop anomalous and bizarre postoperative scars, with relatively huge and protruded polypoid nodular neoformation, an entity that has not been described until our first report^[4]. Biopsy specimens taken from these scars have demonstrated regenerative mucosa without recurrent neoplastic cells. However, in our practice, such intriguing findings can make both patients and physician concern about the reliability of the endoscopic curative resection, and may imply a request for closer follow-up or discussion about endoscopic, or even surgical, re-intervention due to fear of tumor recurrence.

The objectives of this study are to describe a series of cases with aberrant polypoid nodule scar (PNS) after gastric ESD experienced in two referral centers in Latin America (Center 1) and Asia (Center 2), and to discuss the pathogenesis and propositions about the clinical management.

MATERIALS AND METHODS

The study was carried out in accordance with the Helsinki Declaration. All patients that underwent ESD provided informed consent preoperatively. Clinical information was extracted retrospectively from the endoscopy database of both institutions, which register all patients with gastric neoplasms managed by ESD.

Inclusion criteria

Eligibility for ESD was assessed preoperatively by means of white-light endoscopy, digital chromoendoscopy, magnifying observation, indigo carmine staining and

endoscopic ultrasound (in selected cases). The following criteria were utilized for patients enrollment in this study: (1) successful *en bloc* ESD procedure with confirmatory histology of R0 and curative resection; (2) postoperative endoscopic examination with identification of a polypoid nodule scar corresponding to the site where ESD was undertaken; and (3) biopsies of the PNS with histological assessment demonstrating hyperplastic or regenerative tissue. Two independent experienced gastrointestinal pathologists, one from each center, reviewed PNS biopsies. Data were examined for patient demographics, *Helicobacter pylori* (*H. pylori*) status, precise neoplastic lesion location in the stomach, tumor and specimen size, histopathological assessment of the ESD specimen, postoperative information including medical management, endoscopic and histological findings, and clinical outcome.

ESD procedure

ESD technique has been described in detail elsewhere^[5,6]. Briefly, markings were placed at least 2 mm beyond the borders of the lesion after careful endoscopic assessment by chromoendoscopy and/or magnifying endoscopy with narrow band imaging (NBI) or Fuji intelligent chromoendoscopy (FICE). Viscous solutions such as 0.4% hyaluronic acid (Muco-up[®], Johnsons and Johnsons, Japan) or 0.4% hydroxypropyl-methylcellulose^[7] were used for submucosal (SM) injection. ESD was undertaken with 2.5 Flush-Knife Ball Tipped (Fujifilm Co., Japan) in Center 1 or ceramic-ball insulated tip knife (IT knife, Olympus Co., Japan) in Center 2. Mucosal incision was undertaken around the tumor in a circumferential or semi-circumferential manner. SM dissection was performed in the deep submucosa, just above the proper muscle layer, with identification and hemostasis of the penetrating vessels. After complete tumor resection, the ulcer site was assessed and visible vessels were coagulated with a hemostatic forceps. The specimen was stretched and fixed in a styrofoam plate, immersed in 10% formaldehyde solution and sent to the pathology department.

Histological assessment and definitions

After being embedded in 10% paraffin, the specimens were cut into 2-mm slices and stained with hematoxylin and eosin. Additional immunohistochemistry studies with D2-40 and CD34 were carried out for lymphatic and vascular invasion assessment, at the discretion of the pathologist. Tumor size, depth of invasion, lymphatic and vascular invasion, grade of differentiation, and resection margins were histopathologically examined^[8]. *En bloc* resection was defined endoscopically as the complete removal of the tumor including the markings into one non-fragmented piece^[2]. R0 resection was defined histologically as complete tumor removal with both lateral and deep margins free of neoplastic cells. Endoscopic resection was considered curative when pathology report demonstrated adenoma with low or high-grade dysplasia, well or moderately well differentiated adenocarcinoma, depth of invasion restricted to mucosa

or superficial submucosal (SM1), with free vertical and radial margins and no lymphatic or vascular invasion^[2,3,9]. ESD was considered non-curative according to the following criteria^[2,3,5]: Undifferentiated cancer greater than 2 cm, deep submucosal tumor invasion (SM2), tumor compromise of lateral or profound borders, and lymphovascular invasion. Patients with non-curative resection were not included in this study. PNS was defined as a protuberant polypoid appearing nodule situated exactly in the post ESD scar site, with or without converging folds and with histological assessment demonstrating only regenerative or hyperplastic tissue growth without any residual or recurrent neoplastic tissue, confirmed by two experienced gastrointestinal pathologists, one from each center.

Postoperative care

Patients remained hospitalized for postoperative observation ranging from 2 to 7 d. Intravenous proton pump inhibitors (PPI) were administered to all patients during the first postoperative days followed by an 8-wk course of oral PPI after hospital discharge. If ESD procedure was considered curative, first follow-up endoscopy was scheduled in between 3 and 6 mo, and annually thereafter. ESD scar was inspected carefully for any abnormality such as residual tumor or polypoid nodule growth and multiple forceps biopsies were performed.

RESULTS

A total of 14 patients (10 men/4 women) fulfilled the inclusion criteria and were enrolled in this series. One center contributed with 8 cases (13.3%) out of 60 patients that underwent ESD for gastric tumors from 2008 to 2015. The second center contributed with 6 cases (1.7%) out of 343 patients from 2003 to 2015. Table 1 demonstrates the total number of cases performed in each center, and the incidence of PNS according to the region of the stomach. A total of 8 patients (57%) tested positive for *H. pylori* and received eradication therapy ahead of the procedure. The remaining 6 patients were negative for *H. pylori* infection.

Postoperative endoscopic follow-up revealed similar findings in all 14 patients: A protruded polypoid appearing nodule situated in the center of the ESD scar surrounded or not by convergence of folds. Biopsies were taken from the nodular part of the scar and histological assessment showed a similar pattern in all cases characterized by hyperplastic regenerative mucosa on the fibrotic tissue in the submucosa, without any signs of residual or recurrent dysplasia or tumor. Table 2 summarizes clinical and histological information of the 14 cases. Primary neoplastic lesions were located in the antrum, except for one patient that presented a lesion situated in the angle. Specimen size ranged from 20 mm to 82 mm (mean size of 36 mm). All patients have been followed periodically on an annual basis and no malignant recurrence in the ESD scar has been identified (mean follow-up period of 45 mo; range: 6 to 144 mo). Figures 1 and 2 are illustrative of

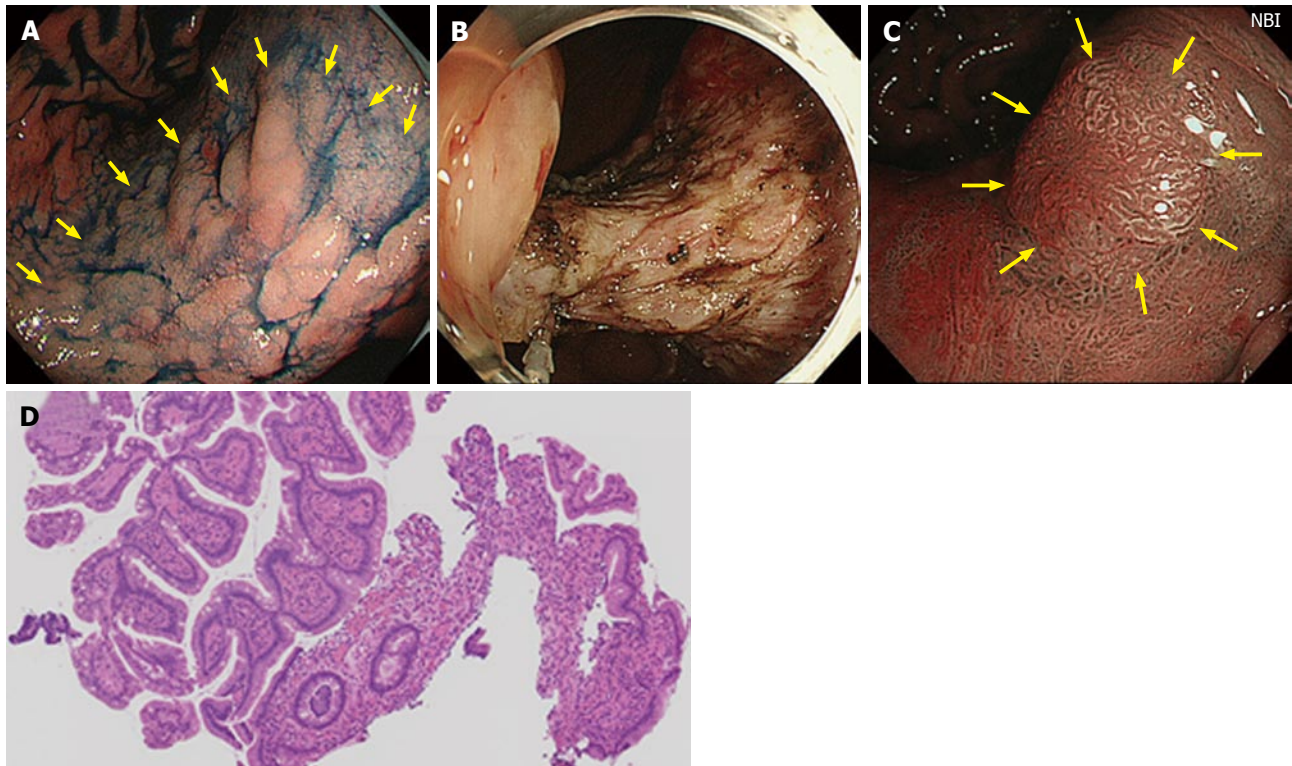


Figure 1 Case from Japan. A: A large superficial elevated lesion was found at the lesser curvature of the gastric angle (yellow arrows); B: The lesion was removed by endoscopic submucosal dissection technique. The lesion was diagnosed as well differentiated adenocarcinoma confined to the mucosa and resection margin was free from the tumor; C: One year later, a polypoid nodule was noted at the center of the scar (yellow arrows). Narrow band image suspected irregular surface structure on the surface of the nodule; D: Biopsy specimens were taken from the polypoid nodule. Histological examination showed hyperplastic change of the foveolar epithelium and increased capillaries and inflammatory cell infiltration in the lamina propria.

Table 1 Endoscopic submucosal dissection procedures distribution in Centers 1 and 2 and incidence of polypoid nodule scar according to region of the stomach *n* (%)

ESD procedures	Center 1 (Brazil)	Center 2 (Japan)
Total number of gastric ESD (<i>n</i>)	60	343
ESD in antrum	37 (62%)	158 (46%)
ESD in proximal stomach	23 (36%)	185 (54%)
Total number of PNS cases	8 (13.3%)	6 (1.7%)
Number of PNS in antrum lesions	8 (21.6%)	6 (3.8%)
Number of PNS in proximal stomach	0 (0%)	0 (0%)

ESD: Endoscopic submucosal dissection; PNS: Polypoid nodule scar.

two cases of PNS, one from Japan and the other from Brazil respectively, with the characteristic endoscopic and histologic findings.

DISCUSSION

The healing process of a post ESD ulcer is still not completely understood. In general, after a successful curative endoscopic resection, follow-up endoscopy is supposed to demonstrate a homogeneous and flat epithelized scar covered by a regular appearing mucosa with some grade of fibrosis. In the present study we originally report a series of 14 patients with gastric lesions located predominantly in the antrum, that underwent a curative

ESD R0 resection confirmed by histological criteria, and that developed an aberrant polypoid nodule in the post ESD scar. Histological assessment of the tissue growth, examined independently by two experienced gastrointestinal pathologists, were all very similar among the 14 cases, and revealed regenerative and hyperplastic tissue growth, without residual or recurrent neoplasia.

Ito *et al*^[10] reported that polypoid nodule at ulcer scar was observed in 12 (6%) of 200 patients with gastric ulcer. Interestingly all lesions were located in the antrum^[10]. In old days, some of these patients underwent gastric resection because these alterations were suspected to be malignant^[11]. For development of polypoid nodule at ulcer scar, Kato *et al*^[12] investigated the gastric ulcer healing process by endoscopy and indicated that, in some patients, granulation tissue protruded in healing ulcer. This is more frequently observed in patients that received histamine-2 receptor antagonist compared to those treated with drugs other than acid suppressant (22.0% vs 9.7%). The protruded granulation tissue develops in 17.5%-66.6% of patents with gastric ulcer treated with PPI^[13,14]. The protruded granulation tissue tends to disappear after scarring, while in some patients it may remain at the center of the scar for a long time^[13,15], a finding that we also noted in our series and is illustrated in Figure 2 (images show PNS still present 3 years after ESD). Histological finding of the polypoid nodule at ulcer scar is indicated as hyperplastic regenerative mucosa on

Table 2 Characteristics of tumors and follow-up data

Case list	Gastric region	Location	Tumor size (mm)	<i>H. pylori</i> status before ESD	Specimen size (mm)	Histology	Tumor depth	Post-ESD treatment	Follow-up (yr)
1	Antrum	Anterior wall	8	Positive	30	Moderately differentiated adenocarcinoma	M	Rabeprazole	8
2	Antrum	Greater curvature	13	Positive	37	Well differentiated adenocarcinoma	M	Omeprazole	11
3	Antrum	Lesser curvature	25	Positive	50	Well differentiated adenocarcinoma	M	Rabeprazole	13
4	Antrum	Greater curvature	15	Positive	32	Well differentiated adenocarcinoma	M	Rabeprazole	5
5	Antrum	Lesser curvature	8	Negative	20	Well differentiated adenocarcinoma	M	Rabeprazole	2
6	Antrum	Greater curvature	10	Negative	20	High-grade dysplasia	M	Omeprazole	7
7	Antrum	Lesser curvature	25	Positive	40	Well differentiated adenocarcinoma	M	Omeprazole + sucralfate	4
8	Antrum	Greater curvature	20	Positive	40	High-grade dysplasia	M	Esomeprazole + sucralfate	4
9	Antrum	Anterior wall	12	Positive	22	High-grade dysplasia	M	Omeprazole + sucralfate	4
10	Antrum	Greater curvature	25	Negative	40	Inflammatory lesion indefinite for dysplasia	M	Esomeprazole + sucralfate	4
11	Antrum	Anterior wall	20	Negative	35	Inflammatory fibroid polyp	SM	Omeprazole + sucralfate	2
12	Antrum	Greater curvature	30	Positive	40	High-grade dysplasia	M	Omeprazole + sucralfate	1
13	Angle	Lesser curvature	45	Negative	82	Well differentiated adenocarcinoma	M	Rabeprazole	2
14	Antrum	Posterior wall	20	Negative	32	High-grade dysplasia	M	Omeprazole + sucralfate	1

ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*; M: Mucosa; SM: Submucosa.

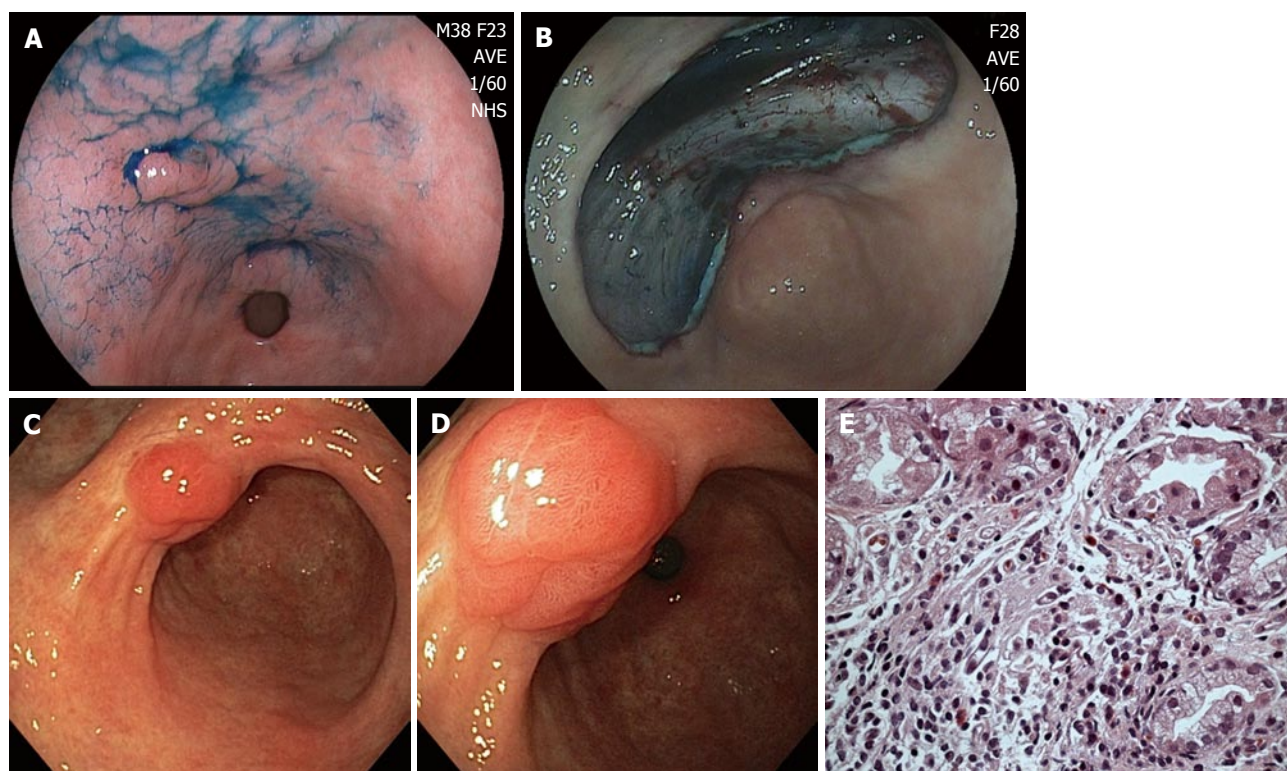


Figure 2 Case from Brazil. A: A depressed lesion (0IIc) was found at the lesser curvature of antrum; B: The lesion was removed by endoscopic submucosal dissection technique. The lesion was diagnosed as well differentiated adenocarcinoma confined to the muscularis mucosae and resection margins were free of tumor; C: Patient developed a polypoid nodule at the center of the scar. Three years later, polypoid nodule scar (PNS) with convergence of folds is still present; D: Closer view of PNS, demonstrating irregular surface and suspicious appearance on white-light image; E: Biopsy specimens were taken from the polypoid nodule. Histological examination showed similar findings to case illustrated in Figure 1: Regenerative hyperplastic tissue with inflammatory cell infiltration.

the fibrotic tissue^[11].

In our series all patients received PPI in the post-

operative period to speed up the healing process, a clinical management that is adopted universally in ESD referral

centers^[16]. PPI accelerates ulcer healing mainly due to potent gastric acid secretion inhibition. However, PPI also increases the cyclooxygenase-2 (COX-2) expression and prostaglandin E synthases in the ulcerated mucosa^[17]. COX-2 generated Prostaglandin E2 stimulates the expression of growth factors in the mucosa, such as vascular endothelial growth factor^[18], hepatocyte growth factor^[19], basic fibroblast growth factor^[20]. This accelerated mucosal repair and angiogenesis may contribute to nodular overgrowth of the regenerative mucosa.

There still remain some questions unanswered concerning the occurrence and pathogenesis of PNS. A unique characteristic of PNS is that we noted this finding only after ESD performed in the distal stomach (antrum or incisura). In both centers, we did not notice PNS after ESD for lesions located in the gastric body, fundus or cardia. Likewise we did not observe this finding after esophageal or colorectal ESD. The reason for this phenomenon is unclear. We postulate that the frequent gastric peristalsis may enhance development of PNS in the antrum. Moreover, submucosal layer in the antrum is thicker; therefore inflammatory or regenerative reaction in the submucosa can be more obvious in the antrum than in the corpus of fundus. Another interesting question is whether PNS may also occur after EMR. Although in the present study we did not look specifically for patients that underwent EMR, data in the literature support that even peptic ulcer causes PNS, therefore it seems fair to assume that PNS may develop after EMR. The importance of *H. pylori* infection is also undetermined. Our data do not show a clear association between PNS and *H. pylori* status, as 8 patients (57%) tested positive and the other 6 (43%) were negative for *H. pylori* infection. However, more investigation is needed to draw firm conclusions about predisposing factors involved with PNS development.

Endoscopists should acknowledge the occurrence of aberrant polypoid nodules at ESD scar, particularly in antral lesions. Such occurrence, to our knowledge, has only been reported recently and we proposed to adopt the terminology PNS to describe this phenomenon^[4]. It is of paramount importance to distinguish PNS from residual carcinoma or submucosal tumor recurrence. PNS is composed of granulation tissue or regenerative mucosa, and the surface structure and vasculature are as irregular as those of intramucosal carcinoma. Therefore, the first priority is to make sure that the endoscopic resection was R0 and curative by histologic criteria, ruling out a residual carcinomatous tumor. Secondly, to distinguish PNS from submucosal recurrence is not so difficult because surface structure of PNS is irregular, in contrast to submucosal recurrence that tends to present a smooth and regular surface, covered with normal gastric mucosa. Image enhanced endoscopy with magnifying endoscopy associated with indigo carmine and digital chromoendoscopy with NBI or FICE potentially are useful tools to facilitate the differential diagnosis.

The incidence of PNS post ESD is still undetermined, though expected to be rare. Apparently the size of the

lesion or the size of the resected area, do not seem to be directly involved in PNS development, since we noted a wide variation in tumor size (8 mm to 82 mm), and even small lesions under 10 mm developed PNS. In this study, the incidence of PNS was significantly different between the two centers (Center 1%-13.3%; Center 2%-1.7%). This difference can be justified, at least in part, because Center 1 performed ESD more frequently for tumors located in the antrum (62%) in comparison to Center 2 (46%). Perhaps, the ESD technique could also influence the occurrence of PNS. There was a difference between the 2 centers in terms of ESD knives (Center 1 - needle type knife; Center 2 - insulated tip knife), settings of electrosurgical unit and operator's experience. Moreover, because this was a retrospective study, the incidence of PNS may be underestimated, due to cases lost for follow-up or unavailability of the endoscopic images. A prospective large-scale multicenter study enrolling multiple ESD centers is needed to assess the true incidence of PNS.

PNS endoscopically looks concerning, especially for the patient and the family doctor. Nevertheless, as long as the ESD procedure is considered curative, with R0 resection confirmed by a standardized histological evaluation, and multiple biopsies taken from the scar rule out tumor recurrence and reveals only hyperplastic changes, PNS should be viewed as a regenerative lesion with an expected benign behavior. Over time PNS may become less protruded, as we noted in some of our patients, or even disappear. Most importantly, endoscopists when facing a PNS should refrain to indicate any type of invasive measure such as endoscopic or surgical reintervention, and recommend annual endoscopic surveillance.

In summary, we report the first series of aberrant polypoid nodule scars observed after gastric ESD that corresponds to a regenerative healing process and that requires no additional treatment other than periodic endoscopic follow-up.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is considered by current guidelines as the treatment of choice for patients with superficial gastric neoplasms with little or no risk of lymph nodes metastasis. It permits *en bloc* resection of tumors and reliable histological assessment of the resected specimen to determine the potential curability of the endoscopic resection. Postoperative endoscopic examination is recommended to all patients after curative ESD with two main purposes: (1) inspection of the scar to rule out residual tumor or recurrence; and (2) surveillance for metachronous neoplastic lesions.

Research frontiers

After a curative ESD, postoperative scar is expected to look consolidated and homogeneous without residual tumor, infiltration or polypoid formation. However, there is scarce data about the healing process of post-ESD defects and ulcers.

Innovations and breakthroughs

In this study, the authors report the first series of 14 patients from two Academic Institutions from Brazil and Japan, that developed aberrant polypoid nodule scars

after curative gastric ESD, undertaken for neoplastic lesions located in the distal stomach (antrum and incisura). They denominated this new entity as polypoid nodule scar (PNS). PNS endoscopically looks concerning, especially for the patient and the family doctor. Nevertheless, as long as the ESD procedure was curative, with R0 resection confirmed by a standardized histological evaluation, and multiple biopsies taken from the scar rule out tumor recurrence and reveals only hyperplastic changes, PNS should be viewed as a regenerative lesion with an expected benign behavior, that requires no additional treatment other than periodic endoscopic follow-up.

Applications

ESD has been increasingly utilized to treat early gastric neoplasms all over the world. This study brings new concepts about the healing process of ESD defects, particularly for antral lesions. The understanding and knowledge of this new entity by endoscopists involved with ESD procedure is crucial to prevent unnecessary and aggressive reintervention to manage a benign hyperplastic tissue reaction that may be confounded with tumor recurrence.

Terminology

PNS refers to polypoid nodule scar, an aberrant and protuberant nodular scar that develops after ESD and has no histological evidence of tumor recurrence or dysplasia. PNS corresponds to a hyperplastic regenerative healing process, already known in the past to occur after the healing of gastric peptic ulcers.

Peer-review

Available papers dedicated to understand the healing process of ESD defects are scarce. The authors in this study reported a new entity named PNS that occurs after gastric ESD for lesions located mainly in the antrum. Although, the occurrence of this phenomenon is supposed to be rare, the true incidence of PNS remains to be determined. Large-scale multicenter and prospective study are needed to better investigate this newly described finding.

REFERENCES

- 1 **Pimentel-Nunes P**, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, Amato A, Berr F, Bhandari P, Bialek A, Conio M, Haringsma J, Langner C, Meisner S, Messmann H, Morino M, Neuhaus H, Piessevaux H, Rugge M, Saunders BP, Robaszekiewicz M, Seewald S, Kashin S, Dumonceau JM, Hassan C, Deprez PH. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; **47**: 829-854 [PMID: 26317585 DOI: 10.1055/s-0034-1392882]
- 2 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123 [PMID: 21573742 DOI: 10.1007/s10120-011-0042-4]
- 3 **Ono H**, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, Iishi H, Oka M, Ajioka Y, Ichinose M, Matsui T. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016; **28**: 3-15 [PMID: 26234303 DOI: 10.1111/den.12518]
- 4 **Arantes V**, Uedo N, Pedrosa MS. Endoscopic management of bariatric surgery complications: what the gastroenterologist should know. *Rev Gastroenterol Mex* 2016; **81**: 35-47 [PMID: 26552500 DOI: 10.1016/j.rgm.2015.06.012]
- 5 **Piñeros EAF**, Arantes V, Toyonaga T. Endoscopic submucosal dissection of early gastric cancer: State of the art. *Rev Col Gastroenterol* 2012; **27**: 194-214
- 6 **Arantes V**, Albuquerque W, Freitas Dias CA, Demas Alvares Cabral MM, Yamamoto H. Standardized endoscopic submucosal tunnel dissection for management of early esophageal tumors (with video). *Gastrointest Endosc* 2013; **78**: 946-952 [PMID: 23810327 DOI: 10.1016/j.gie.2013.05.031]
- 7 **Arantes V**, Albuquerque W, Benfica E, Duarte DL, Lima D, Vilela S, Lima G, Sakai P, Filho FM, Artifon E, Halwan B, Kumar A. Submucosal injection of 0.4% hydroxypropyl methylcellulose facilitates endoscopic mucosal resection of early gastrointestinal tumors. *J Clin Gastroenterol* 2010; **44**: 615-619 [PMID: 20351567 DOI: 10.1097/MCG.0b013e3181d6bd8e]
- 8 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
- 9 **Yamamoto H**. Endoscopic submucosal dissection--current success and future directions. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 519-529 [PMID: 22664591 DOI: 10.1038/nrgastro.2012.97]
- 10 **Ito S**, Kishi S, Ishikawa K, Urugami K, Seki H. A case of gastric ulcer scar with type IIa-like elevation in center of the lesion. *Gastroenterol Endosc* 1974; **16**: 194-197
- 11 **Ito S**, Kishi S, Mori H, Akagi G. An elevated type of gastric ulcer scar. *Gastrointest Endosc* 1979; **25**: 58-60 [PMID: 488651]
- 12 **Kato H**, Hattori K, Nishikawa H, Hayashi R, Kawamoto M, Fujiwara N. Endoscopic study on healing of gastric ulcer by the treatment with H2-blocker. *Gastroenterol Endosc* 1986; **28**: 2291-2296
- 13 **Nakamura T**, Tsukamoto Y, Yamanaka T, Hayashi S. A study on the whitish protrusion appearing in the base of peptic ulcer during the administration of proton pump inhibitor. *Gastroenterol Endosc* 1992; **34**: 1548-1554
- 14 **Ashida K**, Osaka N, Tei H, Takiuchi H, Sakaguchi M, Tanaka M, Okumura Y, Asada S, Irata I, Oshiba S. Studies on the mechanism of the protrusion of the base of the ulcer during the administration of omeprazole. *Gastroenterol Endosc* 1989; **31**: 1776-1782
- 15 **Tanaka T**, Kimura M, Akiyama T, Suzuki S. Long follow-up study of elevated scar of acute antral kissing ulcers. *Gastroenterol Endosc* 1984; **26**: 1534-1537
- 16 **Uedo N**, Takeuchi Y, Yamada T, Ishihara R, Ogiyama H, Yamamoto S, Kato M, Tatsumi K, Masuda E, Tamai C, Yamamoto S, Higashino K, Iishi H, Tatsuta M. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol* 2007; **102**: 1610-1616 [PMID: 17403076 DOI: 10.1111/j.1572-0241.2007.01197.x]
- 17 **Okazaki M**, Shimizu I, Ishikawa M, Fujiwara S, Yamamoto H, Shiraishi T, Horie T, Iuchi A, Ito S. Gastric mucosal levels of prostaglandins and leukotrienes in patients with gastric ulcer after treatment with rabeprazole in comparison to treatment with ranitidine. *J Med Invest* 2007; **54**: 83-90 [PMID: 17380018]
- 18 **Wallace JL**, Devchand PR. Emerging roles for cyclooxygenase-2 in gastrointestinal mucosal defense. *Br J Pharmacol* 2005; **145**: 275-282 [PMID: 15778736 DOI: 10.1038/sj.bjp.0706201]
- 19 **Brzozowski T**, Konturek PC, Konturek SJ, Pajdo R, Schuppan D, Drozdowicz D, Ptak A, Pawlik M, Nakamura T, Hahn EG. Involvement of cyclooxygenase (COX)-2 products in acceleration of ulcer healing by gastrin and hepatocyte growth factor. *J Physiol Pharmacol* 2000; **51**: 751-773 [PMID: 11192947]
- 20 **Sakai Y**, Fujita K, Sakai H, Mizuno K. Prostaglandin E2 regulates the expression of basic fibroblast growth factor messenger RNA in normal human fibroblasts. *Kobe J Med Sci* 2001; **47**: 35-45 [PMID: 11565193]

P- Reviewer: Aoyagi K, Kim JJ, Morgagni P, Muguruma N, Skok P
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 October 16; 8(18): 635-683





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

ASSOCIATE EDITORS

Chisato Hamashima, *Tokyo*

GUEST EDITORIAL BOARD MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Dimitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *Udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Naoki Hotta, *Nagoya*

Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurionhoj*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iruru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satohiro Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Nosho, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *UiJeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornnotin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentis, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *Albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciaccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

REVIEW

- 635 Update on endoscopic management of gastric outlet obstruction in children
Chao HC

ORIGINAL ARTICLE

Retrospective Study

- 646 Efficacy and safety of endoscopic papillary balloon dilation for the removal of bile duct stones: Data from a "real-life" multicenter study on Dilation-Assisted Stone Extraction
Di Mitri R, Mocciaro F, Pallio S, Pecoraro GM, Tortora A, Zulli C, Attardo S, Maurano A

Observational Study

- 653 Recommendations to quantify villous atrophy in video capsule endoscopy images of celiac disease patients
Ciaccio EJ, Bhagat G, Lewis SK, Green PH

Prospective Study

- 663 Prior minimal endoscopic sphincterotomy to prevent pancreatitis related to endoscopic balloon sphincteroplasty
Kanazawa R, Sai JK, Ito T, Miura H, Ishii S, Saito H, Tomishima K, Shimizu R, Sato K, Hayashi M, Watanabe S, Shiina S

CASE REPORT

- 669 Same site submucosal tunneling for a repeat per oral endoscopic myotomy: A safe and feasible option
Wehbeh AN, Mekaroonkamol P, Cai Q
- 674 Plexiform angiomyxoid myofibroblastic tumor of stomach: A rare case
Jonaitis L, Kiudelis M, Slepavicius P, Poskienė L, Kupcinskas L
- 679 Balloon-assisted enteroscopy for suspected Meckel's diverticulum and indefinite diagnostic imaging workup
Gomes GF, Bonin EA, Noda RW, Cavazzola LT, Bartholomei TF

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 18 October 16, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Naoki Hotta, PhD, Assistant Professor, Department of Hepatology, Masuko Memorial Hospital, Nagoya 453-8566, Japan

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com>

www.wjgnet.com/1948-5190/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
Fang-Fang Ji, Vice Director
World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
October 16, 2016

COPYRIGHT
© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

Update on endoscopic management of gastric outlet obstruction in children

Hsun-Chin Chao

Hsun-Chin Chao, Division of Gastroenterology, Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan 33305, Taiwan

Author contributions: Chao HC contributed to the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Hsun-Chin Chao, MD, Associate Professor, Division of Gastroenterology, Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, 5 Fu-Hsing Street, Gueishan District, Taoyuan City 33305, Taiwan. chaohero@yahoo.com
Telephone: +886-3-3281200
Fax: +886-3-3288957

Received: March 27, 2016

Peer-review started: March 28, 2016

First decision: May 23, 2016

Revised: June 18, 2016

Accepted: August 6, 2016

Article in press: August 8, 2016

Published online: October 16, 2016

Abstract

Endoscopic balloon dilatation (EBD) and surgical intervention are two most common and effective treat-

ments for gastric outlet obstruction. Correction of gastric outlet obstruction without the need for surgery is an issue that has been tried to be resolved in these decades; this management has developed with EBD, advanced treatments like local steroid injection, electrocauterization, and stent have been added recently. The most common causes of pediatric gastric outlet obstruction are idiopathic hypertrophic pyloric stenosis, peptic ulcer disease followed by the ingestion of caustic substances, stenosis secondary to surgical anastomosis; antral web, duplication cyst, ectopic pancreas, and other rare conditions. A complete clinical, radiological and endoscopic evaluation of the patient is required to make the diagnosis, with complimentary histopathologic studies. EBD are used in exceptional cases, some with advantages over surgical intervention depending on each patient in particular and on the characteristics and etiology of the gastric outlet obstruction. Local steroid injection and electrocauterization can augment the effect of EBD. The future of endoscopic treatment seems to be aimed at the use of endoscopic electrocauterization and balloon dilatations.

Key words: Gastric outlet obstruction; Endoscopic balloon dilatation; Electrocauterization; Steroid injection; Children

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Correction of gastric outlet obstruction without the need for surgery is an issue that has been tried to be resolved in these decades; this management has evolved with the development of pneumatic dilators and, more recently, local steroid injection and electrocauterization have been added. Endoscopic balloon dilatation (EBD) are used in exceptional cases, some with advantages over surgical intervention depending on each patient in particular and on the characteristics and etiology of the gastric outlet obstruction. Local steroid injection and electrocauterization can augment the effect of EBD.

Chao HC. Update on endoscopic management of gastric outlet obstruction in children. *World J Gastrointest Endosc* 2016; 8(18): 635-645 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/635.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.635>

INTRODUCTION

In the last few decades, upper gastrointestinal endoscopy is a technique widely employed for diagnostic and therapeutic purposes for evaluation of esophageal, gastric or duodenal diseases. Upper gastrointestinal endoscopy has become the common complementary test for investigation of gastric diseases due to its accessibility and safety assures extensive clinical utilization in patients with gastric or duodenal diseases. Recent technological advances in endoscopic imaging and tissue analysis obtained from the stomach aid to identify the characterization of diseases such as inflammation, infection and neoplasia. Recent technological advances have increased the capability of endoscopy in treating gastrointestinal diseases, including those affecting the stomach.

Diseases affecting the stomach have been described and eventually treated by endoscopy in routine clinical practice. Using endoscopy to elucidate gastric outlet obstruction (GOO) in children has been still a field of intensive and challenging research. This review provides an update on the role of endoscopy in the management of GOO, highlights the latest advances in the endoscopic management of GOO, and focuses on the efficacy of endoscopic balloon dilatation (EBD) in the pediatric population. We also point out recent evidence regarding the utility of magnifying endoscopy in the management of GOO.

Data search

The searches were limited to articles published in English as well as clinical articles or case studies to identify objective articles related to GOO from January 1975 to June 2016. All articles considered eligible were evaluated, and finally selected on the basis of research and case series. The articles of gastric volvulus were searched, but this entity is excluded from this review, due to gastric volvulus is specific complex disease entity with varied causes (congenital, idiopathic, or acquired), and the gold standard treatment of pediatric gastric volvulus remains surgical intervention.

ETIOLOGY

GOO is an obstruction in the antrum, pylorus or bulbar duodenum. Unlike adult patients, most of the pediatric patients with GOO have benign disease. Peptic ulcer disease and corrosive ingestion are the leading causes of benign outlet obstruction in adults^[1], while idiopathic hypertrophic pyloric stenosis (IHPS) and peptic ulcer

Table 1 Etiology of gastric outlet obstruction in children

Idiopathic hypertrophic pyloric stenosis
Peptic ulcer disease
Caustic injury
Congenital causes
Gastric antral web
Duplication cyst
Ectopic pancreas
Annular pancreas
Gastric volvulus
Inflammatory causes
Cholecystitis
Pancreatitis
Eosinophilic gastritis
Crohn's disease
Tuberculosis
NSAID induced stricture
Iatrogenic (secondary to surgery)
Post-anastomosis stricture
Post-pylorotomy
Post-esophagectomy
Post-vagotomy
Polyps/tumors
Hyperplastic polyp
Inflammatory polyp
Adenomyoma
Inflammatory myofibroblastoma
Lymphoma
Other causes
Bezoars (lactobezoar, trichobezoar)
Cytomegalovirus infection
Late onset primary gastric outlet obstruction
Idiopathic gastric outlet obstruction
Idiopathic or acquired gastric volvulus
Foveolar cell hyperplasia

NSAID: Nonsteroidal Anti-inflammatory Drug.

disease (PUD) remains the two most common cause of GOO in children^[2-4]. Table 1 shows the etiology of GOO in children. IHPS are the most common cause of GOO in children. The typical presentation is increasing vomiting that becomes projectile between 2 and 8 wk in age. Gastric retention after prolonged obstruction contributes to gastric atony, while most cases are caused by antral, pyloric or duodenal ulceration. Scarring and tissue remodeling may cause GOO in chronic PUD. A significant decline of the incidence of PUD due to the discovery of *Helicobacter pylori* (*H. pylori*) and proton pump inhibitors (PPI)^[5,6]. *H. pylori* infection participated a less significant role in children with GOO, compared to adults^[3].

Caustic ingestion remains a major social and medical issue in children, especially for infants and young children. Case series of corrosive injury related gastric outlet obstruction have still been reported in these two decades^[7-9]. GOO is a significant complication of corrosive ingestion^[8]. Caustic ingestion (alkali or acid) can cause GOO as a result of antral/pyloric scarring. Other rare causes are gastric antral web^[10], gastric duplication^[11], ectopic pancreas^[12], gastric volvulus^[3], gastric polyps^[3], idiopathic gastric outlet obstruction^[13], foveolar cell hyperplasia^[14], and bezoars^[15,16]. Antral web, known as antral mucosal diaphragm or prepyloric web,

is a rare etiology in pediatric GOO. Histologically the web is composed of normal, non-inflamed mucosal and submucosal gastric mural layers. Gastric duplication cyst are the least common of the alimentary duplications, they usually presented before 1 year of age with symptoms of obstruction, pain, bleeding or ulceration^[11]. Heterotopic pancreas is generally an asymptomatic lesion and is a rare cause of GOO. Gastric volvulus is characterized by a rotation of the stomach of more than 180° along its short or long axis causing variable extents of GOO. Acute gastric volvulus may create a closed-loop obstruction leading to incarceration and strangulation. In general, emergency surgery remains the standard treatment for acute gastric volvulus. Foveolar cell hyperplasia is a rare disease entity, described as a possible cause of for long-lasting GOO in patients with IHPS, it requires the excision to resolve the obstruction. Gastric polyps are often hyperplastic and asymptomatic. Gastric polyps are usually diagnosed at endoscopy incidentally. Lactobezoar is a condensed mass of undigested milk concretions to be found within the gastrointestinal tract^[14]. Lactobezoar is often found in infants, it can precipitate GOO, resulting in medical or surgical conditions. The trichobezoar is another rare cause of obstruction of the gastrointestinal tract, and it is usually presented as GOO^[15].

Inflammatory causes like Crohn's disease and tuberculosis have been reported in adult patients with pyoric obstruction^[17,18], these two disease entities are relatively rarely reported in pediatric patients. Isolated gastroduodenal Crohn's disease is rare, occurring in fewer than 5% of patients. A continuity that involves the antrum, pylorus, and proximal duodenum have been reported in about 60% of patients^[17]. In tuberculosis, involvement of stomach or duodenum occurs in 0.3% to 2.3% of patients, and 61% of patients with gastroduodenal tuberculosis present as GOO^[18]. Gastric polyps or neoplasms are rare in children but should always be considered as an etiology of GOO in children, especially in older patients^[19].

EVALUATION

Clinical manifestations

The usual presentations were nausea, vomiting, epigastric pain, early satiety, abdominal distention, abdominal mass, visible peristalsis, weight loss and electrolyte imbalances. Epigastric pain, nausea and vomiting, abdominal distention, early satiety and weight loss are the most common presenting symptoms of GOO^[20]. The onset of symptoms varies based on the etiology, symptoms usually occur rapidly with gastric volvulus, corrosive injury, food impaction (bezoar), prolapse of a large gastric polyp^[3,8,15]. Other causes are inclined to follow a more slothful course. Malignant cause usually has a shorter duration of symptoms compared with benign causes. Patients with benign causes commonly presented with early satiety (53%) and bloating (50%) whereas in the patients with malignant causes presented

more commonly with vomiting, pain, and weight loss^[20].

Persistent succussion splash (a "splash" reflective of retained gastric material) detected by auscultation of for more than four after meals, suggesting GOO with a sensitivity of 50%^[21].

Investigations

GOO patients with repeated vomiting may have electrolyte imbalances with hypokalemia or a hypochloremic metabolic alkalosis. Anemia, elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), and abnormal biochemical tests in hepatobiliary function, pancreatic function, or renal function may reflect the underlying disease. Elevation of serum gastrin concentration as a result of distention-induced gastrin release may occur in GOO patients and this condition can be confused with Zollinger-Ellison syndrome.

Plain radiographs may demonstrate an enlarged stomach. Small bowel may not be visualized because of air paucity. Calcified gall stone and/or pancreatic calcification may be revealed. Diagnosis was easy clinically and confirmed by barium studies and/or upper gastrointestinal endoscopy. Contrast studies with barium or water soluble contrast aid in providing diagnostic clues to the underlying diseases. Failure of contrast passing into the small bowel is highly suggestive of complete GOO. Barium studies are helpful in delineating the site of obstruction as well its extent. Adequate gastric decompression should be initiated before performing barium or water soluble contrast to reduce the risk of aspiration. Computed tomography (CT) scan may disclose additional anatomical details, specially the wall thickness in the stomach, pylorus and duodenum, biliary lesions, pancreatic abnormalities or lesions, and enlarged lymph nodes not visualized on regular imaging studies^[21].

Endoscopy is often required to ascertain the diagnosis of GOO and identify a specific etiology in company with a therapeutic assistance. Patients should fast for at least four hours before the endoscopic procedure. Nasogastric tube suction is recommended before endoscopic procedure to reduce the risk of aspiration. Endoscopic biopsy provides histological diagnosis in specific diseases and aid in confirming or excluding malignancy.

MANAGEMENT

All patients with symptoms of persistent GOO need hospitalization. Intravenous volume resuscitation with normal saline; replacement of electrolytes; and measurements of electrolytes and arterial pH are the principles of fluid and electrolyte resuscitation for GOO^[21]. Hypokalemia and metabolic alkalosis should be looked for and treated.

Gastric decompression by nasogastric tube should be done at admission, this procedure is useful in relieving pain and discomfort of distention in patients who have edema and spasm due to active ulceration. Nasogastric

decompensation also helps to clear the stomach for endoscopic procedures and reduce gastric capacity which is essential for endoscopic examination and further surgery or endoscopic treatment. Administration of antacid (H₂-receptor antagonists or proton pump inhibitors) is usually required.

ENDOSCOPIC INTERVENTION

A definite treatment is required if the GOO is persistent, secondary to fibrotic scarring, or an irreversible condition. In place of traditional surgical intervention or rigid esophagoscopy, therapeutic fibreoptic endoscopy is concluded to be an effective and safe treatment modality in pediatric patients^[22]. Endoscopic treatment offered depended on the cause of GOO. Unless the etiology of GOO is evident from the antecedent history, such as PUD, caustic ingestion, or prior surgery, one must exclude rare diseases like Crohn disease, tuberculosis or malignancy by endoscopy and biopsy.

EBD

The through-the-scope (TTS) balloon catheter with variable diameter balloons are available from 6 mm to 20 mm which are inflated with a hydrostatic device attached to a pressure gauge. A radio-opaque wire can guide the stricture segment and augment the efficacy of the EBD in difficult strictures. A single and short stricture provides the best result with EBD; hence patients should be evaluated with proper imaging studies (barium studies/CT scan) before EBD procedure.

Although the devices and techniques used in the EBD procedure for pediatric patients are basically identical to those procedures in adult patients, several anatomic limitations must be addressed. Endoscopic procedure is difficult in newborns due to remarkable anatomic limitations. The length and diameter of esophagus is 8-10 cm, and around 5 mm in neonates, causing compression of trachea during endoscopic intervention. TTS balloon dilations are possibly performed in toddlers and children, but this technique is limited in neonates or small infants as there are no balloon catheters that fit through a 2-mm channel. Balloon dilatation can be performed in neonates or infants who cannot tolerate a standard-size endoscopy by using biliary dilation balloons in size of 4-10 mm and length of 2-8 cm. These balloons can be applied endoscopically with 0.035-inch guide-wires. Balloon sizes are usually increased by 2 mm for subsequent EBD sessions. The balloon catheter upon removal may reveal blood clots or bloods if an effective dilatation had been reached.

Experiences of EBD in recent decades

Most reports regarding EBD management of GOO were found in adult population, the technique of EBD in GOO is less performed in pediatric population. A series of case studies observed that surgical treatment can give definitive therapy in PUD related GOO without

H. pylori infection^[2]. Until the advent of EBD, surgery was the only treatment for these patients. Vagotomy with antrectomy or pyloroplasty was performed in PUD patients with GOO who were refractory to medical therapy^[4].

Many evidences prove that EBD is an effective alternative in the management of GOO^[17,23-39]. The EBD management combined endoscopic placement of guide-wire with fluoroscopically-guided balloon dilation to treat GOO. A study of EBD of upper digestive tract stricture in 23 adult patients had gastric or pyloric strictures were evaluated. Percent of 92 were successfully dilated, with a complication rate of 3%^[23]. EBD has become the first-line therapy in most of the patients with benign causes of GOO^[24]. Subsequently, a number of reports appeared highlighting the safety and efficacy of the procedure^[24,25,27-36].

Compared to adult patients, endoscopic management in pediatric patients is limited by their anatomical limitation with difficulty in passing endoscopy through pharyngeal inlet and difficulty to perform EBD because of smaller size of pylorus and duodenal bulb, especially in neonates or infants. Besides, a relatively higher risk of complications was noted in pediatric population. In pediatric patients, the technique of EBD treatment in esophageal stricture is relatively more mature than EBD treatment in pyloric stricture. We reviewed the endoscopic management both in adult and pediatric patients with GOO, and further point to recent evidence regarding the utility of magnifying endoscopic treatment in the management of pediatric diseases related GOO.

PUD

Fibrotic scarring in PUD may cause irreversible GOO which requires intervention. Traditionally, surgery has been the standard mode of treatment for PUD-related GOO. In adult series of patients with PUD-related GOO, 80%-90% underwent surgery^[40], about 60% received surgery in the first hospitalization and 20% in the subsequent hospitalizations^[41]. Recently, many case series studies indicate that balloon dilatation is an effective alternative to surgery in adult patients with PUD-related GOO^[28-35]. A major surgery and associated morbidity can be obviated with the development of TTS EBD. EBD has emerged as an effective alternative to surgery in selected groups of patients. EBD has been shown to be effective in ulcer related GOO. The performance of EBD is preferred with balloon catheters of incremental diameter gradually to achieve the end-point of 15 mm. Fluoroscopic study is not routinely used by most endoscopists although fluoroscopic evaluation it is recommended for EBD. Previous experiences indicated that the requirement of EBD varied from once a week to once in three weeks in PUD-related GOO. EBD procedure related complications are uncommon, massive bleeding is rare, perforation occurs more frequent with balloon sizes larger than 15 mm. A Review of cumulative experience in 30 patients who underwent

EBD for peptic ulcer-induced GOO and had follow-up of a mean of 15 mo (range 4-28 mo), 6-18-mm (median 15-mm) balloons were inflated a median of 2 times (range 1-4 times) for a median of 60 s (range 30-180), 20 (67%) patients had one treatment and 10 (33%) had multiple treatments, 24 (80%) patients achieved sustained symptom relief. The authors concluded that EBD is safe and effective for most patients with ulcer-induced GOO^[16].

In view of the confounding factors of *H. pylori* eradication, chronic usage of NSAID, use of PPI in patients with PUD-related GOO, immediate response is prominent, but with variable long-term results. EBD must be combined with eradication of *H. pylori*. Studies specify that the eradication of *H. pylori* contributed to a good long-term response in 70%-80% of patients during a follow-up period of 9-98 mo^[29,32,34,37]. In an adult series, 25 patients with proven GOO secondary to PUD were managed with EBD using TTS balloons, 80 % of patients remained asymptomatic (follow-up: median 9 mo, range 2-24 mo)^[39].

Literatures regarding to the use of EBD in pediatric GOO patients are limited in recent decades. Chan *et al*^[42] reported 3 children (ages 2, 4, and 8 years) suffering from peptic pyloric stenosis with EBD followed by H₂-receptor antagonist therapy. There were no complications due to the procedures, and no recurrences of symptoms over a follow-up of 5-30 mo (mean, 17 mo). The authors suggest that EBD is an option for the initial nonoperative treatment of pediatric peptic pyloric stenosis.

IHPS

IHPS is typically treated with surgical pyloromyotomy. If the child is well-hydrated with normal electrolytes, and if surgeons with expertise in the procedure are available, surgery usually takes place on the day of diagnosis. EBD had been used to treat IHPS in recent decades. EBD was considered as a safe procedure for treating IHPS infants and was recommend to be as an initial approach before pyloroplasty in such presentations^[43-45]. Recurrent pyloric stenosis is rare in IHPS patients after balloon dilatation^[43]. However, because balloon dilatation does not consistently destroy the muscular ring^[46], EBD is preferably reserved for patients in whom with a significant risk for general anesthesia or in whom with difficulty for surgical intervention.

Caustic injury

GOO is one of the most common gastric complications of caustic agent ingestion that may require surgical treatment^[7-9]. Sodium hydroxide and potassium hydroxide, and hydrochloric acid were the common ingested caustic agents for GOO^[7].

The severity of mucosal injury at the antrum and pylorus decided the variety of surgical treatment. Moderate mucosal injury (superficial ulcerations with intact mucosa) may induce partial pyloric obstruction;

severe mucosal injury (deep ulcerations, hemorrhagic erosions, eschar formation) may cause complete pyloric obstruction. For adult patients with caustic-induced GOO, surgery had been the only option available as well^[47]. The standard treatment of pediatric caustic-induced GOO is surgery, gastrojejunostomy provides good long-term results with minimal morbidity particularly in patients without severe gastric injury^[9]. An early surgical intervention has decreased the morbidity and mortality^[7].

Adult experiences specify more difficulty of using EBD to dilate caustic-induced GOO than PUD-related GOO, besides; those patients with caustic-induced GOO have more recurrences and requiring more sessions of EBD. The mean number of sessions (range, 2-13) for caustic GOO is significantly more than the number of sessions for peptic GOO which required only 1-3 sessions^[32].

Successful results of a caustic stricture by EBD management offers guidelines for the use of this procedure^[37,48]. Kochhar *et al*^[37] reviewed 41 patients with EBD management, 39 (95.1%) underwent successful responses after repeated dilations with a mean (SD) of 5.8 (2.6) sessions (range, 2-13) to reach the end point of 15 mm. The mean (SD) size of the initial dilatation was 8.2 (0.6) mm (range, 8-10). Finally, 2 patients received surgery including one with perforation and the other with intractable pain every time he received EBD. Other complications included minor self-limiting pain ($n = 8$) or bleeding ($n = 7$). The authors concluded that EBD is a safe, effective, and long-term alternative to surgery for caustic GOO^[37]. Another adult report ($n = 31$) of caustic GOO found all patients successfully respond to repeated dilations to reach the end point of 15 mm with a range of 3-18 (median, 9) sessions of dilations during a mean period of 7 wk (range, 1.5-16) of follow-up^[49].

There are only few reports of EBD management in pediatric cases with caustic injury related GOO. A pediatric study enrolled 8 cases caustic ingestion indicated that caustic injury related GOO could be successfully treated through EBD in suitable patients, surgery can be avoided^[50].

A pediatric case series of 6 children (mean age was 2.9 years, range 1.5-3 years) with caustic injury related GOO (2 ingested acid corrosives, 4 ingested alkali corrosives). Balloon dilatation of the pylorus was performed in 1 patient successfully, the others received pyloroplasty (3 patients), and Billroth I procedures (2 patients). The authors recommended early definitive surgical intervention in cases with severe pyloric stricture^[51].

Gastric antral web

Treatment of antral web usually consisted of incision of the web and construction of a patulous gastric outlet by surgery, and most patients remained asymptomatic after operation^[10]. Endoscopic treatment had been

used to treat antral web, endoscopic diathermy and EBD successfully resolved the pyloric web^[10,21,51]. Lu *et al*^[52] successfully treated antral web with EBD in a young infant, the EBD was attempted sequentially using different sized water-inflated balloons (8, 10 and 12 mm). The stenosis was dilated with balloons incrementally to 12 mm diameter.

Post-operative GOO

EBD resolved the in nearly 70% of GOO patients with postvagotomy gastric outlet stenosis^[30]. Lanuti *et al*^[53] evaluated the role of pyloromyotomy and management with endoscopic pyloric dilatation in the patients with Post-esophagectomy GOO, the results showed that post-operative GOO could be effectively managed with endoscopic pyloric dilatation, the authors concluded that routine pyloromyotomy for the prevention of post-esophagectomy GOO may be unwarranted. Swanson *et al*^[54] affirmed that EBD could obviate the requirement of pyloroplasty at esophagectomy.

The application of EBD as treatment of post-operative GOO was described in an 11-year-old boy with surgical injury to the vagus and two infants after insufficient pyloromyotomy, EBD achieved successful results and was considered a good alternative to surgery in these conditions^[55].

EBD has successfully dilated the anastomotic strictures following gastric bypass surgery or vertical band gastropasty in the patients with morbid obesity^[56].

Late-onset primary GOO

Late-onset primary GOO in childhood is a rare condition. A series of 8 pediatric cases received succeeded in treating late-onset primary GOO by using EBD, there is no recurrence for one year^[57]. Another experience successfully used EBD to treat 5 pediatric cases with late-onset pyloric stenosis, 3 cases need repeated EBD^[58].

Nonsteroidal Anti-inflammatory Drug related GOO

NSAIDs are among the most frequently prescribed medications. Although NSAID related GOO is a rare condition, chronic NSAID consumption could cause GOO^[58-60]. Duodenal web-like strictures associated with long-term NSAID use has been described^[61].

The literature about the role of EBD management in NSAID-induced GOO is still scarce. A case series ($n = 10$) with endoscopic management for NSAID-induced pyloroduodenal obstruction found that duodenum was the most common site of involvement (50%), followed by both pylorus and duodenum (40%) and pylorus (10%). The strictures in a majority of patients were web-like, 90% of cases were successfully treated with repeated EBD. Among these successful cases, a 15-mm balloon diameter was achieved after a mean (SD) of 2 (1.6) sessions, and a mean (SD) of 5.3 (2.7) sessions was required to during a mean period of 4.5 mo (range, 2-15). There were no complications or mortality. The literature in relation to EBD management of pediatric

NSAID related GOO is scant, EBD was used to treat NSAID related GOO successfully in a child^[62].

Inflammatory conditions

A definite treatment for the antecedent disease is crucial and may avert the need for EBD or surgery in inflammatory diseases (eosinophilic gastritis, Crohn's disease, etc.) or infectious disease like tuberculosis related GOO, Crohn's disease or tuberculosis related GOO may respond to balloon dilatation, however, multiple recurrences usually occurs if the underlying disease is not effectively treated. Gastroduodenal Crohn's disease and tuberculosis had been successfully treated with EBD procedure^[31,63].

Complications of EBD

In general, EBD is relatively a safe procedure with infrequent complications. Perforation and bleeding are rarely reported for balloon dilatation smaller than 15 mm. Two of 30 patients (6.7%) dilated to 18 mm suffered perforation^[6]. Both recovered uneventfully after surgery. A large case series of 23 patients with PUD related stenosis encountered only one perforation with EBD management^[35]. Another large series of 54 cases by Lau *et al*^[28] reported 4 perforations with EBD management, 2 of 16 patients who underwent EBD with a 16-mm diameter balloon encountered perforation while 2 of 3 patient with 20-mm diameter balloon had perforation. It therefore appears that EBD management with balloon diameter greater than 15 mm is more prone to be complicated with perforation.

Pain during EBD is not uncommon, but is often self-limited. A recent study observed that 19.5% of patients with caustic GOO had self-limiting pain during EBD^[37]. The complications with EBD procedure observed in a case series ($n = 31$) with caustic GOO included self-limiting pain ($n = 10$), bleeding at the time of the procedure ($n = 9$), and one perforation (3.2%) who required surgery^[41]. Kochhar *et al*^[37] reviewed 41 corrosive injury patients with GOO could be successfully taken for EBD, and self-limiting pain ($n = 8$) or bleeding ($n = 7$), perforation ($n = 1$) were noted among these patients.

Outcome of EBD intervention

A good result can be anticipated in the majority of patients with PUD- and corrosive-related GOO after EBD intervention^[32]. EBD for benign GOO in adults is a generally accepted method of treatment. Previous literatures advocate that more than 75% of patients with PUD-related GOO respond to EBD and the long-term use of proton pump inhibitor is needed to obviate recurrences after *H. pylori* eradication. The results of EBD for PUD-related GOO is variable because not all studies consider the confounding factors, such as *H. pylori* infection, use of NSAIDs, practice and compliance of proton pump inhibitor. Immediate relief of obstruction with EBD has been commonly found in the majority of patients, but achieved varied long-term response from

16%^[36] to 100%^[32]. The eradication of *H. pylori* have reported a good long-term response in 70%-80% of patients over a period of 9-98 mo^[6,29,30,35,39].

Lam *et al*^[38] compared the response rates of EBD between 14 patients with positive *H. pylori* infection and 11 *H. pylori*-negative. EBD management was responsive in 78.6% of *H. pylori*-positive, while only 45.4% in *H. pylori* negative patients. Eradication of *H. pylori* combined with EBD had a lower rate of ulcer complications such as bleeding or obstruction compared to *H. pylori* negative group (21% vs 55%) over a follow-up of 24 mo. A case series ($n = 11$) indicated that eradication of *H. pylori* with 1-3 sessions of EBD successfully resolved obstruction in all of the patients^[32]. A study by Cherian *et al*^[34] indicated comparable results in long-term follow-up of their Peptic-GOO patients with EBD and drug therapy.

Patients with young age, continuous use of NSAIDs, or long-lasting symptoms requiring repeated EBD had unfavorable outcomes with the need for multiple dilations or surgery for GOO^[40]. DiSario *et al*^[6] observed that a long-length stricture was associated with poor outcome for GOO. The majority of studies did not describe the duration of proton pump inhibitors making comparisons incomparable between studies.

Need of more than 2 sessions of dilations is a risk factor for EBD failure and requirement for surgery. Rapid recurrence of symptoms is found in patients with malignant GOO. As many benign GOO patients had underlying PUD, eradication of *H. pylori* at the time of balloon dilation will guarantee higher long-term successful rates^[25].

An adult study of 45 patients with pyloric stenosis did a follow-up of mean 32 mo (range, 4-126) indicated that immediate response rate of the EBD treatment was observed in 43 cases (95.6%), and clinical remission was observed in 38 cases (84.4%)^[64]. Over a period of 30 mo, no recurrence was noted in 55.8% of patients with clinical remission, relapse was observed in 39.5% of patients over a mean period of 22.9 mo. Three patients (6.7%) had complications (one bleeding and 2 perforations). Thirteen patients (29%) underwent surgery. *H. pylori* was positive in 97.7% of the patients, and 78.4% of them had successful eradication of *H. pylori*. This study further found that unsuccessful eradication of *H. pylori* and smoking were two risk factors for the recurrence of pyloric stenosis^[64].

EBD can make surgery unnecessary for postoperative GOO and later for peptic, corrosive and postvagotomy gastric outlet stenosis in nearly 70% of patients with benign GOO^[30]. Kochhar *et al*^[37] performed EBD in 31 patients with caustic-induced gastric injury, 30 (96.8%) did not have recurrence of stenosis over a mean follow-up of 21 mo (range, 3-72).

There is less experience of evaluating outcome of EBD for GOO in children. A pediatric case series ($n = 14$) evaluated the effect of endoscopic balloon dilatation and surgical treatment in children's pyloric stricture, surgical correction is still the most common treatment

in the majority of cases of pyloric stenosis^[50]. In this series, the authors stated that benign GOO can be effectively and successfully treated through EBD in suitable patients, surgery can be avoided in patients with successful pyloric balloon dilatation^[50]. There are two long-term studies on EBD management for children with benign pyloric stenosis, response rates were varied between 16% and 80%^[6,36].

Advanced techniques augmenting EBD

A number of practitioners have used supplementary techniques to augment the efficacy of EBD. EBD could be augmented with local (intralesional) steroid injections and endoscopic incision with electrocauterization.

Intralesional steroid injections

Intralesional steroid injections augmented the effect of balloon dilation had been reported in patients with caustic GOO^[65,66], the GOO responded with 1-2 sessions of steroid injections. Intralesional steroid injections have been illustrated to inhibit stricture formation by impeding the synthesis of collagen, chronic scarring, and fibrosis^[66]. Ketchum *et al*^[67] specify that steroid (Triamcinolone) offers cross linking of collagen leading to scar contracture; the contracture will not occur if stretch of scar occurs with steroid injection. Steroids may diminish scar formation by reduction of fibrotic healing that appears after balloon dilation^[68]. Efficacy of steroids augmenting EBD in GOO has been also demonstrated in the other two studies by Kochhar *et al*^[69] and Lee *et al*^[70]. Successfully cases treated with steroids and balloon dilations included three patients with caustic GOO, one peptic, and another post-pyloroplasty.

Endoscopic incision

EBD with additional endoscopic incision achieved successful results in caustic-induced GOO. Boron *et al*^[71] successfully used electrocauterization endoscopically to incise the stenotic segment with standard sphincterotomy in a patient with refractory pyloric stenosis. Hagiwara *et al*^[72] also successfully resolved the stenosis by using combined EBD with electrosurgical incisions in the patients with refractory post-operative pyloric stenosis. I have also successfully used this technique in a young infant with refractory pyloric stenosis secondary to surgical excision of gastric antral web, a satisfactory result after 2 sessions of combined endoscopic electrocauterization and balloon dilatation was achieved^[73].

END POINT OF EBD

No consensus has been reached on the issue of end point of EBD for GOO, especially in pediatric cases. Most experts^[27,29,32-73] have used 15 mm balloons as the end point for GOO while some of them have only dilated to 10-12 mm^[30,35]. Balloons of 16, 18 and 20 mm are uncommonly used^[28,30,35]. The size of balloon catheters for adult GOO was recommended to be used with step-

wise manner, from 10-12mm to 12-15 mm^[31,72] The EBD should be more cautiously performed on pediatric patients than on adult ones if with peptic, caustic or post-operative causes induced GOO. I usually dilate with step-wise manner of catheter balloons inflated with the use of a pressure gauge system for 60-120 s in pediatric patients. Balloon catheter sizes were increased by 2 mm for subsequent EBD sessions, from 6-8 mm to 10-12 mm in infants and toddlers, from 8-10 mm to 10-12 mm in younger children, and from 10-12 mm to 12-15 mm subsequently in older children.

OTHER INTERVENTIONS

Gastric peroral endoscopic pyloromyotomy

Gastric peroral endoscopic pyloromyotomy (G-POEM) is performed with similar techniques to esophageal per-oral endoscopic myotomy. Replacing traditional laparotomy and laparoscopic approaches, G-POEM provides a natural orifice procedure to incise and divide the pyloric sphincter.

Surgical pyloromyotomy has shown to be effective in reducing pyloric stenosis or gastroparesis symptoms, but it requires advanced skills for laparoscopic suturing and carries a risk of leakage and potential further narrowing of gastric outlet. Therefore, G-POEM as a less invasive treatment, is used to deal with gastroparesis recently.

Although laparoscopic pyloromyotomy is still considered as a simple, and safe treatment for pediatric IHPS, G-POEM technique is similarly simple, safe, but less invasiveness, and this procedure can be performed at outpatient department^[74]. A case series of 10 IHPS infants (7 boys, 3 girls; aged 3-7 wk) underwent endoscopic pyloromyotomy with an electrosurgical needle knife to incise the pylorus from antral to duodenal side, most (90%) of the patients were done at outpatient department. All patients did not encounter any complications and tolerated regular feedings as they recovered from sedation. All of them were discharged on the same day of endoscopic procedure and doing well during follow-up (range, 6 mo-2 years)^[74].

A growing body of evidence suggests that G-POEM may be a salvage therapy improves gastric emptying in patients with different types of refractory gastroparesis. Those patients with refractory gastroparesis may respond to endoscopic pyloromyotomy. An adult case series of G-POEM using selective circular myotomy for patients with refractory gastroparesis symptoms due to varied cause (post-infectious, post-surgical, or idiopathic) were successfully performed without any complications. All cases experienced obvious success after G-POEM^[75,76].

Endoscopic stent

Endoscopic stent was usually used to manage malignant GOO. As gastric or duodenal malignancy is very rare in children, there is no pediatric literature about the use

of endoscopic stent for malignant GOO. Palliation of the obstructive symptoms is the primary aim of treatment in the cancer related GOO. Self-expandable metal stents have emerged as a promising treatment option^[77]. Topazian *et al*^[78] firstly reported endoscopic treatment of GOO with endoluminal self-expanding metallic stents in 1992. In recent two decades, experiences of the use of endoscopic stents have gradually increased. Several studies have reported that patients who are having high risk for long-term GOO should undergo endoscopic stents, given its safety, minimal invasiveness, and cost-effectiveness^[79,80].

Endoscopic mucosal resection for gastric polyps

Although most pediatric gastric polyps are considered benign lesions, removal of symptomatic polyps are necessary for symptom relief, histological diagnosis, and avoidance of malignant potential. A standard-size polypectomy snare can be accessed through a 2.8-mm channel endoscopically to do polypectomy in the majority of children. Pontone *et al*^[81] did the endoscopic mucosal resection in the patients with multiple large antral hyperplastic polyps causing GOO with the use of a submucosal cushion under the lesion allowing a steady positioning of the polyp in the gastric lumen without further infiltration. The authors concluded that endoscopic mucosal resection provides tissue for histopathology to diagnose the nature of the polyp and achieves symptomatic resolution.

Endoscopic fragmentation for bezoars

Surgery is the treatment of choice for tricobezoar. However, endoscopic treatments have been described, such as endoscopic fragmentation, extracorporeal lithotripsy and laparoscopic extraction^[16].

SURGERY

Benign GOO may, however, still require operative intervention when non-operative treatment fails^[82]. Peptic ulcer-induced gastric outlet obstruction can be treated safely with EBD. About 65% of patients have sustained symptom relief, but many require more than one dilation session. Outcomes may be improved with effective ulcer therapy with acid reduction and eradication of *H. pylori*^[82]. Compared to endoscopic access, surgical approach is more associated with morbidity and mortality, surgery is considered to be reserved for failure of endoscopic treatment^[83]. Surgeries for peptic GOO include antrectomy with vagotomy, pyloroplasty with vagotomy, gastrojejunostomy with truncal vagotomy, and pyloroplasty. In peptic GOO gastrojejunostomy can be combined with truncal vagotomy and antrectomy, gastrojejunostomy (Billroth II reconstruction) was considered in peptic GOO with altered anatomy. Laparoscopic gastrojejunostomy become a favorable modality of surgery in peptic GOO for its shorter hospitalization due to quick postoperative recovery compared with

conventional laparotomy surgery^[84].

FUTURE DIRECTIONS

With further development of technologies in therapeutic endoscopy, EBD could become the worldwide treatment of choice for pediatric GOO. The future of endoscopic treatment seems to be aimed at the combined use of endoscopic electrocauterization with balloon dilatations in intractable pyloric stricture, and G-POEM appears to be technically feasible and effective in IHPS or gastroparesis patients.

CONCLUSION

Correction of GOO without the need for surgery is an issue that has been tried to be resolved in these decades. With the development of therapeutic endoscopy in pediatric patients, the therapeutic endoscopy becomes an integral part of the management of pediatric patients with GOO.

In recent decades, the endoscopic management of GOO has developed with EBD and additional advanced devices and techniques like local steroid injection, electrocauterization, G-POEM, and stent have been added to augment the efficacy of EBD.

With improvements in techniques and devices, therapeutic results of EBD have been achieved in pediatric patients with peptic pyloric stricture, IHPS, caustic injury related pyloric stricture, congenital antral web, post-operative GOO, and NSAID related GOO despite the inherent technical difficulties of this procedure in children. Local steroid injection and electrocauterization can augment the effect of EBD. Gastric peroral endoscopic pyloromyotomy (G-POEM) appears to be technically feasible in IHPS patients. Clinical applications of G-POEM in pediatric patients with gastroparesis can be considered after confirmation of its efficacy and safety in additional pediatric studies.

REFERENCES

- Kochhar R, Kochhar S. Endoscopic balloon dilation for benign gastric outlet obstruction in adults. *World J Gastrointest Endosc* 2010; **2**: 29-35 [PMID: 21160676 DOI: 10.4253/wjge.v2.i1.29]
- Patel RA, Baker SS, Sayej WN, Baker RD. Two Cases of Helicobacter pylori-Negative Gastric Outlet Obstruction in Children. *Case Rep Gastrointest Med* 2011; **2011**: 749850 [PMID: 22606426 DOI: 10.1155/2011/749850]
- Yen JB, Kong MS. Gastric outlet obstruction in pediatric patients. *Chang Gung Med J* 2006; **29**: 401-405 [PMID: 17051838]
- Edwards MJ, Kollenberg SJ, Brandt ML, Wesson DE, Nuchtern JG, Minifee PK, Cass DL. Surgery for peptic ulcer disease in children in the post-histamine2-blocker era. *J Pediatr Surg* 2005; **40**: 850-854 [PMID: 15937829 DOI: 10.1016/j.jpedsurg.2005.01.056]
- Graham DY. Ulcer complications and their nonoperative treatment. In: Sleisenger M, Fordtran J (eds). *Gastrointestinal Disease* 1993: 698
- DiSario JA, Fennerty MB, Tietze CC, Hutson WR, Burt RW. Endoscopic balloon dilation for ulcer-induced gastric outlet obstruction. *Am J Gastroenterol* 1994; **89**: 868-871 [PMID: 8198096]
- Ciftci AO, Senocak ME, Büyükpamukçu N, Hiçsönmez A. Gastric outlet obstruction due to corrosive ingestion: incidence and outcome. *Pediatr Surg Int* 1999; **15**: 88-91 [PMID: 10079337 DOI: 10.1007/s003830050523]
- Ozokutan BH, Ceylan H, Ertaşkin I, Yapici S. Pediatric gastric outlet obstruction following corrosive ingestion. *Pediatr Surg Int* 2010; **26**: 615-618 [PMID: 20443118 DOI: 10.1007/s00383-010-2613-6]
- Ozcan C, Ergün O, Sen T, Mutaf O. Gastric outlet obstruction secondary to acid ingestion in children. *J Pediatr Surg* 2004; **39**: 1651-1653 [PMID: 15547828 DOI: 10.1016/j.jpedsurg.2004.07.008]
- Bell MJ, Ternberg JL, McAlister W, Keating JP, Tedesco FJ. Antral diaphragm--a cause of gastric outlet obstruction in infants and children. *J Pediatr* 1977; **90**: 196-202 [PMID: 830910 DOI: 10.1016/s0022-3476(77)80629-x]
- Macpherson RI. Gastrointestinal tract duplications: clinical, pathologic, etiologic, and radiologic considerations. *Radiographics* 1993; **13**: 1063-1080 [PMID: 8210590 DOI: 10.1148/radiographics.13.5.8210590]
- Ozcan C, Celik A, Güçlü C, Balık E. A rare cause of gastric outlet obstruction in the newborn: Pyloric ectopic pancreas. *J Pediatr Surg* 2002; **37**: 119-120 [PMID: 11782002 DOI: 10.1053/jpsu.2002.29443]
- Sharma KK, Ranka P, Goyal P, Dabi DR. Gastric outlet obstruction in children: an overview with report of Jodhpur disease and Sharma's classification. *J Pediatr Surg* 2008; **43**: 1891-1897 [PMID: 18926227 DOI: 10.1016/j.jpedsurg.2008.07.001]
- Morinville V, Bernard C, Forget S. Foveolar hyperplasia secondary to cow's milk protein hypersensitivity presenting with clinical features of pyloric stenosis. *J Pediatr Surg* 2004; **39**: E29-E31 [PMID: 14694404 DOI: 10.1016/j.jpedsurg.2003.09.040]
- DuBose TM, Southgate WM, Hill JG. Lactobezoars: a patient series and literature review. *Clin Pediatr (Phila)* 2001; **40**: 603-606 [PMID: 11758960 DOI: 10.1177/000992280104001104]
- Ruiz HD, Palermo M, Ritondale O, Pest E, Pest P, Villafañe V, Bruno M, Tarsitano FJ. Gastro-duodenal trichobezoars: a rare cause of obstruction of the gastrointestinal tract. *Acta Gastroenterol Latinoam* 2005; **35**: 24-27 [PMID: 15954733]
- Nugent FW, Roy MA. Duodenal Crohn's disease: an analysis of 89 cases. *Am J Gastroenterol* 1989; **84**: 249-254 [PMID: 2919581]
- Padussis J, Loffredo B, McAneny D. Minimally invasive management of obstructive gastroduodenal tuberculosis. *Am Surg* 2005; **71**: 698-700 [PMID: 16217956]
- Miner PB, Harri JE, McPhee MS. Intermittent gastric outlet obstruction from a pedunculated gastric polyp. *Gastrointest Endosc* 1982; **28**: 219-220 [PMID: 7129059 DOI: 10.1016/S0016-5107(82)73075-5]
- Jaka H, Mchembe MD, Rambau PF, Chalya PL. Gastric outlet obstruction at Bugando Medical Centre in Northwestern Tanzania: a prospective review of 184 cases. *BMC Surg* 2013; **13**: 41 [PMID: 24067148 DOI: 10.1186/1471-2482-13-41]
- Ferzoco SJ, Soybel DI. Gastric outlet obstruction, perforation and other complications of gastroduodenal ulcer. In: Wolfe HM, editor. *Therapy of digestive disorders*. 2007: 357-375
- Goenka AS, Dasilva MS, Cleghorn GJ, Patrick MK, Shepherd RW. Therapeutic upper gastrointestinal endoscopy in children: an audit of 443 procedures and literature review. *J Gastroenterol Hepatol* 1993; **8**: 44-51 [PMID: 8439662 DOI: 10.1111/j.1440-1746.1993.tb01174.x]
- Lindor KD, Ott BJ, Hughes RW. Balloon dilatation of upper digestive tract strictures. *Gastroenterology* 1985; **89**: 545-548 [PMID: 4018500 DOI: 10.1016/0016-5085(85)90449-4]
- Rana SS, Bhasin DK, Chandail VS, Gupta R, Nada R, Kang M, Nagi B, Singh R, Singh K. Endoscopic balloon dilatation without fluoroscopy for treating gastric outlet obstruction because of benign etiologies. *Surg Endosc* 2011; **25**: 1579-1584 [PMID: 21052720 DOI: 10.1007/s00464-010-1442-y]
- Yusuf TE, Brugge WR. Endoscopic therapy of benign pyloric stenosis and gastric outlet obstruction. *Curr Opin Gastroenterol* 2006; **22**: 570-573 [PMID: 16891891 DOI: 10.1097/01.mog.0000239874.13867.41]
- Benjamin SB, Cattau EL, Glass RL. Balloon dilation of the pylorus: therapy for gastric outlet obstruction. *Gastrointest Endosc* 1982; **28**: 253-254 [PMID: 7173580 DOI: 10.1016/S0016-5107(82)73105-0]
- Benjamin SB, Glass RL, Cattau EL, Miller WB. Preliminary

- experience with balloon dilation of the pylorus. *Gastrointest Endosc* 1984; **30**: 93-95 [PMID: 6714610 DOI: 10.1016/S0016-5107(84)72329-7]
- 28 **Lau JY**, Chung SC, Sung JJ, Chan AC, Ng EK, Suen RC, Li AK. Through-the-scope balloon dilation for pyloric stenosis: long-term results. *Gastrointest Endosc* 1996; **43**: 98-101 [PMID: 8635729 DOI: 10.1016/S0016-5107(06)80107-0]
 - 29 **Boylan JJ**, Gradzka MI. Long-term results of endoscopic balloon dilatation for gastric outlet obstruction. *Dig Dis Sci* 1999; **44**: 1883-1886 [PMID: 10505729]
 - 30 **Solt J**, Bajor J, Szabó M, Horváth OP. Long-term results of balloon catheter dilation for benign gastric outlet stenosis. *Endoscopy* 2003; **35**: 490-495 [PMID: 12783346 DOI: 10.1055/s-2003-39664]
 - 31 **Misra SP**, Dwivedi M. Long-term follow-up of patients undergoing balloon dilation for benign pyloric stenoses. *Endoscopy* 1996; **28**: 552-554 [PMID: 8911802 DOI: 10.1055/s-2007-1005553]
 - 32 **Kochhar R**, Sethy PK, Nagi B, Wig JD. Endoscopic balloon dilatation of benign gastric outlet obstruction. *J Gastroenterol Hepatol* 2004; **19**: 418-422 [PMID: 15012779 DOI: 10.1111/j.1440-1746.2003.03283.x]
 - 33 **Perng CL**, Lin HJ, Lo WC, Lai CR, Guo WS, Lee SD. Characteristics of patients with benign gastric outlet obstruction requiring surgery after endoscopic balloon dilation. *Am J Gastroenterol* 1996; **91**: 987-990 [PMID: 8633593]
 - 34 **Cherian PT**, Cherian S, Singh P. Long-term follow-up of patients with gastric outlet obstruction related to peptic ulcer disease treated with endoscopic balloon dilatation and drug therapy. *Gastrointest Endosc* 2007; **66**: 491-497 [PMID: 17640640 DOI: 10.1016/j.gie.2006.11.016]
 - 35 **Kozarek RA**, Botoman VA, Patterson DJ. Long-term follow-up in patients who have undergone balloon dilation for gastric outlet obstruction. *Gastrointest Endosc* 1990; **36**: 558-561 [PMID: 2279642 DOI: 10.1016/S0016-5107(90)71163-7]
 - 36 **Kuwada SK**, Alexander GL. Long-term outcome of endoscopic dilation of nonmalignant pyloric stenosis. *Gastrointest Endosc* 1995; **41**: 15-17 [PMID: 7698619 DOI: 10.1016/S0016-5107(95)70270-9]
 - 37 **Kochhar R**, Dutta U, Sethy PK, Singh G, Sinha SK, Nagi B, Wig JD, Singh K. Endoscopic balloon dilation in caustic-induced chronic gastric outlet obstruction. *Gastrointest Endosc* 2009; **69**: 800-805 [PMID: 19136104 DOI: 10.1016/j.gie.2008.05.056]
 - 38 **Lam YH**, Lau JY, Fung TM, Ng EK, Wong SK, Sung JJ, Chung SS. Endoscopic balloon dilation for benign gastric outlet obstruction with or without *Helicobacter pylori* infection. *Gastrointest Endosc* 2004; **60**: 229-233 [DOI: 10.1016/S0016-5107(04)01569-X]
 - 39 **Griffin SM**, Chung SC, Leung JW, Li AK. Peptic pyloric stenosis treated by endoscopic balloon dilatation. *Br J Surg* 1989; **76**: 1147-1148 [PMID: 2597970 DOI: 10.1002/bjs.1800761112]
 - 40 **Weiland D**, Dunn DH, Humphrey EW, Schwartz ML. Gastric outlet obstruction in peptic ulcer disease: an indication for surgery. *Am J Surg* 1982; **143**: 90-93 [PMID: 7053661 DOI: 10.1016/0002-9610(82)90135-0]
 - 41 **Jaffin BW**, Kaye MD. The prognosis of gastric outlet obstruction. *Ann Surg* 1985; **201**: 176-179 [PMID: 3970597 DOI: 10.1097/00000658-198502000-00007]
 - 42 **Chan KL**, Saing H. Balloon catheter dilatation of peptic pyloric stenosis in children. *J Pediatr Gastroenterol Nutr* 1994; **18**: 465-468 [PMID: 7915308 DOI: 10.1097/00005176-199405000-00011]
 - 43 **Nasr A**, Ein SH, Connolly B. Recurrent pyloric stenosis: to dilate or operate? A preliminary report. *J Pediatr Surg* 2008; **43**: e17-e20 [PMID: 18280264 DOI: 10.1016/j.jpedsurg.2007.10.039]
 - 44 **Karnsakul W**, Cannon ML, Gillespie S, Vaughan R. Idiopathic non-hypertrophic pyloric stenosis in an infant successfully treated via endoscopic approach. *World J Gastrointest Endosc* 2010; **2**: 413-416 [PMID: 21191516 DOI: 10.4253/wjge.v2.i12.413]
 - 45 **Ogawa Y**, Higashimoto Y, Nishijima E, Muraji T, Yamazato M, Tsugawa C, Matsumoto Y. Successful endoscopic balloon dilatation for hypertrophic pyloric stenosis. *J Pediatr Surg* 1996; **31**: 1712-1714 [PMID: 8986998 DOI: 10.1016/S0022-3468(96)90059-7]
 - 46 **Hayashi AH**, Giacomantonio JM, Lau HY, Gillis DA. Balloon catheter dilatation for hypertrophic pyloric stenosis. *J Pediatr Surg* 1990; **25**: 1119-1121 [PMID: 2273424 DOI: 10.1016/0022-3468(90)90744-T]
 - 47 **Chaudhary A**, Puri AS, Dhar P, Reddy P, Sachdev A, Lahoti D, Kumar N, Broor SL. Elective surgery for corrosive-induced gastric injury. *World J Surg* 1996; **20**: 703-706; discussion 706 [PMID: 8662156 DOI: 10.1007/s002689900107]
 - 48 **Treem WR**, Long WR, Friedman D, Watkins JB. Successful management of an acquired gastric outlet obstruction with endoscopy guided balloon dilatation. *J Pediatr Gastroenterol Nutr* 1987; **6**: 992-996 [PMID: 3681588 DOI: 10.1097/00005176-198711000-00031]
 - 49 **Kochhar R**, Poornachandra KS, Dutta U, Agrawal A, Singh K. Early endoscopic balloon dilation in caustic-induced gastric injury. *Gastrointest Endosc* 2010; **71**: 737-744 [PMID: 20363415 DOI: 10.1016/j.gie.2009.11.038]
 - 50 **Temiz A**, Oguzkurt P, Ezer SS, Ince E, Gezer HO, Hicsonmez A. Management of pyloric stricture in children: endoscopic balloon dilatation and surgery. *Surg Endosc* 2012; **26**: 1903-1908 [PMID: 22234589 DOI: 10.1007/s00464-011-2124-0]
 - 51 **Tekant G**, Eroğlu E, Erdoğan E, Yeşiladağ E, Emir H, Büyükcinal C, Yeker D. Corrosive injury-induced gastric outlet obstruction: a changing spectrum of agents and treatment. *J Pediatr Surg* 2001; **36**: 1004-1007 [PMID: 11431765 DOI: 10.1053/jpsu.2001.24725]
 - 52 **Lu JP**, Huang Y, Wu J, Chen SY. Uncommon congenital antral web misdiagnosed twice as a pyloric ulcer: successful treatment with endoscopic balloon dilatation. *Turk J Pediatr* 2014; **56**: 100-102 [PMID: 24827957]
 - 53 **Lanuti M**, de Delva PE, Wright CD, Gaissert HA, Wain JC, Donahue DM, Allan JS, Mathisen DJ. Post-esophagectomy gastric outlet obstruction: role of pyloromyotomy and management with endoscopic pyloric dilatation. *Eur J Cardiothorac Surg* 2007; **31**: 149-153 [PMID: 17166733 DOI: 10.1016/j.ejcts.2006.11.010]
 - 54 **Swanson EW**, Swanson SJ, Swanson RS. Endoscopic pyloric balloon dilatation obviates the need for pyloroplasty at esophagectomy. *Surg Endosc* 2012; **26**: 2023-2028 [PMID: 22398960 DOI: 10.1007/s00464-012-2151-5]
 - 55 **Heymans HS**, Bartelsman JW, Herweijer TJ. Endoscopic balloon dilatation as treatment of gastric outlet obstruction in infancy and childhood. *J Pediatr Surg* 1988; **23**: 139-140 [PMID: 3343648 DOI: 10.1016/S0022-3468(88)80142-8]
 - 56 **Sataloff DM**, Lieber CP, Seinige UL. Strictures following gastric stapling for morbid obesity. Results of endoscopic dilatation. *Am Surg* 1990; **56**: 167-174 [PMID: 2316938]
 - 57 **Boybeyi O**, Karnak I, Ekinci S, Ciftci AO, Akçören Z, Tanyel FC, Senocak ME. Late-onset hypertrophic pyloric stenosis: definition of diagnostic criteria and algorithm for the management. *J Pediatr Surg* 2010; **45**: 1777-1783 [PMID: 20850620 DOI: 10.1016/j.jpedsurg.2010.04.014]
 - 58 **Geraghty RJ**, Black D, Bruce SA. The successful medical management of gastric outflow obstruction associated with the use of non-steroidal anti-inflammatory drugs in the elderly. *Postgrad Med J* 1991; **67**: 1004-1007 [PMID: 1775405 DOI: 10.1136/pgmj.67.793.1004]
 - 59 **Weaver GA**, Harper RL, Storey JA, Jenkins PL, Merrell NB. Nonsteroidal antiinflammatory drugs are associated with gastric outlet obstruction. *J Clin Gastroenterol* 1995; **20**: 196-198 [PMID: 7797825 DOI: 10.1097/00004836-199504000-00006]
 - 60 **Kannan S**, McGreevy PS, Fullerton TE. Nonsteroidal anti-inflammatory drug induced duodenal web. *S D J Med* 1997; **50**: 393-394 [PMID: 9401436]
 - 61 **Puri AS**, Monga R, Garg S, Sharma BC, Satapathy S, Sarin SK. Diaphragm disease of duodenum following long-term NSAIDs use: endoscopic management. *Indian J Gastroenterol* 2004; **23**: 189-190 [PMID: 15599008]
 - 62 **Gobbi D**, Billi P, Fascetti Leon F, Alvisi P, Lambertini A, Lima M. Pneumatic pyloric dilatation for the treatment of gastric outlet obstruction in a child. *Pediatr Int* 2013; **55**: 382-385 [PMID: 23782371 DOI: 10.1111/ped.12022]
 - 63 **Kim JH**, Shin JH, Di ZH, Ko GY, Yoon HK, Sung KB, Song HY. Benign duodenal strictures: treatment by means of fluoroscopically guided balloon dilation. *J Vasc Interv Radiol* 2005; **16**: 543-548 [PMID: 15802456 DOI: 10.1097/01.RVI.0000150033.13928.D4]

- 64 **Hamzaoui L**, Bouassida M, Ben Mansour I, Medhioub M, Ezzine H, Touinsi H, Azouz MM. Balloon dilatation in patients with gastric outlet obstruction related to peptic ulcer disease. *Arab J Gastroenterol* 2015; **16**: 121-124 [PMID: 26440958 DOI: 10.1016/j.ajg.2015.07.004]
- 65 **Kochhar R**, Sriram PV, Ray JD, Kumar S, Nagi B, Singh K. Intralesional steroid injections for corrosive induced pyloric stenosis. *Endoscopy* 1998; **30**: 734-736 [PMID: 9865568 DOI: 10.1055/s-2007-1001400]
- 66 **Ashcraft KW**, Holder TM. The experimental treatment of esophageal strictures by intralesional steroid injections. *J Thorac Cardiovasc Surg* 1969; **58**: 685-691 [PMID: 5348158]
- 67 **Ketchum LD**, Smith J, Robinson DW, Masters FW. The treatment of hypertrophic scar, keloid and scar contracture by triamcinolone acetonide. *Plast Reconstr Surg* 1966; **38**: 209-218 [PMID: 5919604 DOI: 10.1097/00006534-196609000-00005]
- 68 **Gandhi RP**, Cooper A, Barlow BA. Successful management of esophageal strictures without resection or replacement. *J Pediatr Surg* 1989; **24**: 745-749; discussion 749-750 [DOI: 10.1016/S0022-3468(89)80529-9]
- 69 **Kochhar R**, Ray JD, Sriram PV, Kumar S, Singh K. Intralesional steroids augment the effects of endoscopic dilation in corrosive esophageal strictures. *Gastrointest Endosc* 1999; **49**: 509-513 [PMID: 10202068 DOI: 10.1016/S0016-5107(99)70052-0]
- 70 **Lee M**, Kubik CM, Polhamus CD, Brady CE, Kadakia SC. Preliminary experience with endoscopic intralesional steroid injection therapy for refractory upper gastrointestinal strictures. *Gastrointest Endosc* 1995; **41**: 598-601 [PMID: 7672557 DOI: 10.1016/S0016-5107(95)70199-0]
- 71 **Boron B**, Gross KR. Successful dilatation of pyloric stricture resistant to balloon dilatation with electrocautery using a sphinctertome. *J Clin Gastroenterol* 1996; **23**: 239-241 [PMID: 8899513 DOI: 10.1097/00004836-199610000-00020]
- 72 **Hagiwara A**, Sonoyama Y, Togawa T, Yamasaki J, Sakakura C, Yamagishi H. Combined use of electrosurgical incisions and balloon dilatation for the treatment of refractory postoperative pyloric stenosis. *Gastrointest Endosc* 2001; **53**: 504-508 [PMID: 11275897 DOI: 10.1067/mge.2001.113281]
- 73 **Chao HC**, Luo CC, Wang CJ. Elimination of postoperative pyloric stricture by endoscopic electrocauterization and balloon dilatation in an infant with congenital antral web. *Pediatr Neonatol* 2011; **52**: 106-109 [PMID: 21524632 DOI: 10.1016/j.pedneo.2011.02.005]
- 74 **Ibarguen-Secchia E**. Endoscopic pyloromyotomy for congenital pyloric stenosis. *Gastrointest Endosc* 2005; **61**: 598-600 [PMID: 15812419 DOI: 10.1016/S0016-5107(05)00075-1]
- 75 **Khashab MA**, Stein E, Clarke JO, Saxena P, Kumbhari V, Chander Roland B, Kalloo AN, Stavropoulos S, Pasricha P, Inoue H. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2013; **78**: 764-768 [PMID: 24120337 DOI: 10.1016/j.gie.2013.07.019]
- 76 **Mekaroonkamol P**, Li LY, Dacha S, Xu Y, Keilin SD, Willingham FF, Cai Q. Gastric peroral endoscopic pyloromyotomy (G-POEM) as a salvage therapy for refractory gastroparesis: a case series of different subtypes. *Neurogastroenterol Motil* 2016; **28**: 1272-1277 [PMID: 27197717 DOI: 10.1111/nmo.12854]
- 77 **van Hooft J**, Mutignani M, Repici A, Messmann H, Neuhaus H, Fockens P. First data on the palliative treatment of patients with malignant gastric outlet obstruction using the WallFlex enteral stent: a retrospective multicenter study. *Endoscopy* 2007; **39**: 434-439 [PMID: 17516350 DOI: 10.1055/s-2007-966338]
- 78 **Topazian M**, Ring E, Grendell J. Palliation of obstructing gastric cancer with steel mesh, self-expanding endoprotheses. *Gastrointest Endosc* 1992; **38**: 58-60 [PMID: 1377147 DOI: 10.1016/S0016-5107(92)70334-4]
- 79 **Adler DG**. Enteral stents for malignant gastric outlet obstruction: testing our mettle. *Gastrointest Endosc* 2007; **66**: 361-363 [PMID: 17643713 DOI: 10.1016/j.gie.2006.12.053]
- 80 **Tringali A**, Didden P, Repici A, Spaander M, Bourke MJ, Williams SJ, Spicak J, Drastich P, Mutignani M, Perri V, Roy A, Johnston K, Costamagna G. Endoscopic treatment of malignant gastric and duodenal strictures: a prospective, multicenter study. *Gastrointest Endosc* 2014; **79**: 66-75 [PMID: 23932009 DOI: 10.1016/j.gie.2013.06.032]
- 81 **Pontone S**, Pironi D, Eberspacher C, Pontone P, Filippini A. Endoscopic management of multiple large antral hyperplastic polyps causing gastric outlet obstruction. *Ann Ital Chir* 2011; **82**: 297-300 [PMID: 21834480]
- 82 **Soreide K**, Sarr MG, Soreide JA. Pyloroplasty for benign gastric outlet obstruction--indications and techniques. *Scand J Surg* 2006; **95**: 11-16 [PMID: 16579249]
- 83 **Khullar SK**, DiSario JA. Gastric outlet obstruction. *Gastrointest Endosc Clin N Am* 1996; **6**: 585-603 [PMID: 8803569]
- 84 **Al-Rashedy M**, Dadibhai M, Shareif A, Khandelwal MI, Ballester P, Abid G, McCloy RF, Ammori BJ. Laparoscopic gastric bypass for gastric outlet obstruction is associated with smoother, faster recovery and shorter hospital stay compared with open surgery. *J Hepatobiliary Pancreat Surg* 2005; **12**: 474-478 [PMID: 16365822 DOI: 10.1007/s00534-005-1013-0]

P- Reviewer: Rustagi T, Tomizawa M, Tanimoto MA **S- Editor:** Qi Y
L- Editor: A **E- Editor:** Wu HL



Retrospective Study

Efficacy and safety of endoscopic papillary balloon dilation for the removal of bile duct stones: Data from a "real-life" multicenter study on Dilation-Assisted Stone Extraction

Roberto Di Mitri, Filippo Mocciaro, Socrate Pallio, Giulia Maria Pecoraro, Andrea Tortora, Claudio Zulli, Simona Attardo, Attilio Maurano

Roberto Di Mitri, Filippo Mocciaro, Giulia Maria Pecoraro, Simona Attardo, Gastroenterology and Endoscopy Unit, ARNAS Civico-Di Cristina-Benfratelli Hospital, 90127 Palermo, Italy

Socrate Pallio, Andrea Tortora, Endoscopy Unit, Policlinico G. Martino, Messina University, 98122 Messina, Italy

Claudio Zulli, Attilio Maurano, Endoscopy Unit, Amico Gaetano Fucito Hospital, 84045 Mercato San Severino (Salerno), Italy

Author contributions: Di Mitri R and Mocciaro F designed and performed the research and wrote the paper; Mocciaro F and Pecoraro GM contributed to the analysis; Pallio S, Tortora A, Zulli C, Attardo S and Maurano A supervised the report.

Institutional review board statement: This study was approved by the Ethics Committee of the ARNAS Civico-Di Cristina-Benfratelli Hospital, Palermo, Italy.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Roberto Di Mitri, MD, Gastroenterology and Endoscopy Unit, ARNAS Civico-Di Cristina-Benfratelli Hospital, Piazza N. Leotta 4, 90127 Palermo, Italy. robdimitri68@gmail.com
Telephone: +39-33-88931234
Fax: +39-09-16663053

Received: June 28, 2016

Peer-review started: July 21, 2016

First decision: August 5, 2016

Revised: August 24, 2016

Accepted: September 7, 2016

Article in press: September 8, 2016

Published online: October 16, 2016

Abstract

AIM

To report data on Dilation-Assisted Stone Extraction (DASE) use in clinical practice and its efficacy and safety through three Italian referral centers for biliopancreatic diseases treatment.

METHODS

From January 2011 to December 2015 we collected data on 120 patients treated with DASE. Technical success was obtained when the endoscopist was able to place the balloon through the papilla inflating the balloon until the final diameter for an adequate time (at least 30 s). Clinical success was obtained after complete stone removal (no remaining stones were visible at the cholangiogram).

RESULTS

Forty-nine male (40.8%) and 71 female (59%) were enrolled. The mean age was 67.8 years \pm 15.7. The mean common bile duct (CBD) dilation was 19.2 mm

± 3.9 and the mean size of stones 15.8 ± 2.9 . DASE was applied as first approach in 38% (62% after initial failure of stones extraction). Technical and clinical success was of 91% and 87% respectively. In those in which DASE failed alternative treatment were adopted. After DASE 18% of patients experienced a complication (bleeding 9%, pancreatitis 8%, perforation 0.8%). At univariable analysis, elective endoscopic retrograde cholangiopancreatography ($P = 0.031$), DASE as first approach ($P = 0.032$), and cannulation of major papilla followed by guidewire insertion ($P = 0.004$) were related to low risk of complications. Pre-cut was related to an increased risk of complications ($P = 0.01$).

CONCLUSION

DASE allowed a higher first-session success rate and can be considered a valid alternative to endoscopic sphincterotomy not only for bigger CBD stones.

Key words: Endoscopic retrograde cholangiopancreatography; Dilation-Assisted Stone Extraction; Common bile duct stone; Endoscopic sphincterotomy; Endoscopic papillary balloon dilation

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic papillary large-balloon dilation after endoscopic sphincterotomy resulted effective for "difficult" common bile duct (CBD) stones treatment. This endoscopic technique has gradually spread to the current Dilation-Assisted Stone Extraction (DASE), in which balloon dilation was associated to a full or partial incision of the transverse fold, enhancing stones removal and reducing the risk of complications. Technical and clinical success was of 91% and 87% respectively; 18% of patients experienced a complication (bleeding 9%, pancreatitis 8%, perforation 0.8%). DASE allowed a higher first-session success rate and can be considered a valid alternative to endoscopic sphincterotomy not only for bigger stones of the CBD.

Di Mitri R, Mocciano F, Pallio S, Pecoraro GM, Tortora A, Zulli C, Attardo S, Maurano A. Efficacy and safety of endoscopic papillary balloon dilation for the removal of bile duct stones: Data from a "real-life" multicenter study on Dilation-Assisted Stone Extraction. *World J Gastrointest Endosc* 2016; 8(18): 646-652 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/646.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.646>

INTRODUCTION

Endoscopic sphincterotomy (EST) during endoscopic retrograde cholangiopancreatography (ERCP) represents the standard endoscopic treatment for common bile duct (CBD) stones, present in up to 10% of patients who underwent cholecystectomy^[1]. EST was introduced in 1974^[2], and up to now is widely used in the current

clinical practice despite 5%-15% of all CBD stones are unable to be managed with EST alone (e.g., large CBD stones) increasing the number of complications as cholangitis and pancreatitis^[3]. In patients with large CBD stones, endoscopic mechanical lithotripsy (EML) using a mechanical lithotripter^[4], extra-corporeal shock wave lithotripsy or laser lithotripsy have proven useful to enhance stones removal^[5]. In 2003 some authors showed as endoscopic papillary large-balloon dilation (EPLBD) after EST resulted effective for "difficult" CBD stones (≥ 15 mm)^[6]. This "combined" endoscopic technique has gradually spread to the current Dilation-Assisted Stone Extraction (DASE) in which balloon dilation was associated to a full or partial incision of the transverse fold^[7,8], enhancing stones removal and reducing the risk of post-ERCP pancreatitis compared to EPLBD alone^[9,10]. This endoscopic approach can be applied safely for the treatment of CBD stones of all size as showed in a large randomized trial published in 2014 by Li *et al*^[8].

In the current study we reported "real-life" data on DASE use in clinical practice and its efficacy and safety through three Italian referral centers for biliopancreatic diseases treatment.

MATERIALS AND METHODS

Patients and study design

This retrospective study collected data from three referral centers for biliopancreatic diseases diagnosis and treatment [Gastroenterology and Endoscopy Unit, ARNAS Civico-Di Cristina-Benfratelli Hospital, Palermo; Endoscopy Unit, Policlinico G. Martino, Messina University, Messina; Endoscopy Unit, Amico Gaetano Fucito Hospital, Mercato San Severino (SA)].

All the included patients had either a single or more CBD stones documented through one or more abdominal imaging technique (ultrasound, computer tomography scan or magnetic resonance imaging). DASE was performed due to failure of the standard approach or as first approach due to the large size of the stones (≥ 12 mm).

Endoscopic technique

ERCP were performed by experienced endoscopists, and with patients under conscious or deep sedation according to the hospital guidelines of each center (short-acting benzodiazepine either alone or in combination with an opioid analgesic for conscious sedation, while propofol for deep sedation). Full blood count, biochemistry and coagulation parameters were obtained before the ERCP. Prior to the ERCP antimicrobial agent was administered in all patients to prevent post-procedural infection. ERCP was performed using a side-viewing endoscope (JF or TJF series scopes, Olympus Medical Systems, Co. Ltd, Tokyo, Japan). After selective cannulation, the CBD was imaged using diluted contrast medium injection and the endoscopist was able to evaluate the number and

the size of stones, and the diameter of the distal bile duct. In "naïve" patients, EST was performed before attempting to remove the CBD stones. The breadth of the sphincterotomy incision was performed according to endoscopist evaluation, the limit of the transverse fold or the presence of ampullary/periampullary diverticulum. After EST, stones were removed with retrieval balloon catheter or Dormia basket according to the decision of each endoscopist. In those with stones removal failure, DASE was applied in order to reach or complete stones removal. DASE was performed using a balloon catheter (CRE Wireguided, Boston Scientific, Massachusetts, United States) passed over the guidewire and positioned across the main duodenal papilla. X-ray markers confirmed the correct placement of the balloon. The final diameter of the balloon was selected to correspond to the diameter of the distal bile duct. The balloon was gradually pressurized using diluted contrast medium injection through each diameter according to the corresponding atmosphere, reported by the manufacturer's instructions, and until waist disappearance. Final balloon dilation was maintained until 60 s thereafter. After that the balloon was gradually deflated and removed. Finally the stones were extracted using a retrieval balloon catheter or a Dormia basket. In patients with difficult-to-extract stones, the stones were removed after being crushed using EML. If the stones could not be removed a plastic stent insertion was performed and alternative approaches were planned (extra-corporeal shock wave lithotripsy, laser lithotripsy or surgical treatment).

Evaluation of efficacy and complications

To confirm the complete cleaning of the CBD each patient underwent contrast-enhanced imaging after occlusion with the retrieval balloon catheter. Technical success was obtained when the endoscopist was able to place the balloon through the papilla inflating the balloon until the final diameter for an adequate time (at least 30 s). Clinical success was obtained after complete stone removal (no remaining stones were visible at the cholangiogram).

All post-ERCP complications were recorded according to definitions standardized in the 1991 consensus conference. Post-ERCP pancreatitis were defined as clinical evidence of pancreatitis and elevation of pancreatic enzymes to three times the upper limit of normal 24 h after the procedure (mild if 2-3 d duration, moderate if 4-9 d, severe if longer than 10 d). Hemorrhage was considered only if there was clinical evidence of bleeding (melena or hematemesis), with an associated decrease in the hemoglobin concentration of at least 2 g/dL, the need for a blood transfusion or significant bleeding requiring endoscopic hemostasis. Cholangitis was recorded if there were symptoms as right upper quadrant abdominal tenderness, a temperature of 38 °C, and elevated liver enzyme levels. Perforation was recorded if evident during the ERCP or according to postoperative patient's symptoms combined with

abdominal radiography and/or abdominal computed tomography.

Statistical analysis

All data were collected by the three centers through an excel database. Each center filled out the own database according to a unique encoding of the variables so that to have uniform data for the final analysis. Data were analysed using the SPSS 15 (SPSS Inc., Chicago, IL, United States) software package. Continuous variables were summarized as mean (\pm SD) or median (range) according to their distribution. Categorical variables were summarized as frequency and percentage. Significant differences were calculated using a χ^2 test for categorical variables, and logistic regression for continuous variables. Differences were considered significant at a "P value" of less than 0.05. The variables that were significant on univariate analysis were evaluated in a subsequent multivariate model.

RESULTS

From January 2011 to December 2015, 1908 ERCP for CBD stones were performed in the three included referral centers. Finally we collected data on 120 patients treated with DASE (20% of all ERCP): 49 male (40.8%) and 71 female (59%), mean age of 67.8 years \pm 15.7. Patient characteristics are summarized in Table 1. There were no significant differences between the three enrolled centers and the baseline characteristics were well balanced. Indication for DASE was large stones in 69.2% (83/120 patients) and periampullary diverticulum in 30.8% (37/120 patients) as showed in Table 2. Almost all ERCP were performed electively and only 2.5% of those treated with DASE underwent rescue ERCP due to acute severe cholangitis. The majority of the treated patients underwent ERCP for the first time and only 1/4 of the patients presented an ampullary/periampullary diverticulum. The mean CBD dilation was 19.2 mm \pm 3.9 and the mean size of stones 15.8 \pm 2.9. In 87.5% of patients, CBD cannulation was made through cannulation of major papilla followed by guidewire insertion and contrast medium injection. After cholangiogram the endoscopists decided to perform DASE as first approach in 45 out of 120 patients (38%) while 62% of patients were treated after initial failure of stones extraction. The EST before DASE was "full length" in nearly half of patients, but as expected was much less common in those with ampullary/periampullary diverticulum (9/52 vs 43/52). After DASE technical success was of 91% with a significant rate of clinical success and stones extraction (87%). The mean size of the balloon dilation was 16.7 mm \pm 3.6. There were no differences between in retrieval balloon or Dormia basket using to achieve CBD clearance. In those in which DASE failed (16 patients), alternative treatment were adopted (mechanical lithotripsy in 12 patients, extra-corporeal shock wave lithotripsy in 3 patients, laser lithotripsy in one patient). Eighty-two

Table 1 Patients' characteristics

Gender (male/female), <i>n</i> (%)	49 (40.8)/71 (59)
Age (years), mean \pm SD	67.8 yr \pm 15.7
Patients at 1 st ERCP, <i>n</i> (%)	91 (75.8)
Patients previously treated with endoscopic sphincterotomy, <i>n</i> (%)	29 (24.2)
Ampullary/peripapillary diverticulum, <i>n</i> (%)	37 (30.8)
Bile duct stones size (mm), mean \pm SD	15.8 \pm 2.9
Bile duct size (mm), mean \pm SD	19.2 \pm 3.9
Billroth I reconstruction, <i>n</i> (%)	3 (2.5)

patients were treated with pancreatic stent placement (12%) or with 100 mg indomethacin suppositories (57%) to reduce the risk of post-ERCP pancreatitis.

After DASE in less than ¼ of patients (18%) a complication was recorded. Bleeding and post-ERCP pancreatitis were the most common (9% and 8% respectively), while only in 1 patient a perforation was observed (he underwent DASE after CBD access made through cannulation of major papilla followed by guidewire insertion). The majority of complications occurred during the ERCP or within 24 h, and they were resolved conservatively (59%) or endoscopically (36%); only 1 patient underwent surgery due to post-procedural perforation. No adverse events related to the anesthetic technique were recorded (Table 3).

At univariable analysis, elective ERCP ($P = 0.031$, OR = 0.10; 95%CI: 0.009-1.21), DASE as first approach ($P = 0.032$, OR = 0.35; 95%CI: 0.136-1.11) and cannulation of major papilla followed by guidewire insertion ($P = 0.004$, OR = 0.21; 95%CI: 0.065-6.64), were related to low risk of complications. Pre-cut before DASE was related to an increased risk of complications ($P = 0.01$, OR = 5.11; 95%CI: 1.340-19.492). Indomethacin suppositories reduced the number of post-ERCP pancreatitis despite statistical significance was not reached ($P = 0.07$). Size of sphincterotomy incision, ampullary/peripapillary diverticulum, balloon size, dilation time or devices for stones extraction resulted not related to complications. None of the significant variables resulted significant after multivariable analysis.

DISCUSSION

Our retrospective study showed as, in clinical practice of three referral centers for biliopancreatic diseases treatment, DASE was used in 20% of all ERCP for CBD stones removal. The efficacy and safety of this approach for difficult CBD stones were significant through the three participating centers.

Kawai *et al*^[2] have revolutionized the endoscopic approach of the CBD stones treatment with EST decreasing the need of surgery. Nevertheless 10%-15% of patients had "difficult" CBD stones and EST alone cannot be sufficient to remove the stones from the biliary tract. Difficulties can be related to the bile duct access (acute distal CBD angulation, sigmoid shaped CBD, peripapillary diverticulum, CBD strictures Billroth

Table 2 Final results

Elective ERCP vs rescue ERCP, <i>n</i> (%)	117 (97.5) vs 3 (2.5)
Common bile duct cannulation technique, <i>n</i> (%)	
Cannulation of major papilla followed by contrast medium injection	5 (4.2)
Cannulation of major papilla followed by guidewire insertion	105 (87.5)
Pre-cut	10 (8.3)
Involuntary insertion of the guidewire into Wirsung, <i>n</i> (%)	25 (20.8)
Indication for DASE, <i>n</i> (%)	
Large stones	83 (69.2)
Peripapillary diverticulum	37 (30.8)
DASE, <i>n</i> (%)	
As first approach	45 (38)
After stone extraction	75 (62)
Balloon size (mm), mean \pm SD	16.7 \pm 3.6
Dilation time (s), mean \pm SD	51 \pm 13.8
Sphincterotomy incision, <i>n</i> (%)	
Limited to one-third of the transverse fold	68 (56.7)
Full length of the transverse fold	52 (43.3)
Procedural success, <i>n</i> (%)	
Technical success	109 (90.8)
Clinical success	104 (86.7)
Stones extraction, <i>n</i> (%)	
Retrieval balloon	61 (51.8)
Dormia basket	59 (49.2)
Post-ERCP pancreatitis prophylaxis, <i>n</i> (%)	
None	38 (31.4)
Pancreatic plastic stent	14 (11.8)
Indometacin suppositories	68 (56.8)

ERCP: Endoscopic retrograde cholangiopancreatography; DASE: Dilation-Assisted Stone Extraction.

type I gastrectomy, Roux-en-Y-gastrojejunostomy), the size or number of stones, unusually shaped stones (barrel-shaped), impaction of stones, the location of the stones (intra hepatic, cystic duct), the Mirizzi syndrome^[3]. Staritz *et al*^[11] introduced endoscopic papillary balloon dilation as an alternative approach to EST but, despite the efficacy in CBD clearance, subsequent reports showed as this technique was related to the increased risk of severe pancreatitis (up to 15%) compared to sphincterotomy alone. In 2003 Ersoz *et al*^[6] introduced the combinations of EST and endoscopic papillary balloon dilation revolutionizing the treatment of CBD stones with successful clearance in up to 95% of patients with difficult stones. In the last years the use of EPLBD has evolved to the modern concept of DASE in which the use of this approach it is consolidated with the advantage to dilate both the papillary sphincter and distal bile duct, allowing for easy removal of the stones^[8]. In our retrospective series the technical success of DASE was more than 90% with a final successful clearance of the CBD near to 90%. These data are quite comparable to those from several studies compared EST alone with EST plus EPLBD (size of dilation was between 10 and 20 mm)^[7,12-15]. A systematic review and a recent meta-analysis^[16,17] showed, also, that the combined approach resulted effective and safe as EST alone but with a less needing in EML. Efficacy of DASE improved with increasing in stones size and resulted in low EML

Table 3 Complications after Dilation-Assisted Stone Extraction

Complications, <i>n</i> (%)	
No	98 (81.7)
Yes	22 (18.3)
Type of complications, <i>n</i> (%)	
Bleeding	11 (9.2)
Post-ERCP pancreatitis	10 (8.3)
Perforation	1 (0.8)
Timing of complications, <i>n</i> (%)	
Immediate	8 (6.7)
Within 24 h from the ERCP	11 (9.2)
After 24 h from the ERCP	3 (2.5)
Treatment of complications, <i>n</i> (%)	
Medical	13 (10.8)
Endoscopic	8 (6.7)
Surgical	1 (0.8)
Outcome of complications, <i>n</i> (%)	
Resolved	21 (17.5)
Unresolved (patient's exitus)	1 (0.8)

ERCP: Endoscopic retrograde cholangiopancreatography; DASE: Dilation-Assisted Stone Extraction.

needing, less procedure and fluoroscopy time compared to EST. In the current study only 10% of patients underwent EML due to DASE failure.

As showed in the results section DASE was used as first approach less frequently than as "second line" after stone extraction (38% vs 62%). This evidence is very interesting and it correspond to data reported by Li *et al*^[8] in which DASE was adopted not only for large stones but also for stones ≤ 12 mm difficult to remove at the first session.

In a large studied published in 1996^[18], the overall complications rate of EST was up to 10%: Pancreatitis 5.4% (0.4% severe), haemorrhage 2% (0.5% severe), cholangitis/cholecystitis 1% (0.1% severe), perforation 0.3%. Since its introduction in clinical practice, endoscopic papillary balloon dilation was categorized as one of the important causes of pancreatitis as showed by Disario *et al*^[10]. Nevertheless more recent studies disproved this evidence showing same rate of post-procedural pancreatitis comparing endoscopic papillary balloon dilation with EST^[19]. Some studies, also, reported that the risk of post-ERCP pancreatitis was related to the final diameter of the balloon with lower pancreatitis risk using a balloon ≥ 12 mm than those using a balloon ≤ 10 ^[20-23]. A randomized, controlled trial indicated that the pancreatitis risk for endoscopic papillary balloon dilation could be influenced by the dilation duration (a duration of 5 min is superior to the conventional 1-min duration)^[24]. Interestingly in this study the observed pancreatitis risk and efficacy of 5-min endoscopic papillary balloon dilation were comparable with those of EST, and the authors proposed the possible use of endoscopic papillary balloon dilation not only in selected patients (*e.g.*, patients with coagulopathy) but also in routinely treatment of CBD stones. Concerning other complications, DASE was not

related to an increased risk compared to EST alone^[8]. In Li's study ascending cholangitis was $< 1\%$ and the risk of perforation or bleeding were comparable in those treated with EST alone than in those treated with DASE. A recent meta-analysis by Xu *et al*^[25] confirmed a low rate of post-EPLBD bleeding compared to EST alone maybe because balloon compression of the sphincterotomy site during DASE can explain the low rate of bleeding.

In the current study the mean size of the balloon and the mean time of dilation were 16.7 mm and 51 s respectively with a final rate of post-ERCP pancreatitis or bleeding less than 9%. The majority of complications were immediate or early, and only 1 patient underwent surgery due to post-procedural perforation. No cholangitis/cholecystitis were recorded.

In our study elective ERCP, DASE as first approach and cannulation of major papilla followed by guidewire insertion, were related to low risk of complications. Pre-cut before DASE was related to an increased risk of complications. We can try to explain these findings: (1) patients treated electively are in better clinical condition compared to those treated as rescue therapy (*e.g.*, severe acute cholangitis increases the risk of bleeding); (2) DASE as first approach avoids "handling" of the CBD with retrieval balloon or Dormia basket reducing the risk of iatrogenic lesions or pancreatic injury; (3) cannulation of major papilla followed by guidewire insertion reduce the possibility of involuntary injection of contrast medium both in the Wirsung or submucosally in the papilla; and (4) pre-cut usually is reserved in those in which standard techniques of CBD cannulation failed so the risk of major papilla oedema or bleeding can increase.

No other variables were related to complications included ampullary/peripapillary diverticulum confirming data reported in previous published studies^[26].

The main limit of the current study, despite the interesting findings, is due to the retrospective design that can affect final results. As well know retrospective studies are typically constructed to search records that have already been collected and some data can be missing. Retrospective database would probably be less accurate and consistent than that achieved with a prospective cohort study design. In multicenter retrospective studies, also, many different healthcare professionals are involved in patient care with different endoscopic skills that can affect the final analysis.

In conclusion, DASE allowed a higher first-session success rate and can be consider a valid alternative to EST not only for bigger CBD stones. In experienced hands DASE is a safe procedure with acceptable rate of complications. In clinical practice DASE should be reserved to patients with "difficult" CBD stones and/or in those after failure of CBD clearance with retrieval balloon or Dormia basket. In patients with high risk of post-ERCP complications DASE could be used as first approach instead to second-line option after failure of

CBD. Further well-designed study are needed to assess the routinely use of DASE for CBD stone ≤ 12 mm instead EST alone, and the advent of balloon-equipped sphincterotome could explore this aspect in the near future.

COMMENTS

Background

Endoscopic papillary large-balloon dilation after endoscopic sphincterotomy resulted effective for "difficult" common bile duct (CBD) stones treatment. This endoscopic technique has gradually spread to the current Dilation-Assisted Stone Extraction (DASE), in which balloon dilation was associated to a full or partial incision of the transverse fold, enhancing stones removal and reducing the risk of complications.

Research frontiers

In patients at risk for post-endoscopic retrograde cholangiopancreatography (ERCP) complication DASE could be used as first approach instead to second-line option after failure of CBD clearance with retrieval balloon or Dormia basket.

Innovations and breakthroughs

In this study DASE was useful to manage "difficult" CBD stones not only after failure of CBD clearance with retrieval balloon or Dormia basket but also as first approach in patients at risk for post-ERCP complication. After DASE in less than $\frac{1}{4}$ of patients a complication was recorded. The majority of complications occurred during the ERCP or within 24 h, and they were resolved conservatively or endoscopically in all patients but one (1 patient underwent surgery due to post-procedural perforation).

Applications

This study suggests that DASE allowed a higher first-session success rate and can be consider a valid alternative to EST not only for bigger CBD stones. DASE is a safe procedure in experienced hands.

Terminology

DASE: Dilation-Assisted Stone Extraction is a "combined" endoscopic technique in which balloon dilation was associated to a full or partial incision of the transverse fold after endoscopic sphincterotomy.

Peer-review

It is an interesting, well written manuscript from three referral centres including 120 patients with nice outcome. It gives a novel information as well as technical details.

REFERENCES

- 1 Clayton ES, Connor S, Alexakis N, Leandros E. Meta-analysis of endoscopy and surgery versus surgery alone for common bile duct stones with the gallbladder in situ. *Br J Surg* 2006; **93**: 1185-1191 [PMID: 16964628 DOI: 10.1002/bjs.5568]
- 2 Kawai K, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. *Gastrointest Endosc* 1974; **20**: 148-151 [PMID: 4825160 DOI: 10.1016/s0015-5107(74)73914-1]
- 3 Trikudanathan G, Navaneethan U, Parsi MA. Endoscopic management of difficult common bile duct stones. *World J Gastroenterol* 2013; **19**: 165-173 [PMID: 23345939 DOI: 10.3748/wjg.v19.i2.165]
- 4 Demling L, Seuberth K, Riemann JF. A mechanical lithotripter. *Endoscopy* 1982; **14**: 100-101 [PMID: 7075559 DOI: 10.1055/s-2007-1021591]
- 5 Maple JT, Ikenberry SO, Anderson MA, Appalaneni V, Decker GA, Early D, Evans JA, Fanelli RD, Fisher D, Fisher L, Fukami N, Hwang JH, Jain R, Jue T, Khan K, Krinsky ML, Malpas P, Ben-Menachem T, Sharaf RN, Dominitz JA. The role of endoscopy in the management of choledocholithiasis. *Gastrointest Endosc* 2011; **74**: 731-744 [PMID: 21951472 DOI: 10.1016/j.gie.2011.04.012]
- 6 Ersoz G, Tekesin O, Ozutemiz AO, Gunsar F. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. *Gastrointest Endosc* 2003; **57**: 156-159 [PMID: 12556775 DOI: 10.1067/mge.2003.52]
- 7 Heo JH, Kang DH, Jung HJ, Kwon DS, An JK, Kim BS, Suh KD, Lee SY, Lee JH, Kim GH, Kim TO, Heo J, Song GA, Cho M. Endoscopic sphincterotomy plus large-balloon dilation versus endoscopic sphincterotomy for removal of bile-duct stones. *Gastrointest Endosc* 2007; **66**: 720-726; quiz 768, 771 [PMID: 17905013 DOI: 10.1016/j.gie.2007.02.033]
- 8 Li G, Pang Q, Zhang X, Dong H, Guo R, Zhai H, Dong Y, Jia X. Dilation-assisted stone extraction: an alternative method for removal of common bile duct stones. *Dig Dis Sci* 2014; **59**: 857-864 [PMID: 24254339 DOI: 10.1007/s10620-013-2914-4]
- 9 Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. *Am J Gastroenterol* 2004; **99**: 1455-1460 [PMID: 15307859 DOI: 10.1111/j.1572-0241.2004.30151.x]
- 10 Disario JA, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, Morales TG, Hixson LJ, Sherman S, Lehman GA, Jamal MM, Al-Kawas FH, Khandelwal M, Moore JP, Derfus GA, Jamidar PA, Ramirez FC, Ryan ME, Woods KL, Carr-Locke DL, Alder SC. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004; **127**: 1291-1299 [PMID: 15520997 DOI: 10.1053/j.gastro.2004.07.017]
- 11 Staritz M, Ewe K, Meyer zum Büschenfelde KH. Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy. *Lancet* 1982; **1**: 1306-1307 [PMID: 6123047 DOI: 10.1016/S0140-6736(82)92873-2]
- 12 Kim HG, Cheon YK, Cho YD, Moon JH, Park DH, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304 [PMID: 19750573 DOI: 10.3748/wjg.15.4298]
- 13 Kim TH, Oh HJ, Lee JY, Sohn YW. Can a small endoscopic sphincterotomy plus a large-balloon dilation reduce the use of mechanical lithotripsy in patients with large bile duct stones? *Surg Endosc* 2011; **25**: 3330-3337 [PMID: 21533521 DOI: 10.1007/s00464-011-1720-3]
- 14 Tsuchida K, Iwasaki M, Tsubouchi M, Suzuki T, Tsuchida C, Yoshitake N, Sasai T, Hiraishi H. Comparison of the usefulness of endoscopic papillary large-balloon dilation with endoscopic sphincterotomy for large and multiple common bile duct stones. *BMC Gastroenterol* 2015; **15**: 59 [PMID: 25980964 DOI: 10.1186/s12876-015-0290-6]
- 15 Guo Y, Li C, Lei S, Zhi F. Effects Comparison between Endoscopic Papillary Large Balloon Dilatation and Endoscopic Sphincterotomy for Common Bile Duct Stone Removal. *Gastroenterol Res Pract* 2015; **2015**: 839346 [PMID: 26351452 DOI: 10.1155/2015/839346]
- 16 Jin PP, Cheng JF, Liu D, Mei M, Xu ZQ, Sun LM. Endoscopic papillary large balloon dilation vs endoscopic sphincterotomy for retrieval of common bile duct stones: a meta-analysis. *World J Gastroenterol* 2014; **20**: 5548-5556 [PMID: 24833886 DOI: 10.3748/wjg.v20.i18.5548]
- 17 Madhoun MF, Wani S, Hong S, Tierney WM, Maple JT. Endoscopic papillary large balloon dilation reduces the need for mechanical lithotripsy in patients with large bile duct stones: a systematic review and meta-analysis. *Diagn Ther Endosc* 2014; **2014**: 309618 [PMID: 24729674 DOI: 10.1155/2014/309618]
- 18 Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]
- 19 Lai KH, Chan HH, Tsai TJ, Cheng JS, Hsu PI. Reappraisal of endoscopic papillary balloon dilation for the management of common bile duct stones. *World J Gastrointest Endosc* 2015; **7**: 77-86 [PMID: 25685263 DOI: 10.4253/wjge.v7.i2.77]

- 20 **Attasaranya S**, Cheon YK, Vittal H, Howell DA, Wakelin DE, Cunningham JT, Ajmere N, Ste Marie RW, Bhattacharya K, Gupta K, Freeman ML, Sherman S, McHenry L, Watkins JL, Fogel EL, Schmidt S, Lehman GA. Large-diameter biliary orifice balloon dilation to aid in endoscopic bile duct stone removal: a multicenter series. *Gastrointest Endosc* 2008; **67**: 1046-1052 [PMID: 18178208 DOI: 10.1016/j.gie.2007.08.047]
- 21 **Minami A**, Hirose S, Nomoto T, Hayakawa S. Small sphincterotomy combined with papillary dilation with large balloon permits retrieval of large stones without mechanical lithotripsy. *World J Gastroenterol* 2007; **13**: 2179-2182 [PMID: 17465497 DOI: 10.3748/wjg.v13.i15.2179]
- 22 **Youn YH**, Lim HC, Jahng JH, Jang SI, You JH, Park JS, Lee SJ, Lee DK. The increase in balloon size to over 15 mm does not affect the development of pancreatitis after endoscopic papillary large balloon dilatation for bile duct stone removal. *Dig Dis Sci* 2011; **56**: 1572-1577 [PMID: 20945093 DOI: 10.1007/s10620-010-1438-4]
- 23 **Li NP**, Liu JQ, Zhou ZQ, Ji TY, Cai XY, Zhu QY. Ampulla dilation with different sized balloons to remove common bile duct stones. *World J Gastroenterol* 2013; **19**: 903-908 [PMID: 23431070 DOI: 10.3748/wjg.v19.i6.903]
- 24 **Liao WC**, Lee CT, Chang CY, Leung JW, Chen JH, Tsai MC, Lin JT, Wu MS, Wang HP. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. *Gastrointest Endosc* 2010; **72**: 1154-1162 [PMID: 20869710 DOI: 10.1016/j.gie.2010.07.009]
- 25 **Xu L**, Kyaw MH, Tse YK, Lau JY. Endoscopic sphincterotomy with large balloon dilation versus endoscopic sphincterotomy for bile duct stones: a systematic review and meta-analysis. *Biomed Res Int* 2015; **2015**: 673103 [PMID: 25756050 DOI: 10.1155/2015/673103]
- 26 **Kim HW**, Kang DH, Choi CW, Park JH, Lee JH, Kim MD, Kim ID, Yoon KT, Cho M, Jeon UB, Kim S, Kim CW, Lee JW. Limited endoscopic sphincterotomy plus large balloon dilation for choledocholithiasis with periampullary diverticula. *World J Gastroenterol* 2010; **16**: 4335-4340 [PMID: 20818818 DOI: 10.3748/wjg.v16.i34.4335]

P- Reviewer: Amornyotin S, Neri V, Pavlidis TE **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL



Observational Study

Recommendations to quantify villous atrophy in video capsule endoscopy images of celiac disease patients

Edward J Ciaccio, Govind Bhagat, Suzanne K Lewis, Peter H Green

Edward J Ciaccio, Govind Bhagat, Suzanne K Lewis, Peter H Green, Celiac Disease Center, Department of Medicine, Columbia University Medical Center, New York, NY 10032, United States

Govind Bhagat, Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY 10032, United States

Author contributions: Ciaccio EJ did the quantitative analyses and wrote the manuscript; Bhagat G, Lewis SK, Green PH reviewed the manuscript and made corrections; Lewis SK provided the clinical data.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board, Columbia University Medical Center.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Edward J Ciaccio, PhD, Celiac Disease Center, Department of Medicine, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, United States. ciaccio@columbia.edu
Telephone: +1-212-3055447
Fax: +1-212-3420447

Received: April 13, 2016

Peer-review started: April 18, 2016

First decision: May 19, 2016

Revised: June 15, 2016

Accepted: August 15, 2016

Article in press: August 16, 2016

Published online: October 16, 2016

Abstract

AIM

To quantify the presence of villous atrophy in endoscopic images for improved automation.

METHODS

There are two main categories of quantitative descriptors helpful to detect villous atrophy: (1) Statistical and (2) Syntactic. Statistical descriptors measure the small intestinal substrate in endoscope-acquired images based on mathematical methods. Texture is the most commonly used statistical descriptor to quantify villous atrophy. Syntactic descriptors comprise a syntax, or set of rules, for analyzing and parsing the substrate into a set of objects with boundaries. The syntax is designed to identify and distinguish three-dimensional structures based on their shape.

RESULTS

The variance texture statistical descriptor is useful to describe the average variability in image gray level representing villous atrophy, but does not determine the range in variability and the spatial relationships between regions. Improved textural descriptors will incorporate these factors, so that areas with variability gradients and regions that are orientation dependent can be distinguished. The protrusion syntactic descriptor is useful to detect three-dimensional architectural components, but is limited to identifying objects of a certain shape. Improvement in this descriptor will require incorporating flexibility to the prototypical

template, so that protrusions of any shape can be detected, measured, and distinguished.

CONCLUSION

Improved quantitative descriptors of villous atrophy are being developed, which will be useful in detecting subtle, varying patterns of villous atrophy in the small intestinal mucosa of suspected and known celiac disease patients.

Key words: Celiac disease; Endoscopy; Small intestine; Video capsule; Villous atrophy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Celiac disease is a relatively common ailment throughout the world, affecting approximately 1% of the population. Yet, it is little known and rarely diagnosed. Untreated, it can lead to severe intestinal disturbance, cancer, neurological problems, fertility problems, and other disorders. Villous atrophy of the small intestine is often present in untreated celiac patients. Better quantitative image analysis is important to detect areas of pathology in the small intestine endoscopically. In this study the main approaches for automatically detecting villous atrophy by computerized means are described, which can be helpful to map areas of pathology and determine disease status.

Ciaccio EJ, Bhagat G, Lewis SK, Green PH. Recommendations to quantify villous atrophy in video capsule endoscopy images of celiac disease patients. *World J Gastrointest Endosc* 2016; 8(18): 653-662 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/653.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.653>

INTRODUCTION

Celiac disease is prevalent throughout the entire world, though it varies in frequency, and averages about 1% of the population^[1]. An important clinical problem is that the definitive diagnosis of celiac disease is difficult and requires serologic testing and endoscopy with biopsy, which is not available with accuracy in all areas of the world. Therefore geographic regions with lesser frequencies of celiac disease may simply be regions with a lack of experience in diagnosis and/or areas without the facilities necessary for definitive diagnosis^[2]. The presence of villous atrophy of the small intestinal mucosa, which is determined by examining biopsy slides under light microscopy^[3], may not always be evident in untreated celiac disease patients. Present in the digitized biopsy slides are villous protrusion features, which are blunted in villous atrophy as compared to those found in healthy tissue^[4]. Careful orientation of the biopsy on the slides and their proper examination is crucial, since off angle villi can erroneously appear blunted, mimicking villous atrophy^[5]. Thus the experience of the

pathologist is very important for accurate diagnosis of celiac disease.

Typically, villous atrophy is found in untreated celiac patients at the level of the duodenal bulb and the descending duodenum^[6], but may also be present at the more distal regions of the small intestine, the jejunum and ileum, and be absent more proximally. The presence of villous atrophy tends to be patchy and is interspersed with regions of normal mucosa^[7]. The mucosal abnormalities may be subtle or may even be lacking in images acquired with standard or video endoscopic techniques, due to the limits of resolution and the interpretation of microscopic changes of the intestinal villi, as manifested in the macroscopic image content. Though, more recently-developed high resolution endoscopes may overcome some problems with identification of mucosal structure^[8].

During the last decade video capsule endoscopy has been used to image the entire small intestine with improved spatial resolution^[9]. The video capsule is convenient to use for both adult and pediatric patients suspected of having celiac disease, because it is minimally invasive^[10]. The capsule is swallowed and the video camera contained within the capsule snaps images at the rate of 2 per second or more^[11]. The more recent video capsules have a variable frame rate, increasing in rate as the capsule motion increases, when presumably it is moving along the lumen at a faster rate, and decreasing when the capsule motion slows^[12]. This ensures a more uniform frame rate per unit distance that the capsule travels. As the spatial and temporal resolution of recently commercially available video capsules has increased, it has been proposed that the series of video images can possibly be used to map the presence of villous atrophy all along the small intestinal length.

Prior research has suggested that there are differences in the video capsule endoscopy images of untreated celiac patients vs a control population^[13-19]. Images from untreated celiac patients tend to be less structurally uniform both within a particular image, and across a series of images, as compared with control subjects^[13-19]. In Figure 1, normal images at the top have uniform appearance and smooth folds. The celiac patient images at bottom were acquired from areas where villous atrophy was present, and have a mottled appearance, due to fissuring, and scalloping of the mucosal folds. These differences suggest the possibility that the presence of villous atrophy can be detected and mapped in a sequential series of video capsule images by computerized means. If areas of villous atrophy could be detected and mapped automatically all along the small intestinal tract, it would potentially be very helpful in the diagnosis of celiac disease. It would also be useful to monitor the progress in treatment of celiac disease. Currently, the only treatment is a lifelong gluten free diet^[20]. When the patient goes on the diet, the villi heal, albeit slowly^[21]. Sometimes however, villous atrophy persists. Thus automated monitoring and mapping of

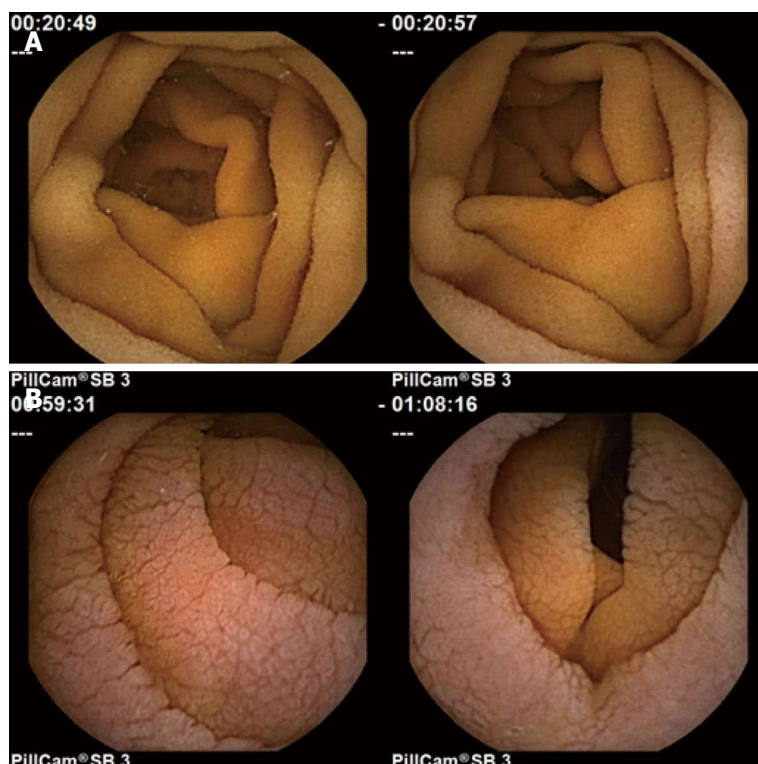


Figure 1 Normal (A) vs untreated celiac patient images (B). Note the presence of mucosal folds, a mottled appearance, and fissuring, in the images from untreated celiac patients (lower).

the location and severity of villous atrophy throughout the small intestine would be very useful. In this work, we describe the main modes of quantitative detection of villous atrophy from video capsule endoscopic images, and possible avenues to improve the detection rate and to better monitor the severity and types of pathology present in endoscopic images which are abnormal due to the presence of villous atrophy. The current detection of villous atrophy is determined by an experienced observer. This introduces bias based on observer experience and knowledge and possibly fatigue. These would be obviated by computerized techniques.

MATERIALS AND METHODS

Statement of the quantitative problem

For quantitative endoscopic image analysis in suspected or known celiac disease patients, it is important to detect areas of villous atrophy that may be present in the small intestinal mucosa. This is still mostly an unsolved problem. It is difficult to detect villous atrophy in part because the spatial resolution of the video capsule system from which discretized images are obtained is limited, and does not in every case clearly detect the individual villi in the small intestinal wall. The resolution in part depends on the video camera to intestinal wall distance, the camera lighting, and the camera angle, and is at best about 1 mm^[17]. All of the factors for which resolution is determined are variable and tend to be random. Thus the identification of small intestinal villi, and the detection and quantification of villous atrophy, poses an important quantitative medical research problem, and a dilemma in terms of selecting the best method for recognition of the villi, and for estimation of

whether or not there are normal or abnormal villi present in the image, as well as the degree and severity of areas of pathology.

Textural methods

To recognize abnormalities in endoscopic images, many investigators have used textural methods in part because of their simplicity and ease of use, as well as being a tried and true method of analysis^[13-19]. Several helpful methods have been developed to describe the presence of villous atrophy as a set of textural features. Image textures can be measured locally using the wavelet operator and a local binary pattern^[22]. It is possible to develop a set of scale invariant texture descriptors by utilizing wavelet analysis^[23]. Over a series of images, texture can be defined by the presence of salient features that tend to reappear from one image to the next. This is illustrated in Figure 2. The panels are composed of basis images - images that contain the most salient features over a series of images acquired from the same patient. At bottom is shown four basis images from a patient with normal villi at the level of the duodenum. The appearance of these basis images is mostly smooth and uniform. The upper basis images were constructed from a series of images acquired from a celiac patient with villous atrophy. Sharp lines resembling actual fissures, as well as highly varied shading and texture is present in each of the basis images. The original images used to make the celiac basis images were highly varied in terms of the number and type of features with differing texture that were present.

For automation of textural properties and their locations in endoscopic images, texture can be defined

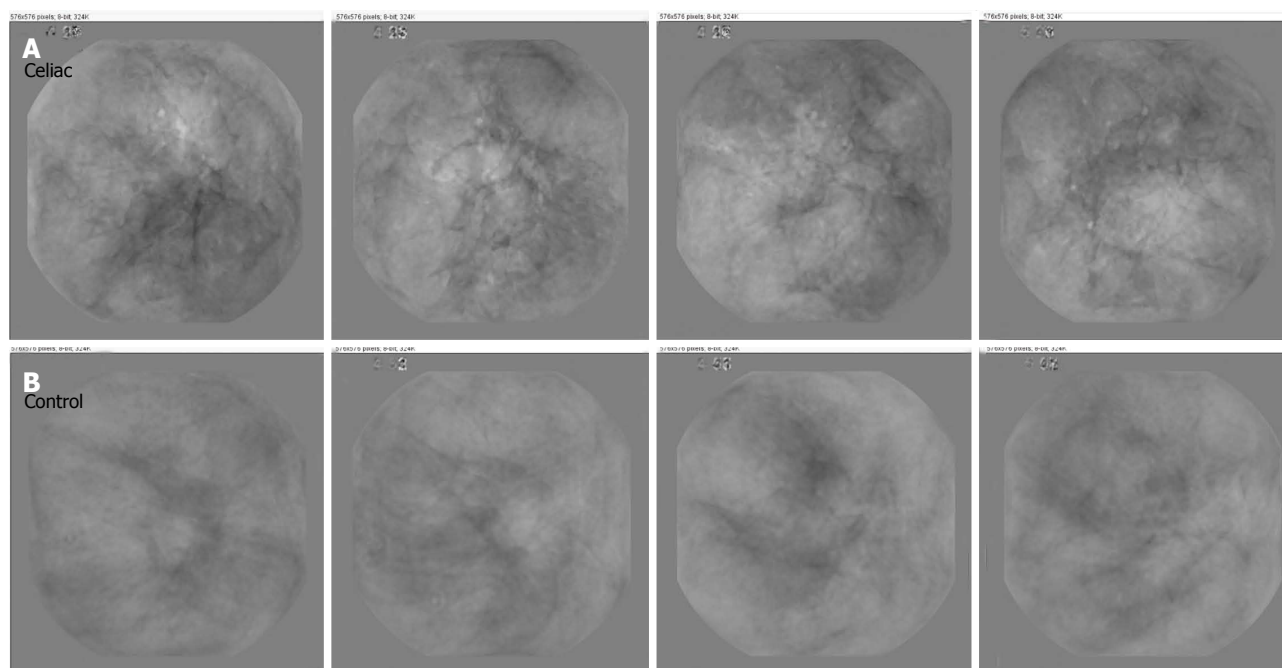


Figure 2 Evidence of more prominent fissuring is present in untreated control images (B) as compared with celiac basis images (A). The basis images are modified from a series of original endoscopic images so that salient features are enhanced.

quantitatively as the value of a statistical measurement of color or grayscale digital image level. For simplicity in initial prior investigations, endoscopic color images were typically reduced to gray level images, with the gray level ranging from 0 (black) - 255 (white)^[13-19]. Values between 1 and 254 inclusive are successively brighter gray shades. For endoscopic image analysis, texture is then determined by measuring and quantifying the gray level of all pixels in an image, or of a subset of pixels in the image. All image pixels are analyzed as a group if one would like to make a broad statement about the image as a whole, and/or to compare successive image frames, *i.e.*, successive time epochs. For video capsule image analysis, successive frames will approximate the movement of the capsule along the gastrointestinal tract. However, because the capsule movement is passive and not likely to be at a constant rate, those successive images will likely represent uneven distances along the gastrointestinal system. The older imaging systems tended to have a fixed frame rate of 2 frames per second^[24]. Newer systems having a variable frame rate^[25] should be taken into account when considering successive image frames.

The simplest statistical measure of texture is the average or mean grayscale level (designated μ). To determine this value for the entire image, the grayscale level of all pixels is averaged. A typical digital endoscopic image will have a size of 576×576 pixels = 331776 pixels^[4]. Thus by summing the values of grayscale levels for all pixels and dividing by 331776, the mean level is obtained. The mean level of one image can have significance in several ways. Firstly it can be compared from one patient to another or from one level of the small intestine to another in the same

patient. When the images are darker, it may signify the presence of darker structures in the substrate, though it can also be due to the presence of a darker shade in the mucosal wall. If darker structures are present in the substrate, these can represent a highly variable three-dimensional topography. For example, when villous atrophy is present, there tends to be fissuring of the small intestinal mucosa. The fissures appear as dark lines in the two-dimensional images, due to the fact that they are deeper within the mucosa and further from the video camera and its light source. The fissures can be variable in length, depth, and breadth (Figure 1, lower panels). They are often random in orientation. Their presence tends to render the image darker in overall gray level. Another phenomenon that tends to signify the presence of villous atrophy is a mottled appearance in the two-dimensional images (Figure 1, lower panels). The mottled appearance can result from the presence of mucosal protrusions of varying height. These protrusions have been proposed to be clumps of villi which have become atrophied and shortened in length^[18,19]. Since the three-dimensional mucosal architecture is therefore uneven, camera and light source distance are important factors for imaging mucosal protrusions. Areas of lower elevation in the images will be partly obscured and shadowed by higher areas and thus appear substantially darker. The average grayscale level may thus decrease when there is mottling of the mucosal surface. Over a short succession of image frames, a high degree of variability in the mean grayscale level would likely indicate the presence of patchy villous atrophy^[26], which is common in celiac disease patients. Lesser variability at more distal regions of the small intestine would be indicative of a lesser

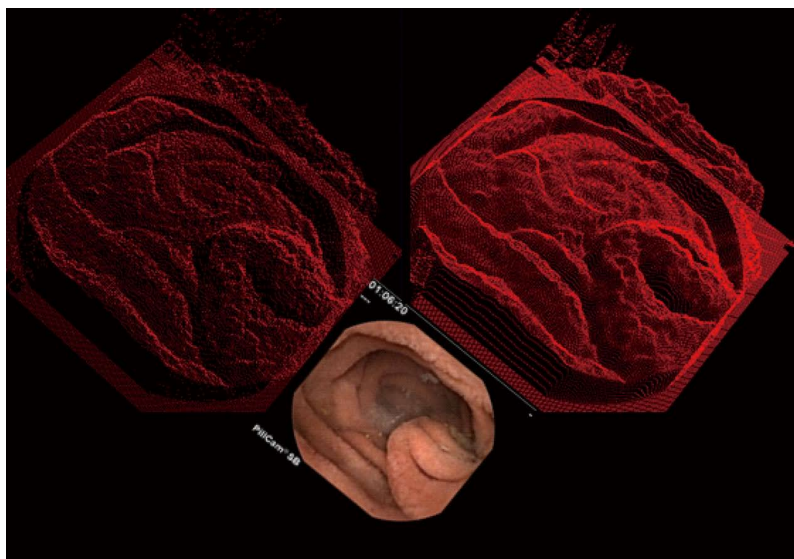


Figure 3 Shape-from-shading is used to render two-dimensional endoscopic images (lower panel) into three-dimensional constructs. First the color image is converted to grayscale. Then the degree of pixel brightness is linearly interpreted as depth in the constructs at top. Lighter areas in the lower image appear as taller protrusions in the images at top. Top left: Half resolution three-dimensional reconstruction; Top right: Full resolution three-dimensional reconstruction.

presence of villous atrophy and a more uniform, more normal mucosal surface, which is normally the case in untreated celiac disease patients. These patients tend to have the greatest presence of villous atrophy, which is patchy, at the level of the duodenal bulb and in the distal duodenum, and lesser degrees of villous atrophy in the jejunum and in the ileum^[27]. When a comparison between celiac patients is made, darker mean grayscale level would be expected to indicate the presence of a greater degree of villous atrophy, though this hypothesis has yet to be proven. Likewise, when the same patient is compared at follow-up after starting the gluten free diet, it would be anticipated that a lighter average grayscale level would signify diminishing levels of villous atrophy.

A second main measure of image texture, and perhaps the most important to current systems used for quantitative analysis, is the second central moment, or variance (σ)^[13,14]. Its positive square root is the standard deviation. This moment is a measure of the spread of the distribution of grayscale levels. A larger value of σ indicates greater range of gray shading about the mean level. The standard deviation or variance from the mean pixel level has been used as a textural feature to measure the variability in brightness of image features^[13,14]. When more features are present with different brightness levels, for example when fissuring is evident as a series of many dark lines in the image, the standard deviation increases. Likewise, a mottled image appearance due to villous atrophy will cause an increase in the standard deviation of grayscale image brightness.

Although not currently implemented, higher-order textural measurements that are potentially useful for quantitative analysis of villous atrophy include the third central moment or skewness (γ) and the fourth central moment or kurtosis (κ). The skewness is an estimate of the degree of lopsidedness in the pixel grayscale distribution about the mean value. It can be helpful to detect spatial non-uniformity in the image brightness. For example if clumps of villi which have atrophied are

present, they will be rendered as blunted protrusions, with a large darker surface area in the image^[18]. This would skew the distribution toward the darker gray level pixel values. The kurtosis is a measure of the heaviness of the tail of the distribution, *i.e.*, how many very bright or very dark pixels are present in the image compared to the rest of the grayscale level values. The kurtosis measurement can therefore be assistive in detecting the presence of numerous very bright or very dark components of the endoscopic image space. These components can include small patches of normal tissue (bright) in areas of villous atrophy, and/or areas with fissuring (dark) among more normal villi.

Syntactic or structural methods

Syntactic methods are a way to model tissue structure based upon a set of prototypical or primitive features. For syntactic analysis, three-dimensional tissue structure should be generated, and can be studied by using shape-from-shading principles as shown in Figure 3. Areas of the original two-dimensional endoscopic image that are bright (lower panel) are converted into a height to render the object in three dimensions (top panels). It is evident in the top panels that the small intestinal mucosa consists of a series of mucosal protrusions. These mucosal protrusions can be modeled as a set of concentric, circular rings or squares (Figure 4). Using this syntactic model, a protrusion is detected when the average grayscale value within the ring or square is above a predefined threshold grayscale level. Based on shape-from-shading principles^[18,19], the mucosal protrusion will appear as a bright spot in the endoscopic image. The outer edges of the spot will be a darker grayscale level, while the inner components will be manifested as progressively brighter pixels. At the pinnacle or center of the protrusion, the brightest grayscale level will occur. This phenomenon is based upon the camera light source to protrusion distance. The pinnacle of the protrusion extends furthest from the mucosal surface, and is therefore closest to the

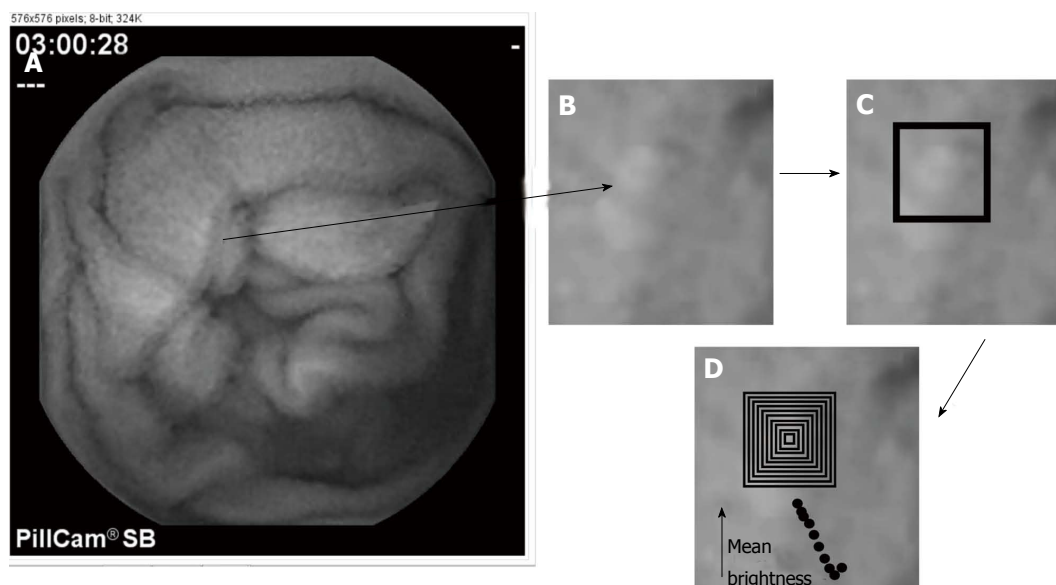


Figure 4 Example of the construction of a syntactic prototypical template. A: Video capsule endoscopic image in grayscale; B: Area with bright center is noted by the arrow; C: A square is used to identify the area of a protrusion; D: The series of concentric squares (rings) are used to determine the protrusion dimensions. The average pixel brightness diminishes from center square to outer square. The width and length of the protrusion is defined based on the outermost square, which is that square after which a larger concentric outer square would have an increased brightness. The height of the protrusion is the difference in brightness level from its center to its outermost concentric square.

video camera lens, which is constrained within the small intestinal lumen as it travels distally. The inverse square law of light states that the light intensity per unit area falling on the mucosal surface will vary in inverse proportion to the square of the distance from the light source. There are nonlinearities imposed on the model, but prior findings have suggested that the approximation is sufficiently accurate to render the two-dimensional image features as three-dimensional constructs which represent actual tissue structure^[18,19]. Likewise, the base of the protrusion will appear darkest since it will be furthest from the camera lens. Taller protrusions will appear in endoscopic images as having brighter central regions due to the inverse square law, and *vice versa* for blunter protrusions. Wider protrusions will appear as image features having longer spatial gradients, from darker pixel areas in the outer portions to brighter pixel regions at the center area. Conversely, narrower protrusions will have sharper spatial gradients, from darker pixel regions at outer edge to the brighter central core in endoscopic images.

The evident three-dimensional mucosal protrusions (Figure 3) can be modeled in the two-dimensional endoscopic images based upon a fixed or flexible template (Figure 4). The simplest modeling method is to use a fixed template. For example, a protrusion can be modeled, and its architectural parameters can be determined, using a concentric series of square or circular shapes, or rings, as alluded to earlier in the text. The algorithm can be stated as follows. Each outlying shape can be made one pixel wide as a first approximation. The width of a mucosal protrusion would then be determined as follows. The average grayscale level of the image pixels

overlapping each ring is first calculated. The brightest ring will be at the center of the protrusion, since it is highest and closest to the camera lens. Successive concentric rings in the outward direction will be darker in gray shade since the protrusion falls off in amplitude there and is further from the camera lens. The base of the protrusion is syntactically defined as the outermost ring that is still diminished in average grayscale level with respect to the adjacent, more inwardly located ring. Thus, the width of the protrusion is obtained, as is shown in Figure 4. To convert the protrusion width from pixels to millimeters would require knowing the camera lens to mucosal surface distance, which can be estimated. Alternatively, mucosal protrusion width can be measured in pixel units, which is the simplest form of this syntactic model. The height of the protrusion would be the difference in average grayscale levels from the innermost to the outermost ring defining the protrusion.

To better syntactically detect mucosal protrusions, a tolerance can be added so that architectures with slightly asymmetrical features, having a less rounded or square form, depending on the model being used, would still be detected as a protrusion. So for example, if an outer ring is only slightly brighter as compared to its inner neighbor, the base of the protrusion would not yet be considered to be reached. Subsequent outer rings would be counted as part of the mucosal protrusion, until arriving at a ring at which a sharp increase in average brightness is noted. Changing the tolerance would enable more or less candidate protrusions to be detected in the image, and with greater accuracy.

Once mucosal protrusions are detected, their statistics can be analyzed^[18,19]. For example, the total number

of protrusions per endoscopic image can be calculated. The mean and variance in the width of the detected protrusions can be determined. And the mean and variance in the height of the detected protrusions can be computed. Greater variance in protrusion dimensions will likely indicate the presence of patchy villous atrophy. Decreased mean height and increased mean width would be suggestive of clumping of the villi, and therefore would be indicative of the presence of greater degrees of villous atrophy.

Another prominent macroscopic feature that is manifested when villous atrophy is present in the small intestinal mucosa that can be modeled syntactically is fissuring. Fissures are areas of the small intestinal mucosa that are devoid of villi. Thus architecturally, they can be described as valleys that are areas in the mucosa which are at greater depth with respect to camera lens location. They will appear in endoscopic images as dark lines of varying length and width^[4,28]. Pixels of darker gray shading represent the fissured areas. One way to model the presence of fissures syntactically is to parse a linear region of darker pixels with a fixed length and width. As was described above for the modeling of mucosal protrusions, the fissures can be detected with the incorporation of a tolerance factor. The syntactic parameters in which a tolerance could be added would be the width, length, and brightness of each fissure. If the model parameters were say, width = 3 pixels, length = 10 pixels, and brightness = gray level 50/255, then tolerances could be imposed of for example ± 1 pixel and ± 10 grayscale levels. If the tolerance is made too small however, many actual fissures can be missed, and if the tolerance is made too large, structures that are not actually fissures may be detected.

Fissuring of the small intestinal mucosa due to villous atrophy does not appear to be dependent on factors such as muscle fiber orientation, and is more or less random^[29]. Thus the fissure syntactic template, although it can be fixed for the length, width, and brightness parameters, needs to be flexible with respect to the orientation parameter. One way to implement this is simply to orient the model fissure at various predefined angles, at a particular location, and determine whether or not there is a satisfactory match of any orientation with the actual pixel content in the image. More orientations used for comparison would enable better detection of any fissure that is present, but at the expense of longer computation time. To reduce computation time, the image can be skeletonized. This is a standard processing technique in which image features are converted to a series of line structures which represent the central locations along each segment of the feature. The line structures in the skeletonized images can each be converted into a straight line approximation using linear regression analysis, and the angle of the straight line is then readily calculated. The prototypical template is then oriented according to the calculated angle of the structure, and a fissure is detected if the actual structure has similar length, width and brightness as the model, to

within the specified tolerance.

Another structure that is often evident in images where villous atrophy is present, which can be modeled syntactically, is the scalloping of mucosal folds. This is a phenomenon in which the edges of the folds become scalloped - consisting of repeated structures with a rounded appearance, which are often of similar size^[30,31]. To syntactically model the presence of scalloping, curved structures with similar brightness should be developed. The scalloping generally appears on edge as the camera viewing angle is toward distal regions along the small intestinal lumen. Thus the scalloped edges along each fold will appear to have similar brightness, as well as similar size and shape. The parameters for modeling the curved structure of each scallop would therefore be the width and height in terms of the number of pixels, and the degree of curvature.

The presence of a mottled appearance in endoscopic images can be modeled as a series of light and dark patches, with the length and width of the patches tailored to fit the observations of actual mottled areas found in exemplar images. It would be anticipated, as a first approximation, that the light and dark patches of mottled regions would be symmetric, and therefore have similar or the same length and width parameter values. The actual shape of each light and dark patch could be modeled as circular or square as a first estimate, with the use of tolerance to detect any mottled components with a more irregular shape. The construction of a small prototype would be useful to detect mottled regions, and by sliding this prototypical template about the image using a computer algorithm, and correlating template to image at each window location, the extent of the mottled region can then be determined.

RESULTS

In this work, several currently proposed methods were described for the detection and measurement of villous atrophy in the small intestinal mucosa by means of quantitative analysis of video capsule images. These methods can be subdivided into statistical and syntactic types of analyses. Both types of analyses seek to automatically detect abnormalities in the endoscopic images. The statistical methods are useful to analyze the entire image, or to analyze predefined portions of it, and to determine whether the statistics are substantially different with respect to control images. Statistical parameters can be compared from one segment, or subimage, to another in a particular endoscopic image, as well as from one endoscopic image to the next over a series of images, as they are obtained from the video capsule when it progresses along the small intestinal lumen. Using a threshold level for each statistical parameter, it is possible to automatically detect the presence of abnormal image regions and/or abnormal locations along the small intestinal lumen over a time lapse sequence of video capsule endoscopic images. Furthermore, the presence of gradients with varying

statistics, either along a single image or across a series of video capsule images, can possibly be detected and measured, though this must be shown in future work. Such gradients would be expected to be indicative of the presence of patchy villous atrophy in celiac patients. The resolution of the statistical measures is limited only by the video camera resolution, which has been steadily improving in recent years^[32].

DISCUSSION

Summary

The advantages of syntactic or structural methods to detect the presence of villous atrophy were also described herein. Syntactic methods seek to model the structure of the small intestinal lumen based upon the presence of abnormal image features, which are indicative of pathology. Although actual villi located within the small intestine are difficult to detect at the current spatial resolution of video capsule camera systems, the manifestation of villous atrophy as structures in the small intestinal mucosa includes the presence of blunted protrusions, fissures, scalloped mucosal folds and a mottled or mosaic appearance of the mucosa. These structures are macroscopic, unlike the microscopic nature of the villi themselves, and can be detected by using appropriate prototypical templates. For simplicity, prototypical templates with fixed parameters can be used, with a tolerance added to all template parameters, so that features which are slightly out of proportion can still be detected. Once abnormal features are detected, they can be analyzed in terms of their density, shape and gray level characteristics, and gradients across individual endoscopic images and along a sequence of images can be determined.

Based on the above measures, automatic detection of regions with pathology indicative of villous atrophy in untreated celiac disease patients may soon be realized, even when the pathology is subtle or variable, and patchy in appearance. By mapping these structures, it would be possible to determine the extent of the pathology, and the change in pathologic region and content during the treatment of the disease.

Other methods

Although the methods described herein were limited to analysis of video capsule endoscopy images, other techniques can be used to potentially improve the detection of pathologic features. In the method of chromoendoscopy, dyes are sprayed onto the mucosal surface *via* a working channel of the endoscope to enable detailed evaluation of the mucosal surface at high magnification^[33]. Fujinon intelligent chromoendoscopy assisted capsule endoscopy is useful to evaluate patients with obscure gastroenterology bleeding^[34,35]. Furthermore, narrow-band imaging is capable of predicting the histological characteristics such as those present in gastric cancer lesions^[36]. Optical coherence tomography has been found useful for noninvasive cross-sectional imaging in

biological systems^[37]. The water-immersion technique may be utilized to minimize patient discomfort and to minimize the need for sedation in children and adults^[38]. Confocal laser endomicroscopy is a technique that involves a miniaturized confocal microscope, and was initially developed and integrated in the distal tip of a conventional colonoscope^[39,40]. High-resolution magnification endoscopy can reliably identify normal vs atrophic mucosal regions^[41]. I-scan technology consists of three types of algorithms: Surface enhancement, contrast enhancement, and tone enhancement, and can lead to easier detection, diagnosis and treatment of gastrointestinal diseases^[42].

Limitations

Currently, video capsule endoscopic imaging is constrained in several respects. Firstly, the images depend upon camera angle with respect to the small intestinal lumen, as well as on the illumination by the camera light source. Poor camera angle can result in an incorrect interpretation of the presence and degree of pathology. Furthermore, for syntactic analysis, the rendering of two-dimensional endoscopic images as three-dimensional constructs depends upon the inverse square law for light illumination, but nonlinearities may be introduced during the process. The nonlinearities can distort the actual small intestinal features and their dimensions, as observed using shape-from-shading principles. The spatial resolution of each image depends on the camera lens to small intestinal mucosal surface distance, which is variable from image to image and even in a single image, whenever the camera angle to mucosal surface angle is not normal, *i.e.*, the light source is not pointed precisely perpendicular to the mucosal surface. For quantitative analysis, color images are typically converted to grayscale level for simplicity. For improved analysis, use of the tricolor image information may be helpful to detect subtle features of villous atrophy, a subject for future investigation.

COMMENTS

Background

This research is of potential importance to treat celiac disease, a common malady. The main symptom used to diagnose villous atrophy is the presence of villous atrophy in the small intestine. The villous atrophy can be subtle and patchy; therefore computerized means may be better at detecting and assessing the severity.

Research frontiers

Quantitative research on analysis of celiac disease using video capsule endoscopy is a new field. Only for the last 12 or so years has this technology been available. In recent versions, time and spatial resolution is markedly improving so that subtle details can be observed without the need for light microscopy.

Innovations and breakthroughs

The use of the video capsule is an improvement over standard endoscopy, because it travels throughout the gastrointestinal tract, not just at the proximal portions. It is also less invasive to the patient and can be used for pediatric patients.

Applications

This methodology could possibly be used with online video capsule software to detect villous atrophy as the capsule travels passively along the gastrointestinal tract. In future manifestations, should biopsy become available, a biopsy could be taken at each region in which villous atrophy is detected.

Terminology

Celiac disease is an autoimmune disease in which the patient is reactive to the protein gluten, which is found in wheat, rye, and barley grains. A video capsule is a device with camera which takes images at 2 frames or more per second and transmits them via radio link as it passes through the gastrointestinal tract.

Peer-review

This study was peer-reviewed by both clinical specialists and bioengineering specialists. The reviews were generally quite favorable. Improvements have been made in describing the data analysis and clinical setting.

REFERENCES

- Green PH, Jabri B. Celiac disease. *Annu Rev Med* 2006; **57**: 207-221 [PMID: 16409146 DOI: 10.1146/annurev.med.57.051804.122404]
- Cataldo F, Montalto G. Celiac disease in the developing countries: a new and challenging public health problem. *World J Gastroenterol* 2007; **13**: 2153-2159 [PMID: 17465493]
- Dickson BC, Streutker CJ, Chetty R. Coeliac disease: an update for pathologists. *J Clin Pathol* 2006; **59**: 1008-1016 [PMID: 17021129 DOI: 10.1136/jcp.2005.035345]
- Ciaccio EJ, Bhagat G, Tennyson CA, Lewis SK, Hernandez L, Green PH. Quantitative assessment of endoscopic images for degree of villous atrophy in celiac disease. *Dig Dis Sci* 2011; **56**: 805-811 [PMID: 20844959 DOI: 10.1007/s1062001013716]
- Corazza GR, Villanacci V, Zambelli C, Milione M, Luinetti O, Vindigni C, Chioda C, Albarello L, Bartolini D, Donato F. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. *Clin Gastroenterol Hepatol* 2007; **5**: 838-843 [PMID: 17544877 DOI: 10.1016/j.cgh.2007.03.019]
- Gonzalez S, Gupta A, Cheng J, Tennyson C, Lewis SK, Bhagat G, Green PH. Prospective study of the role of duodenal bulb biopsies in the diagnosis of celiac disease. *Gastrointest Endosc* 2010; **72**: 758-765 [PMID: 20883853 DOI: 10.1016/j.gie.2010.06.026]
- Lee SK, Green PH. Endoscopy in celiac disease. *Curr Opin Gastroenterol* 2005; **21**: 589-594 [PMID: 16093775]
- Penny HA, Mooney PD, Burden M, Patel N, Johnston AJ, Wong SH, Teare J, Sanders DS. High definition endoscopy with or without IScan increases the detection of celiac disease during routine endoscopy. *Dig Liver Dis* 2016; **48**: 644-649 [PMID: 26995214 DOI: 10.1016/j.dld.2016.02.009]
- Bouchard S, Ibrahim M, Van Gossum A. Video capsule endoscopy: perspectives of a revolutionary technique. *World J Gastroenterol* 2014; **20**: 17330-17344 [PMID: 25516644 DOI: 10.3748/wjg.v20.i46.17330]
- Van Weyenberg SJ, Smits F, Jacobs MA, Van Turenhout ST, Mulder CJ. Video capsule endoscopy in patients with nonresponsive celiac disease. *J Clin Gastroenterol* 2013; **47**: 393-399 [PMID: 23164686 DOI: 10.1097/MCG.0b013e31826bea12]
- Ibrahim M, Van Gossum A. Novel imaging enhancements in capsule endoscopy. *Gastroenterol Res Pract* 2013; **2013**: 304-723 [PMID: 23878532 DOI: 10.1155/2013/304723]
- Fisher LR, Hasler WL. New vision in video capsule endoscopy: current status and future directions. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 392-405 [PMID: 22565098 DOI: 10.1038/nrgastro.2012.88]
- Ciaccio EJ, Tennyson CA, Lewis SK, Krishnareddy S, Bhagat G, Green PH. Distinguishing patients with celiac disease by quantitative analysis of video capsule endoscopy images. *Comput Methods Programs Biomed* 2010; **100**: 39-48 [PMID: 20356648 DOI: 10.1016/j.cmpb.2010.02.005]
- Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Classification of video capsule endoscopy image patterns: comparative analysis between patients with celiac disease and normal individuals. *Biomed Eng Online* 2010; **9**: 44 [PMID: 20815911 DOI: 10.1186/1475925X944]
- Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Transformation of video capsule images to detect small bowel mucosal differences in celiac versus control patients. *Comput Methods Programs Biomed* 2012; **108**: 28-37 [PMID: 22284703 DOI: 10.1016/j.cmpb.2011.12.008]
- Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Quantitative estimates of motility from video capsule endoscopy are useful to discern celiac patients from controls. *Dig Dis Sci* 2012; **57**: 2936-2943 [PMID: 22644741 DOI: 10.1007/s106200122251]
- Ciaccio EJ, Lewis SK, Green PH. Detection of villous atrophy using endoscopic images for the diagnosis of celiac disease. *Dig Dis Sci* 2013; **58**: 1167-1169 [PMID: 23525733 DOI: 10.1007/s1062001326189]
- Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Use of shape-from-shading to estimate three-dimensional architecture in the small intestinal lumen of celiac and control patients. *Comput Methods Programs Biomed* 2013; **111**: 676-684 [PMID: 23816252 DOI: 10.1016/j.cmpb.2013.06.002]
- Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Implementation of a polling protocol for predicting celiac disease in video capsule analysis. *World J Gastrointest Endosc* 2013; **5**: 313-322 [PMID: 23858375 DOI: 10.4253/wjge.v5.i7.313]
- Lee AR, Ng DL, Diamond B, Ciaccio EJ, Green PH. Living with coeliac disease: survey results from the U.S.A. *J Hum Nutr Diet* 2012; **25**: 233-238 [PMID: 22364496 DOI: 10.1111/j.1365277X.2012.01236.x]
- Lebwohl B, Granath F, Ekblom A, Montgomery SM, Murray JA, Rubio-Tapia A, Green PH, Ludvigsson JF. Mucosal healing and mortality in coeliac disease. *Aliment Pharmacol Ther* 2013; **37**: 332-339 [PMID: 23190299 DOI: 10.1111/apt.12164]
- Vécsei A, Amann G, Hegenbart S, Liedlgruber M, Uhl A. Automated Marsh-like classification of celiac disease in children using local texture operators. *Comput Biol Med* 2011; **41**: 313-325 [PMID: 21513927 DOI: 10.1016/j.compbiomed.2011.03.009]
- Hegenbart S, Uhl A, Vécsei A, Wimmer G. Scale invariant texture descriptors for classifying celiac disease. *Med Image Anal* 2013; **17**: 458-474 [PMID: 23481171 DOI: 10.1016/j.media.2013.02.001]
- Fernandez-Urien I, Carretero C, Borobio E, Borda A, Estevez E, Galter S, GonzalezSuarez B, Gonzalez B, Lujan M, Martinez JL, Martinez V, Menchen P, Navajas J, Pons V, Prieto C, Valle J. Capsule endoscopy capture rate: has 4 frames-per-second any impact over 2 frames-per-second? *World J Gastroenterol* 2014; **20**: 14472-14478 [PMID: 25339834 DOI: 10.3748/wjg.v20.i39.14472]
- Adler SN, Bjarnason I. What we have learned and what to expect from capsule endoscopy. *World J Gastrointest Endosc* 2012; **4**: 448-452 [PMID: 23189215 DOI: 10.4253/wjge.v4.i10.448]
- Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. *Ann Intern Med* 2005; **142**: 289-298 [PMID: 15710962]
- Kurien M, Evans KE, Hopper AD, Hale MF, Cross SS, Sanders DS. Duodenal bulb biopsies for diagnosing adult celiac disease: is there an optimal biopsy site? *Gastrointest Endosc* 2012; **75**: 1190-1196 [PMID: 22624810 DOI: 10.1016/j.gie.2012.02.025]
- Ciaccio EJ, Bhagat G, Lewis SK, Green PH. Quantitative image analysis of celiac disease. *World J Gastroenterol* 2015; **21**: 2577-2581 [PMID: 25759524 DOI: 10.3748/wjg.v21.i9.2577]
- Goenka MK, Majumder S, Goenka U. Capsule endoscopy: Present status and future expectation. *World J Gastroenterol* 2014; **20**: 10024-10037 [PMID: 25110430 DOI: 10.3748/wjg.v20.i29.10024]
- Ianiro G, Gasbarrini A, Cammarota G. Endoscopic tools for the diagnosis and evaluation of celiac disease. *World J Gastroenterol* 2013; **19**: 8562-8570 [PMID: 24379573 DOI: 10.3748/wjg.v19.i46.8562]
- Hegenbart S, Uhl A, Vécsei A. Survey on computer aided decision support for diagnosis of celiac disease. *Comput Biol Med* 2015; **65**: 348-358 [PMID: 25770906 DOI: 10.1016/j.compbiomed.2015.02.007]
- Koprowski R. Overview of technical solutions and assessment of

- clinical usefulness of capsule endoscopy. *Biomed Eng Online* 2015; **14**: 111 [PMID: 26626725 DOI: 10.1186/s1293801501083]
- 33 **Jung M**, Kiesslich R. Chromoendoscopy and intravital staining techniques. *Baillieres Best Pract Res Clin Gastroenterol* 1999; **13**: 11-19 [PMID: 11030630]
- 34 **Pohl J**, May A, Rabenstein T, Pech O, NguyenTat M, Fissler-Eckhoff A, Ell C. Comparison of computed virtual chromoendoscopy and conventional chromoendoscopy with acetic acid for detection of neoplasia in Barrett's esophagus. *Endoscopy* 2007; **39**: 594-598 [PMID: 17611913 DOI: 10.1055/s2007966649]
- 35 **Gupta T**, Ibrahim M, Deviere J, Van Gossum A. Evaluation of Fujinon intelligent chromo endoscopy-assisted capsule endoscopy in patients with obscure gastroenterology bleeding. *World J Gastroenterol* 2011; **17**: 4590-4595 [PMID: 22147964 DOI: 10.3748/wjg.v17.i41.4590]
- 36 **Nakayoshi T**, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). *Endoscopy* 2004; **36**: 1080-1084 [PMID: 15578298 DOI: 10.1055/s2004825961]
- 37 **Huang D**, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA. Optical coherence tomography. *Science* 1991; **254**: 1178-1181 [PMID: 1957169]
- 38 **Leung CW**, Kaltenbach T, Soetikno R, Wu KK, Leung FW, Friedland S. Water immersion versus standard colonoscopy insertion technique: randomized trial shows promise for minimal sedation. *Endoscopy* 2010; **42**: 557-563 [PMID: 20593332 DOI: 10.1055/s00291244231]
- 39 **Hoffman A**, Goetz M, Vieth M, Galle PR, Neurath MF, Kiesslich R. Confocal laser endomicroscopy: technical status and current indications. *Endoscopy* 2006; **38**: 1275-1283 [PMID: 17163333 DOI: 10.1055/s2006944813]
- 40 **Kiesslich R**, Goetz M, Neurath MF. Confocal laser endomicroscopy for gastrointestinal diseases. *Gastrointest Endosc Clin N Am* 2008; **18**: 451-466, viii [PMID: 18674696 DOI: 10.1016/j.giec.2008.03.002]
- 41 **Anagnostopoulos GK**, Yao K, Kaye P, Fogden E, Fortun P, Shonde A, Foley S, Sunil S, Atherton JJ, Hawkey C, Ragunath K. High-resolution magnification endoscopy can reliably identify normal gastric mucosa, Helicobacter pylori-associated gastritis, and gastric atrophy. *Endoscopy* 2007; **39**: 202-207 [PMID: 17273960 DOI: 10.1055/s2006945056]
- 42 **Kodashima S**, Fujishiro M. Novel image-enhanced endoscopy with iscan technology. *World J Gastroenterol* 2010; **16**: 1043-1049 [PMID: 20205272 DOI: 10.3748/wjg.v16.i9.1043]

P- Reviewer: Albuquerque A, Ianiro G, Iovino P, Pavlovic M
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Wu HL



Prospective Study

Prior minimal endoscopic sphincterotomy to prevent pancreatitis related to endoscopic balloon sphincteroplasty

Ryo Kanazawa, Jin Kan Sai, Tomoyasu Ito, Hiroko Miura, Shigeto Ishii, Hiroaki Saito, Ko Tomishima, Ryo Shimizu, Koki Sato, Manabu Hayashi, Sumio Watanabe, Shuichiro Shiina

Ryo Kanazawa, Jin Kan Sai, Tomoyasu Ito, Hiroko Miura, Shigeto Ishii, Hiroaki Saito, Ko Tomishima, Ryo Shimizu, Koki Sato, Manabu Hayashi, Sumio Watanabe, Shuichiro Shiina, Department of Gastroenterology, Juntendo University School of Medicine, Tokyo 113-8421, Japan

Author contributions: Kanazawa R and Sai JK contributed equally to this work; Kanazawa R collected and analyzed the data, and drafted the manuscript; Sai JK provided analytical oversight and designed and supervised the study; Watanabe S and Shiina S revised the manuscript for the important intellectual content; Ito T, Miura H, Ishii S, Saito H, Tomishima K, Shimizu R, Sato K and Hayashi M supported collecting the data; all authors have read and approved the final version to be published.

Institutional review board statement: This study was approved by the Institutional Review Board of Juntendo University.

Clinical trial registration statement: In the study period (October 2010 - March 2014), clinical trial registration was not required for our prospective study.

Informed consent statement: Written informed consent for the procedures and treatment was obtained from patients or their next of kin in accordance with normal clinical practice.

Conflict-of-interest statement: No conflict of interests.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at jinkans@juntendo.ac.jp. Participants gave informed consent was not obtained but the presented data are anonymized and risk of identification is low.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

[licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)

Manuscript source: Invited manuscript

Correspondence to: Jin Kan Sai, MD, Department of Gastroenterology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. jinkans@juntendo.ac.jp
Telephone: +81-3-58021061
Fax: +81-3-56845960

Received: February 2, 2016
Peer-review started: February 9, 2016
First decision: March 23, 2016
Revised: July 18, 2016
Accepted: August 6, 2016
Article in press: August 8, 2016
Published online: October 16, 2016

Abstract

AIM

To investigate the efficacy of prior minimal endoscopic sphincterotomy (EST) to prevent pancreatitis related to endoscopic balloon sphincteroplasty (EBS).

METHODS

After bile duct access was gained and cholangiogram confirmed the presence of stones < 8 mm in the common bile duct at endoscopic retrograde cholangiography, patients were subjected to minimal EST (up to one-third of the size the papilla) plus 8 mm EBS (EST-EBS group). The incidence of pancreatitis and the difference in serum amylase level after the procedure were examined and compared with those associated with 8-mm EBS alone in 32 patients of historical control (control group).

RESULTS

One hundred and five patients were included in the EST-EBS group, and complete stone removal was accomplished in all of them. The difference in serum amylase level after the procedure was - 25.0 (217.9) IU/L in the EST-EBS group and this value was significantly lower than the 365.5 (576.3) IU/L observed in the control group ($P < 0.001$). The incidence of post-procedure pancreatitis was 0% (0/105) in the EST-EBS group and 15.6% (5/32) in the control group ($P < 0.001$).

CONCLUSION

Prior minimal EST might be useful to prevent the elevation of serum amylase level and the occurrence of pancreatitis related to EBS.

Key words: Choledocholithiasis; Adverse event; Pancreatitis; Endoscopic sphincterotomy; Endoscopic balloon sphincteroplasty

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We evaluated the efficacy of prior minimal endoscopic sphincterotomy (EST) to prevent pancreatitis related to endoscopic balloon sphincteroplasty (EBS). One hundred and five patients with bile duct stones < 8 mm were subjected to minimal EST (up to one-third of the size the papilla) plus 8 mm EBS (EST-EBS group). The incidence of pancreatitis and the difference in serum amylase level after the procedure were examined and compared with those associated with 8-mm EBS alone in 32 patients of historical control (control group). The difference in serum amylase level after the procedure in the EST-EBS group was significantly lower than that observed in the control group ($P < 0.001$). The incidence of post-procedure pancreatitis was 0% (0/105) in the EST-EBS group and 15.6% (5/32) in the control group ($P < 0.001$).

Kanazawa R, Sai JK, Ito T, Miura H, Ishii S, Saito H, Tomishima K, Shimizu R, Sato K, Hayashi M, Watanabe S, Shiina S. Prior minimal endoscopic sphincterotomy to prevent pancreatitis related to endoscopic balloon sphincteroplasty. *World J Gastrointest Endosc* 2016; 8(18): 663-668 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/663.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.663>

INTRODUCTION

Preventing major adverse events related to endoscopic interventions to remove bile duct stones is a matter of great concern to endoscopists and patients. Endoscopic balloon sphincteroplasty (EBS) using a 6-8 mm balloon is associated with a lower frequency of hemorrhage and perforation compared with endoscopic sphincterectomy (EST)^[1-4]. However, EBS alone is rarely performed these days because of the high risk of acute pancreatitis

and concern for fatal pancreatitis^[2,5,6]. Several studies have recently shown that EST plus large balloon sphincteroplasty (LBS) carries a low risk of post-procedure pancreatitis (0%-3%)^[7,8], although there have been no comparative studies between LBS alone and EST followed by LBS.

In the present study, we investigated the efficacy of prior minimal EST (up to one third of the papilla) to prevent pancreatitis related to EBS by comparing a group subjected to EBS alone with another subjected to minimal EST followed by EBS.

MATERIALS AND METHODS

Patients

Between October 2010 and March 2014, patients aged 18 years or older were prospectively included in the current study after bile duct access was gained and cholangiogram confirmed the presence of bile duct stones (EST-EBS group). Patients were excluded if they had a history of EST or EBS, a choledochoduodenal fistula, concurrent hepatolithiasis, Billroth II or Roux-en-Y anatomy, or a concomitant pancreatobiliary malignancy. Patients with conditions suggesting difficult bile duct cannulation, such as requirement of pancreatic guide-wire, pancreatic stent, precut sphincterotomy, pancreatic sphincterectomy or the Rendezvous technique for difficult bile duct access, were also excluded. Patients under anticoagulant therapy or with a coagulopathy (international normalized ratio > 1.3, partial thromboplastin time greater than twice that of control) and a platelet count of < 50000 × 10³/μL were excluded and subjected to EBS only. Patients with stones ≥ 8 mm were subjected to limited EST (up to half of the papilla) plus LBS and excluded from the current study. The size of bile duct stones was measured on endoscopic retrograde cholangiopancreatography (ERCP) images corrected for magnification using the diameter of the endoscope as a reference.

As the historical control, 32 consecutive patients, who fulfilled the same inclusion criteria as the EST-EBS group and had undergone 8 mm EBS alone between November 2009 and December 2011, served as the control group.

Informed consent was obtained from all patients. The study was approved by the ethics committee of our institution.

Endoscopic procedure

ERCP was performed using a side-viewing duodenoscope (JF-240, JF-260V, TJF-260; Olympus, Tokyo, Japan). Electrocautery was carried out using a 120-watt endocut current (ERBE International, Erlangen, Germany)^[9,10]. One of four trainees (> 100 ERCPs) accompanied by one specialist (> 10000 ERCPs) performed the procedures. Following preparation with pharyngeal anesthesia and intravenous injection of midazolam (0.06 mg/kg), ERCP was performed. After bile duct access

was gained and cholangiogram confirmed the presence of bile duct stones ≤ 8 mm, minimal EST followed by 8-mm EBS was performed. Minimal EST up to one third of the papilla was performed with a 30-mm-pull-type sphincterotome (Clever Cut 3; KD-V41M, Olympus) under the guidewire. EBS was performed with wire-guided hydrostatic balloon catheters (Eliminator, ConMed, NY; balloon length 3 cm, maximum inflated outer diameter 8 mm) placed across the papilla. The balloon was centered at the sphincter, and was dilated to the size of the lower bile duct or 8 mm, whichever was smaller. Inflation time was 30 s.

After the procedure, the stones were retrieved with an extraction balloon under the guidewire. When necessary, a mechanical lithotripter (Lithocrush, Olympus) was used to crush stones. An occlusion cholangiogram was obtained at the end of the procedure. Biliary stents or nasobiliary drains were placed when the stones were not completely removed. None of the patients had prophylactic pancreatic stents placed before or after the procedure.

Each patient was kept under fasting conditions after the procedure and was carefully monitored for the development of any adverse events. Physical examination and laboratory tests were performed daily after the procedure. Serum amylase was checked in all patients before and 24 h after the procedure. If the acute condition had settled and the serum concentration of amylase was below 375 IU/L (normal range: < 125 IU/L), the patient was allowed to take a meal.

Definitions of individual adverse events were similar to those given by Cotton *et al.*^[11]. The severity of adverse events was graded according to the length of hospitalization. Mild adverse events required 2 to 3 d of hospitalization; moderate adverse events required 4 to 10 d; and severe adverse events requiring more than 10 d of hospitalization^[11,12]. Procedure-induced pancreatitis was defined as new or worsened abdominal pain associated with a serum concentration of amylase three or more times the upper limit of normal at 24 h after the procedure, requiring hospitalization or prolongation of planned admission^[11,12]. Hemorrhage was considered clinically significant only if there was clinical evidence of bleeding, such as melena or hematemesis, with an associated decrease of at least 2 g per deciliter in hemoglobin concentration, or the need for a blood transfusion^[11,12]. Cholangitis was diagnosed when there was right upper quadrant abdominal tenderness, body temperature of $> 38^{\circ}\text{C}$, and elevated serum concentrations of liver enzymes. Acute cholecystitis was diagnosed based on suggestive clinical and radiographic signs. Perforation referred to retroperitoneal or bowel-wall perforation documented by any radiographic technique^[11,12].

Outcome measurements

The incidences of procedure related pancreatitis and the differences in serum amylase levels from baseline at 24

h after the procedure were examined in both groups of patients. Secondary outcome measures included the stone clearance rate, and the number of ERCPs required for complete stone clearance. Complete stone clearance was defined as the absence of filling defects on the occlusion cholangiogram as noted by the endoscopists.

Statistical analysis

Statistical analyses were performed using statistical software (SPSS version 17.0 for Windows). Data were presented as the mean \pm SD and were compared using paired *t* test. Mann-Whitney *U* test was used for comparing continuous data with skewed distribution in the two groups. A χ^2 test with Yate's correction was used to analyze gender. The difference in serum amylase level after the procedure and the incidence of post-procedure pancreatitis were compared using Wilcoxon signed-rank test. Statistical significance was defined as a *P* value < 0.05 (two tailed).

RESULTS

Among the 171 consecutive patients with choledocholithiasis who were enrolled in the current study, 8 patients were excluded for a history of EST and/or EBS, 1 was excluded for a choledochoduodenal fistula, 2 for concurrent hepatolithiasis, 6 for Billroth II or Roux-en-Y anatomy, 2 for concomitant biliary malignancies, 13 were excluded for difficult bile duct cannulation; besides, 8 patients who were under anticoagulant therapy or had a coagulopathy and 3 with a platelet count of $< 50000 \times 10^3/\mu\text{L}$ were also excluded. Twenty-three patients with stones larger than 8 mm were subjected to limited EST plus LBS (Figure 1).

Consequently, there were 105 patients in the EST-EBS group. The clinical characteristics of the patients in each group are shown in Table 1. The two groups were similar with respect to demographic features. Minimal EST plus 8 mm EBS was successfully performed in all patients. The waist of the balloon at the papilla was observed under fluoroscopic examination in both groups of patients during inflation of the balloon, and, after inflation, the waist remained in 9 (8.6%) patients of the EST-EBS group and 3 (8.7%) of the control group because of the stenosis or small diameter of the distal bile duct.

Complete duct clearance was accomplished in both groups of patients. The stones were completely removed in the first session in all patients of the EST-EBS group and in 27 (84.3%) of the control group ($P < 0.001$). The other 5 (15.7%) patients of the control group required 2 sessions. Mechanical lithotripsy was required in 2 (1.9%) patients of the EST-EBS group, and in one (4.3%) of the control group due to stenosis or small diameter of the distal bile duct (Table 2).

The mean (SD) serum amylase levels before and after the procedure were 148.2 (301.6) IU/L and 123.3 (138.7) IU/L in the EST-EBS group, and 164.5 (136.3)

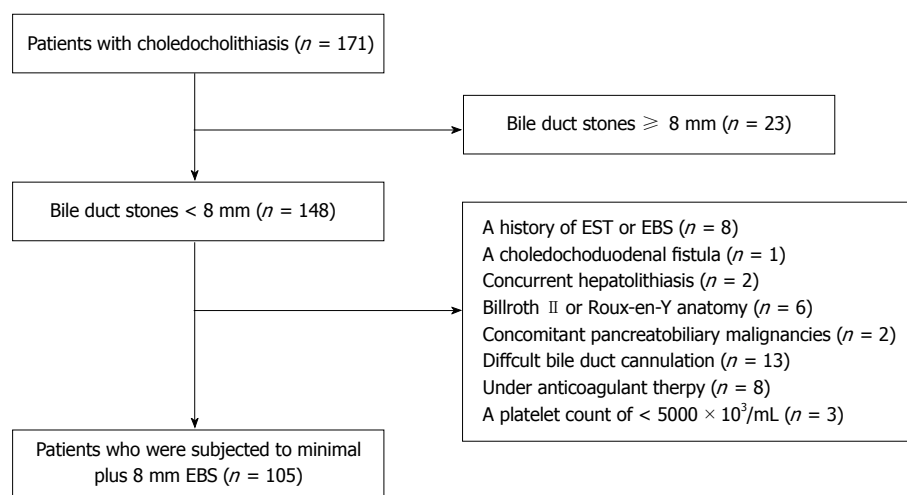


Figure 1 Flow chart of patients in this study. EST: Endoscopic sphincterotomy; EBS: Endoscopic balloon sphincteroplasty.

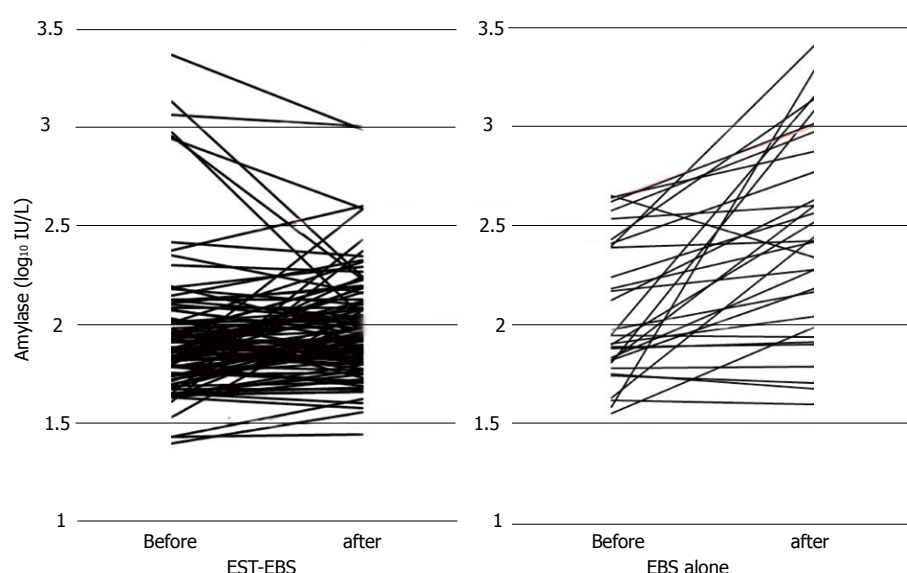


Figure 2 Difference in serum amylase level after the procedure in both groups of patients. The difference in control group was significantly higher than that in EST-EBS group ($P < 0.001$). EST: Endoscopic sphincterotomy; EBS: Endoscopic balloon sphincteroplasty.

IU/L and 530.4 (604.4) IU/L in the control group. The difference in serum amylase level after the procedure was - 25.0 (217.9) IU/L in the EST-EBS group and 365.5 (576.3) IU/L in the control group ($P < 0.001$) (Figure 2). The incidence of post-procedure pancreatitis was 0% (0/105) in the EST-EBS group and 15.6% (5/32) in the control group ($P < 0.001$). Cholangitis occurred in 3.1% (1/32) of the patients in the control group. None of the other patients in either group experienced any adverse event such as hemorrhage, perforation or cholecystitis within 7 d after the procedure.

DISCUSSION

EBS using a 6- to 8-mm balloon is associated with a lower frequency of hemorrhage and perforation compared with EST^[1,2], and allows preservation of sphincter of Oddi function^[3,4]. However, EBS alone has been

associated with a high risk of acute pancreatitis^[2,5,6]. In the study by Disario *et al*^[6], pancreatitis occurred in 17.9% of patients subjected to EBS and in 3.3% of those subjected to EST; besides, 2 (1.7%) patients in the EBS group died because of severe pancreatitis. In addition, in five prospective randomized controlled trials of EBS vs EST^[5,6,13-15], the incidence of pancreatitis after EBS varied between 4.9% and 20%. Furthermore, EBS was identified as an independent risk factor of post-ERCP pancreatitis in a large prospective multicenter study, including one death related to pancreatitis after EBS^[16]. Therefore, it is necessary to modify the EBS technique to reduce the risk of pancreatitis.

EST plus EBS for the extraction of large bile duct stones has shown a low incidence of pancreatitis (0%-4.0%) in large-scale studies^[8,9,17], although pancreatitis was thought to be closely related to balloon sphincteroplasty. Attasaranya *et al*^[8] suggested that

Table 1 Baseline characteristics of the patients

	EST-EBS (<i>n</i> = 105)	EBS alone (<i>n</i> = 32)	<i>P</i> value
Sex (female/male)	61/44	17/15	NS
Age (yr)	70.2 (29-83)	71.4 (28-88)	NS
Maximum CBD diameter (mm)	8.1 ± 4.5	7.7 ± 3.9	NS
Maximum stone diameter (mm)	6.6 ± 1.9	4.9 ± 1.8	NS
Stone number	2.1 ± 1.4	2.3 ± 1.7	NS
Serum amylase (IU/L)	148.2 ± 301.6	164.5 ± 136.3	NS
Periampullary diverticulum, <i>n</i> (%)	41 (32.5)	10 (31.7)	NS
Acute cholangitis before ERCP, <i>n</i> (%)	44 (16.6)	6 (21.8)	NS
Acute cholecystitis before ERCP, <i>n</i> (%)	3 (2.8)	1 (3.1)	NS

NS: Not significant; ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic sphincterotomy; EBS: Endoscopic balloon sphincteroplasty; CBD: Common bile duct.

EST performed before LBS may result in a separation between the pancreatic and biliary orifices, and balloon dilation forces that are exerted away from the pancreatic duct might lead to a lower risk of postprocedure pancreatitis compared with EBS alone.

In the current study, we performed minimal EST before 8-mm EBS in 105 patients with bile duct stones ≤ 8 mm in diameter. We successfully extracted the stones in all the patients with none of them experiencing post-procedure pancreatitis. Furthermore, in this group the difference in serum amylase level between the baseline value and that after the procedure was significantly lower and the incidence of post-procedure pancreatitis was significantly lower compared with the control group subjected to EBS alone. The objective of minimal EST was to separate the pancreatic orifice from the biliary orifice to prevent pancreatitis related to EBS, and to avoid bleeding and perforation related to standard EST. The objective of EBS after EST was to maximize the biliary sphincterotomy orifice and thereby enable free access of a retrieval balloon catheter or basket to the common channel. Actually, all patients in the current study showed a waist at the papilla during balloon dilation after minimal EST, and if the sphincter is not dilated by a balloon, resistance may occur at the biliary outlet during retrieval of the stone using a basket or retrieval balloon catheter; besides papillary edema or spasm may obstruct the flow of pancreatic juice and the pancreas would be injured as a result of these manipulations^[18].

There are some limitations in comparing the current data with previous data from the viewpoint of efficacy and safety. First, the procedure for endotherapy of bile duct stones may depend on the endoscopist, although a trainee attempted the procedure and was supported by an expert on each occasion in our study. Second, our series included patients with a mean age of 70 years, whereas the median age was 49 years in the prospective multicenter trial done in the United States that showed a higher rate of pancreatitis after EBS^[6]. Therefore the risk associated with minimal EST plus EBS in younger patients was not fully estimated in

Table 2 Results of stone retrieval

	EST-EBS (<i>n</i> = 105)	EBS alone (<i>n</i> = 32)	<i>P</i> value
<i>n</i> (%) sessions required			
1	105 (100)	27 (84.3)	< 0.001
2		5 (15.7)	
Complete removal, <i>n</i> (%)	105 (100)	32 (100)	NS
Mechanical lithotripsy, <i>n</i> (%)	2 (1.9)	1 (4.3)	NS
Pancreatogram, <i>n</i> (%)	34 (32.7)	10 (31.2)	NS
Serum amylase (IU/L)	-25.0 ± 217.9	365.5 ± 576.3	< 0.001
Post procedure pancreatitis	0 (0)	5 (15.6)	< 0.001

NS: Not significant; EST: Endoscopic sphincterotomy; EBS: Endoscopic balloon sphincteroplasty.

the current study. Third, the true advantage of one technique over the other can only be assessed in a randomized controlled trial, while the current study was conducted prospectively and the results were compared with a historical control. Fourth, although minimal EST plus 8-mm EBS resulted in a high cost due to the use of a balloon catheter and a sphincterotomy knife, preventing post-procedure pancreatitis was undoubtedly worth the higher cost. Fifth, long-term adverse events including cholangitis, recurrence of bile duct stones, and cholecystitis are an important problem and should be assessed in future studies.

In conclusion, prior minimal EST is expected to significantly reduce the risk of pancreatitis related to EBS for the treatment of patients with bile duct stones. Further studies involving a larger series of patients are required to confirm the reliability of the present results.

COMMENTS

Background

Endoscopic balloon sphincteroplasty (EBS) is associated with lower frequency of bleeding and perforation compared with endoscopic sphincterotomy (EST), as well as preservation of sphincter of Oddi function. But, EBS has a higher risk of acute pancreatitis and concern for fatal pancreatitis. It is necessary to modify the EBS technique to reduce the risk of pancreatitis.

Innovations and breakthroughs

Prior minimal EST is expected to significantly reduce the risk of pancreatitis related to EBS for the treatment of patients with bile duct stones.

Applications

The paper may interest readers because prior minimal EST might be useful to prevent the elevation of serum amylase level and the occurrence of pancreatitis related to EBS.

Terminology

The objective of minimal EST was to separate the pancreatic orifice from the biliary orifice to prevent pancreatitis related to EBS, and to avoid bleeding and perforation related to standard EST. The objective of EBS after EST was to maximize the biliary sphincterotomy orifice and thereby enable free access of a retrieval balloon catheter or basket to the common channel.

Peer-review

In this article, the authors found that the prior minimal EST might be useful to prevent the elevation of serum amylase level and the occurrence of pancreatitis.

This new method would maybe reduce the risk of post ERCP pancreatitis. This is a well-written paper containing interesting results which merit publication.

REFERENCES

- 1 **Staritz M**, Ewe K, Meyer zum Büschenfelde KH. Endoscopic papillary dilation (EPD) for the treatment of common bile duct stones and papillary stenosis. *Endoscopy* 1983; **15** Suppl 1: 197-198 [PMID: 6872989 DOI: 10.1055/s-2007-1021507]
- 2 **Baron TH**, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. *Am J Gastroenterol* 2004; **99**: 1455-1460 [PMID: 15307859 DOI: 10.1111/j.1572-0241.2004.30151.x]
- 3 **Yasuda I**, Tomita E, Enya M, Kato T, Moriwaki H. Can endoscopic papillary balloon dilation really preserve sphincter of Oddi function? *Gut* 2001; **49**: 686-691 [PMID: 11600473 DOI: 10.1136/gut.49.5.686]
- 4 **Sato H**, Kodama T, Takaaki J, Tatsumi Y, Maeda T, Fujita S, Fukui Y, Ogasawara H, Mitsufuji S. Endoscopic papillary balloon dilatation may preserve sphincter of Oddi function after common bile duct stone management: evaluation from the viewpoint of endoscopic manometry. *Gut* 1997; **41**: 541-544 [PMID: 9391256 DOI: 10.1136/gut.41.4.541]
- 5 **Fujita N**, Maguchi H, Komatsu Y, Yasuda I, Hasebe O, Igarashi Y, Murakami A, Mukai H, Fujii T, Yamao K, Maeshiro K. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: A prospective randomized controlled multicenter trial. *Gastrointest Endosc* 2003; **57**: 151-155 [PMID: 12556774 DOI: 10.1067/mge.2003.56]
- 6 **Disario JA**, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, Morales TG, Hixson LJ, Sherman S, Lehman GA, Jamal MM, Al-Kawas FH, Khandelwal M, Moore JP, Derfus GA, Jamidar PA, Ramirez FC, Ryan ME, Woods KL, Carr-Locke DL, Alder SC. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004; **127**: 1291-1299 [PMID: 15520997 DOI: 10.1053/j.gastro.2004.07.017]
- 7 **Ersoz G**, Tekesin O, Ozutemiz AO, Günsar F. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. *Gastrointest Endosc* 2003; **57**: 156-159 [PMID: 12556775 DOI: 10.1067/mge.2003.52]
- 8 **Attasaryanya S**, Cheon YK, Vittal H, Howell DA, Wakelin DE, Cunningham JT, Ajmere N, Ste Marie RW, Bhattacharya K, Gupta K, Freeman ML, Sherman S, McHenry L, Watkins JL, Fogel EL, Schmidt S, Lehman GA. Large-diameter biliary orifice balloon dilation to aid in endoscopic bile duct stone removal: a multicenter series. *Gastrointest Endosc* 2008; **67**: 1046-1052 [PMID: 18178208 DOI: 10.1016/j.gie.2007.08.047]
- 9 **Maydeo A**, Bhandari S. Balloon sphincteroplasty for removing difficult bile duct stones. *Endoscopy* 2007; **39**: 958-961 [PMID: 17701853 DOI: 10.1055/s-2007-966784]
- 10 **Mariani A**, Di Leo M, Giardullo N, Giussani A, Marini M, Buffoli F, Cipolletta L, Radaelli F, Ravelli P, Lombardi G, D'Onofrio V, Macchiarelli R, Iiritano E, Le Grazie M, Pantaleo G, Testoni PA. Early precut sphincterotomy for difficult biliary access to reduce post-ERCP pancreatitis: a randomized trial. *Endoscopy* 2016; **48**: 530-535 [PMID: 26990509 DOI: 10.1055/s-0042-102250]
- 11 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]
- 12 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]
- 13 **Bergman JJ**, Rauws EA, Fockens P, van Berkel AM, Bossuyt PM, Tijssen JG, Tytgat GN, Huibregtse K. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bile duct stones. *Lancet* 1997; **349**: 1124-1129 [PMID: 9113010 DOI: 10.1016/S0140-6736(96)11026-6]
- 14 **Vlavianos P**, Chopra K, Mandalia S, Anderson M, Thompson J, Westaby D. Endoscopic balloon dilatation versus endoscopic sphincterotomy for the removal of bile duct stones: a prospective randomised trial. *Gut* 2003; **52**: 1165-1169 [PMID: 12865276 DOI: 10.1136/gut.52.8.1165]
- 15 **Arnold JC**, Benz C, Martin WR, Adamek HE, Riemann JF. Endoscopic papillary balloon dilation vs. sphincterotomy for removal of common bile duct stones: a prospective randomized pilot study. *Endoscopy* 2001; **33**: 563-567 [PMID: 11473325 DOI: 10.1055/s-2001-15307]
- 16 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]
- 17 **Heo JH**, Kang DH, Jung HJ, Kwon DS, An JK, Kim BS, Suh KD, Lee SY, Lee JH, Kim GH, Kim TO, Heo J, Song GA, Cho M. Endoscopic sphincterotomy plus large-balloon dilation versus endoscopic sphincterotomy for removal of bile-duct stones. *Gastrointest Endosc* 2007; **66**: 720-726; quiz 768, 771 [PMID: 17905013 DOI: 10.1016/j.gie.2007.02.033]
- 18 **Jeong S**, Ki SH, Lee DH, Lee JI, Lee JW, Kwon KS, Kim HG, Shin YW, Kim YS. Endoscopic large-balloon sphincteroplasty without preceding sphincterotomy for the removal of large bile duct stones: a preliminary study. *Gastrointest Endosc* 2009; **70**: 915-922 [PMID: 19647241 DOI: 10.1016/j.gie.2009.04.042]

P- Reviewer: Chow WK, Cuadrado-Garcia A, Giannopoulos GA, Luo HS **S- Editor:** Kong JX **L- Editor:** A **E- Editor:** Wu HL



Same site submucosal tunneling for a repeat per oral endoscopic myotomy: A safe and feasible option

Antonios N Wehbeh, Parit Mekaroonkamol, Qiang Cai

Antonios N Wehbeh, Department of Internal Medicine, Emory University School of Medicine, Atlanta, GA 30322, United States

Parit Mekaroonkamol, Qiang Cai, Department of Internal Medicine, Division of Digestive Diseases, Emory University School of Medicine, Atlanta, GA 30322, United States

Author contributions: Wehbeh AN and Mekaroonkamol P conducted the literature review; Wehbeh AN, Mekaroonkamol P and Cai Q drafted and edited the manuscript, and approved the final version submitted; Cai Q captured the images and is the guarantor of the article.

Institutional review board statement: We submitted a review request to our IRB but based on our institutional policy, a case report of less than 6 patients does not require an IRB review.

Informed consent statement: Patient gave informed consent prior to getting the procedure done.

Conflict-of-interest statement: The authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Qiang Cai, MD, PhD, Professor of Medicine, Director of Advanced Endoscopy Fellowship, Department of Internal Medicine, Division of Digestive Diseases, Emory University School of Medicine, 1365 Clifton Road, B1262, Atlanta, GA 30322, United States. qcai@emory.edu
Telephone: +1-404-7782714
Fax: +1-404-7782578

Received: May 13, 2016
Peer-review started: May 16, 2016
First decision: July 4, 2016

Revised: July 11, 2016

Accepted: July 29, 2016

Article in press: August 1, 2016

Published online: October 16, 2016

Abstract

Per oral endoscopic myotomy (POEM) is a novel endoscopic procedure for achalasia treatment. Due to its novelty and high success rates, a repeat procedure is usually not warranted, making the feasibility and safety of such approach unknown. We report the first case of a successful repeat POEM done at the same site of a previously uncompleted POEM. An 84-year-old female with type 2 achalasia presented for a POEM procedure. The procedure was aborted at the end of tunneling and before myotomy due to hypotension, which later resolved spontaneously. POEM was re-attempted at the same site of the original tunnel 1 year afterward, and surprisingly we didn't encounter any submucosal fibrosis. The procedure felt similar to a native POEM and a myotomy was performed uneventfully. Our case is the first to suggest that submucosal tunneling during a repeat POEM can be done at the same site. Hypotension during POEM is a rare complication that should be recognized as a potential result of tension capnothorax, it can however, be managed with close supportive care.

Key words: Per oral endoscopic myotomy; Achalasia; Myotomy; Submucosal tunnel; Repeat procedure; Submucosal fibrosis

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Per oral endoscopic myotomy (POEM) is a novel method of treating achalasia. More is being learnt about potential complications as it increases in popularity. This is the first case of a repeat submucosal tunneling done at the same site of a prior POEM

attempt which was aborted just before myotomy. No complications or difficulties were encountered during the second attempt. This may suggest that submucosal tunneling does not cause fibrosis, and that repeat POEM after a technically unsuccessful attempt could be done at the same site and orientation of the original tunnel.

Wehbeh AN, Mekaroonkamol P, Cai Q. Same site submucosal tunneling for a repeat per oral endoscopic myotomy: A safe and feasible option. *World J Gastrointest Endosc* 2016; 8(18): 669-673 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/669.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.669>

INTRODUCTION

Per oral endoscopic myotomy (POEM) is a novel endoscopic procedure for achalasia treatment. The principle techniques involve endoscopic submucosal tunneling followed by a myotomy^[1]. Overall, it has success rates reportedly ranging between 82% to 100% and can be safely performed with a small number of reported major complications^[1-3]. However, one of the complications that can occur is hemodynamic instability, which has been reported in up to 20% of patients in one study^[4]. Due to its novelty and the high success rates, repeat procedure is rarely warranted, making the feasibility and safety of such approach unknown. Here, we report the first case of a repeat submucosal tunneling successfully performed at the same site of a previous POEM procedure.

CASE REPORT

An 84-year-old female presented with progressive dysphagia to both solids and liquids and failure to thrive over several months. Her other medical problems included gastroesophageal reflux disease, hypertension, deep vein thrombosis, severe osteoarthritis of both hips, lower extremities contracture, and chronic low back pain. Initial laboratory work up was essentially unrevealing. Manometry study confirmed severe achalasia type 2. The decision was made to proceed with POEM procedure. During endoscopy, she was placed in supine position which was standard practice at our institution. Incision site was first injected with a premixed solution of saline and methylene blue (5 mL/500 mL) followed by careful dissection to the submucosal layer using a triangle-tip knife. A submucosal tunnel was being made from the incision site to 2 cm distal to the cardia, but after a complete submucosal tunneling process just before myotomy (Figure 1), she developed severe hypotension and bradycardia. Consequently, the procedure was aborted. Chest X-ray revealed left apical pneumothorax, pneumomediastinum, pneumoperitoneum, and extensive subcutaneous emphysema. Her hypotension resolved with supportive care within minutes of aborting the procedure. A gastrografin swallow study was

obtained which did not show any evidence of contrast leakage, but it demonstrated a grossly dilated esophagus consistent with achalasia, and postoperative edema with slow emptying at the gastroesophageal junction (Figure 2). Thereafter, she underwent an upper endoscopy with Botulinum injection every 2-3 mo but eventually her symptoms stopped responding to botulinum treatment. Repeat POEM was thus performed 1 year later. She was placed in the same supine position due to her medical comorbidities. A severely dilated sigmoid esophagus was observed (Figure 3A). The GE junction was tight, and some pressure was required to traverse the endoscope, consistent with known achalasia. Due to great difficulty orienting the endoscope on a different plane, submucosal incision was made at the exact same site (Figure 3C) of the original tunnel, and surprisingly we did not encounter any submucosal fibrosis or technical challenges. The repeat tunneling at the same submucosal plane was successfully completed and felt similar to a native POEM (Figure 4). A myotomy was quickly and uneventfully performed followed by mucosal closure with hemostatic clips (Figure 3). The length of the myotomy was 8 cm, which is the standard at our institution. At 4-wk follow up her symptoms remarkably improved, as shown by a decreased Eckhardt score from 9 to 4. Her reflux symptoms also remained stable on the same dose of omeprazole.

DISCUSSION

Our case is the first to highlight the feasibility and safety of performing a repeat POEM at a location where submucosal tunneling was previously performed. As discussed above, there are limited scenarios where repeat POEM would be considered. They include intra-procedural complications resulting in incomplete procedure, insufficient symptomatic relieve, and recurrent symptoms after an initial improvement^[5]. The question remains as whether it is feasible to repeat a POEM procedure, and if so what would the best approach be.

POEM on a site of prior endoscopic mucosal resection is considered relatively contraindicated due to fear of encountering fibrosis^[2]. Recent report on repeat POEM procedures opted to create submucosal tunnel at the opposite side of the scarred mucosectomy area due to concern for an obliterated submucosal space^[5]. However, this did not apply to our case, meaning that submucosal fibrosis does not necessarily result from a first POEM attempt. Although theoretically myotomy may lead to fibrosis, but this hasn't been confirmed in the literature. In addition, myotomy is performed from 3 cm proximal to gastroesophageal junction and is therefore unlikely to impact the development of submucosal fibrosis in the proximal tunnel.

Moreover, the opposite site approach may not always be feasible due to different patient position and endoscopic orientation as in our case where patient position is very limited. Therefore, we opted for the

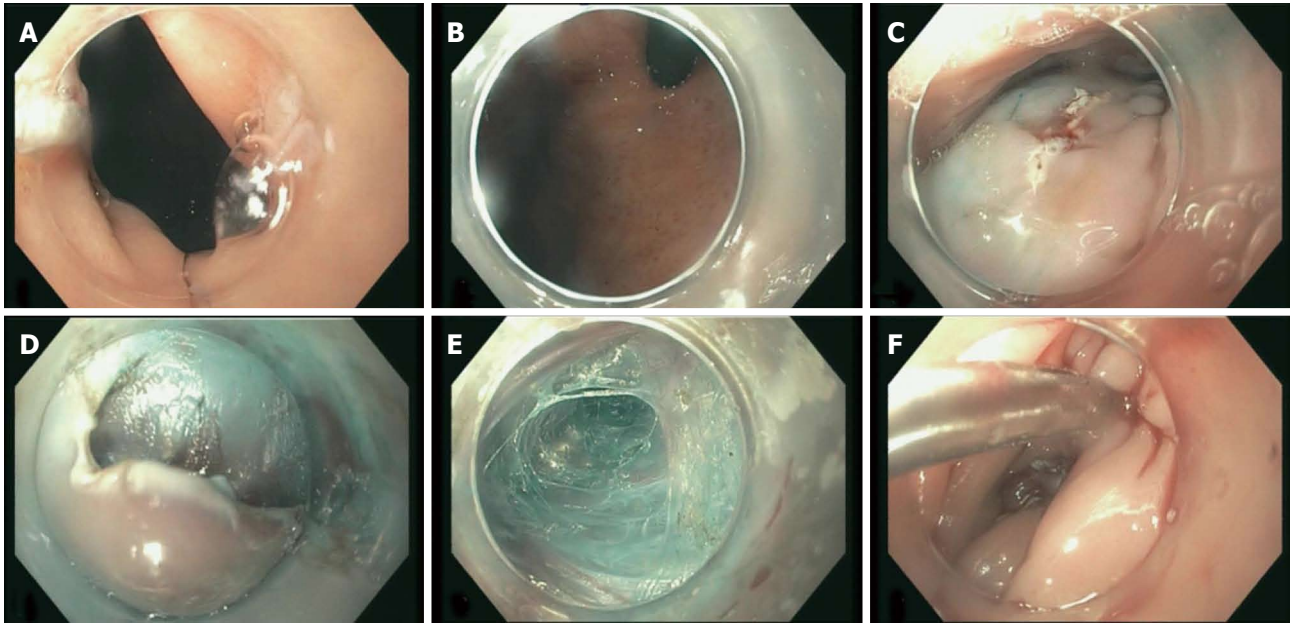


Figure 1 Endoscopic pictures from the first per oral endoscopic myotomy attempt showing: Gastroesophageal junction (A), cardia before myotomy (B), mucosotomy site (C), initial dissection site (D), creating the submucosal tunnel (E), and closure of mucosotomy (F).

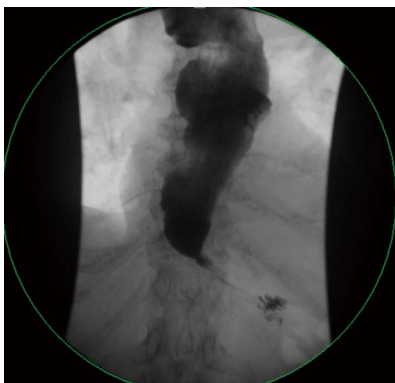


Figure 2 Gastrografin swallow study obtained after the index per oral endoscopic myotomy attempt showing a grossly distended esophagus consistent with achalasia, and postoperative edema with slow emptying at the gastroesophageal junction. No evidence of contrast leakage is seen.

same posterior approach as it allowed most flexible endoscopic maneuverability. Same site repeat POEM also preserves the opposite side of the esophagus for other potential procedures. Similar to our findings, double POEM was recently reported whereby tunneling was done more proximal to original tunnel to extend the myotomy^[6].

Hypotension during POEM is a rare complication that should be recognized as a potential sign of tension capnothorax; it can however, be managed with close supportive care^[7,8]. Other commonly reported physical findings include subcutaneous emphysema, mediastinal emphysema, and pneumoperitoneum without hemodynamic instability, all of which are believed to be normal physiologic reaction to the procedure^[9].

In summary, this report suggests that should POEM need to be re-attempted, same site operation, including

incision, submucosal tunneling and myotomy, is a viable method.

COMMENTS

Case characteristics

An 84-year-old female with progressive dysphagia to both solids and liquids and failure to thrive.

Clinical diagnosis

She had severely dilated sigmoid esophagus and tight gastroesophageal junction upon passing gastroscopy, consistent with manometry-proven achalasia type 2.

Differential diagnosis

Differential includes esophageal cancer causing pseudoachalasia, stricture, extrinsic compressive mass, and esophagogastric junction outflow obstruction.

Laboratory diagnosis

Laboratory testing on initial presentation was essentially unremarkable.

Imaging diagnosis

No imaging was required to make the diagnosis. Manometry study revealed panesophageal pressurization and elevated integrated resting pressure, diagnostic of achalasia type 2.

Pathological diagnosis

Biopsy was not required to establish the diagnosis.

Treatment

Per oral endoscopic myotomy (POEM) was performed twice: the first submucosal tunneling was completed without myotomy due to hemodynamic instability. The second attempt was successfully performed *via* the same site tunneling.

Related reports

Only 2 other reports on repeat POEM were found, but neither of them reports on performing repeat submucosal tunneling on the same site and orientation of the original tunnel.

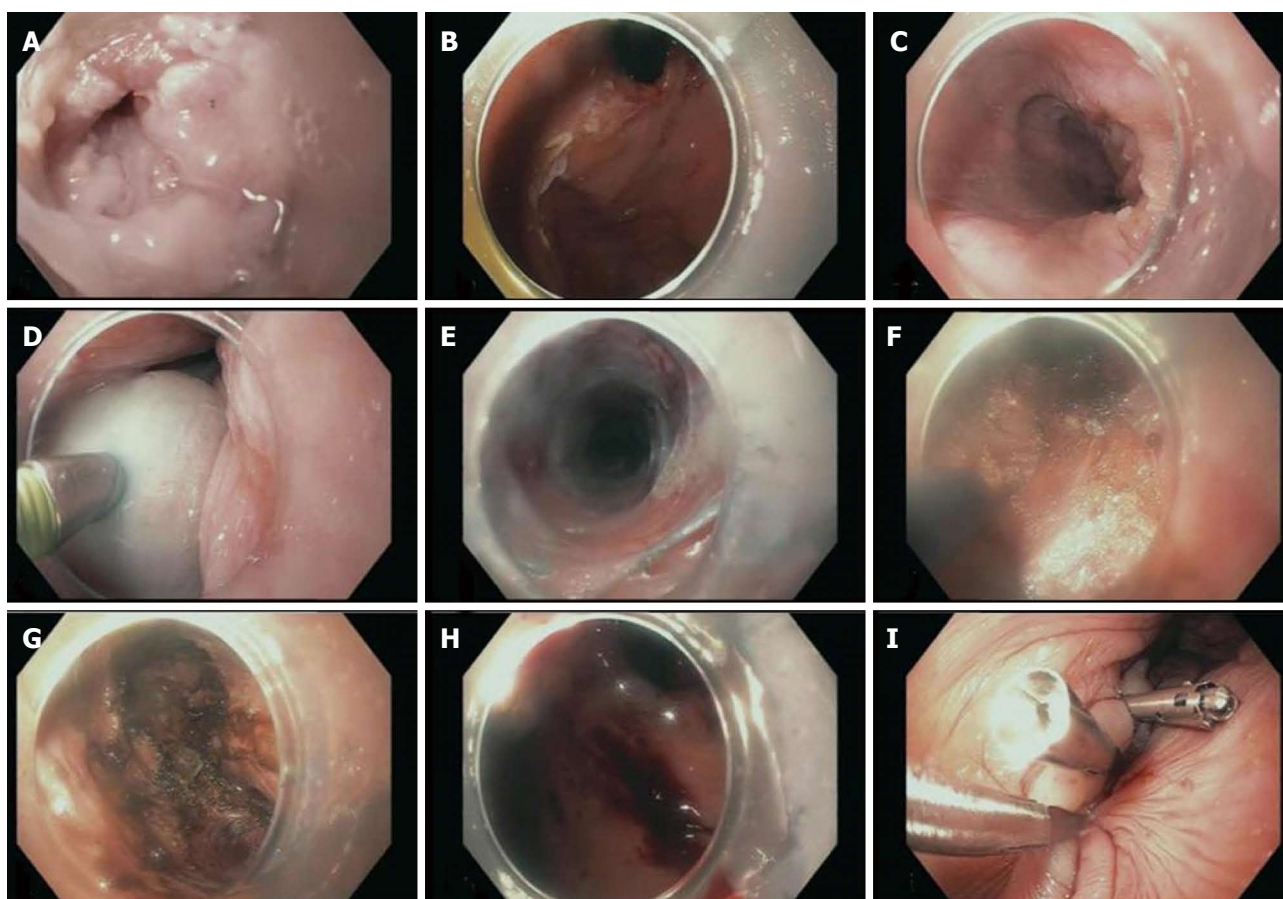


Figure 3 Endoscopic pictures taken from the repeat per oral endoscopic myotomy showing: sigmoid esophagus (A), cardia before myotomy (B), mucosa of previous dissection site (C), Mucosal bleb (D), submucosal tunneling (E), initial myotomy (F), completed myotomy (G), cardia after submucosal tunneling (H), closure of mucosotomy (I).

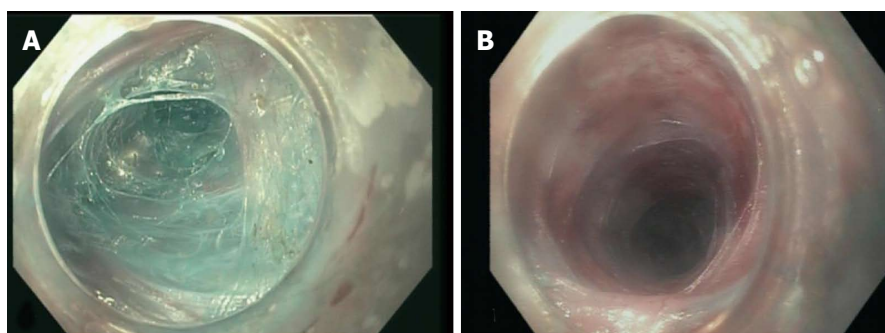


Figure 4 Comparison of submucosal tunnel of the index (A) and repeat (B) per oral endoscopic myotomy.

Peer-review

POEM has been demonstrated to be safe and effective for treating achalasia, regardless of the previous treatment history, including previous POEM therapy. Generally, the opposite site approach was recommended to avoid the potential fibrosis. In the present case, POEM was performed at exactly the same site of a previous POEM procedure.

REFERENCES

- 1 **Bechara R**, Ikeda H, Inoue H. Peroral endoscopic myotomy: an evolving treatment for achalasia. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 410-426 [PMID: 26035678 DOI: 10.1038/nrgastro.2015.87]
- 2 **Stavropoulos SN**, Modayil RJ, Friedel D, Savides T. The International Per Oral Endoscopic Myotomy Survey (IPOEMS): a snapshot of the global POEM experience. *Surg Endosc* 2013; **27**: 3322-3338 [PMID: 23549760 DOI: 10.1007/s00464-013-2913-8]
- 3 **Talukdar R**, Inoue H, Nageshwar Reddy D. Efficacy of peroral endoscopic myotomy (POEM) in the treatment of achalasia: a systematic review and meta-analysis. *Surg Endosc* 2015; **29**: 3030-3046 [PMID: 25539695 DOI: 10.1007/s00464-014-4040-6]
- 4 **Kurian AA**, Dunst CM, Sharata A, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic esophageal myotomy: defining the learning curve. *Gastrointest Endosc* 2013; **77**: 719-725 [PMID: 23394838 DOI: 10.1016/j.gie.2012.12.006]
- 5 **Li QL**, Yao LQ, Xu XY, Zhu JY, Xu MD, Zhang YQ, Chen WF, Zhou PH. Repeat peroral endoscopic myotomy: a salvage option

- for persistent/recurrent symptoms. *Endoscopy* 2016; **48**: 134-140 [PMID: 26349067 DOI: 10.1055/s-0034-1393095]
- 6 **Kumbhari V**, Tieu AH, Azola A, Saxena P, Ngamruengphong S, El Zein MH, Khashab MA. Double peroral endoscopic myotomy for achalasia. *Gastrointest Endosc* 2015; **82**: 953 [PMID: 26119650 DOI: 10.1016/j.gie.2015.05.036]
 - 7 **Phillips S**, Falk GL. Surgical tension pneumothorax during laparoscopic repair of massive hiatus hernia: a different situation requiring different management. *Anaesth Intensive Care* 2011; **39**: 1120-1123 [PMID: 22165368]
 - 8 **Tang A**, Huddleston P, Attaluri P, Cruz A, Joseph S, Lavy D. Clinical cases of nonsurgical pneumoperitoneum: categorizing the disease and treatment options. *Am Surg* 2015; **81**: E206-E208 [PMID: 25975311]
 - 9 **Ren Z**, Zhong Y, Zhou P, Xu M, Cai M, Li L, Shi Q, Yao L. Perioperative management and treatment for complications during and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA) (data from 119 cases). *Surg Endosc* 2012; **26**: 3267-3272 [PMID: 22609984 DOI: 10.1007/s00464-012-2336-y]

P- Reviewer: Liu DL **S- Editor:** Gong ZM **L- Editor:** A
E- Editor: Wu HL



Plexiform angiomyxoid myofibroblastic tumor of stomach: A rare case

Laimas Jonaitis, Mindaugas Kiudelis, Paulius Slepavicius, Lina Poskienė, Limas Kupcinskas

Laimas Jonaitis, Paulius Slepavicius, Limas Kupcinskas,
Department of Gastroenterology, Medical Academy, Lithuanian
University of Health Sciences, 50009 Kaunas, Lithuania

Mindaugas Kiudelis, Department of Surgery, Medical Academy,
Lithuanian University of Health Sciences, 50009 Kaunas, Lithuania

Lina Poskienė, Department of Pathological Anatomy, Medical
Academy, Lithuanian University of Health Sciences, 50009
Kaunas, Lithuania

Author contributions: Jonaitis L carried out the investigations, medical therapy and follow-up of the patient; Kiudelis M performed the surgery; Poskienė L made histological examination; Jonaitis L, Slepavicius P prepared the manuscript; all authors were involved in drafting and revising the manuscript.

Institutional review board statement: The study was reviewed and approved by the Lithuanian University of Health Sciences Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Laimas Jonaitis is a member of the *World Journal of Gastrointestinal Endoscopy* Editorial Board. Mindaugas Kiudelis, Lina Poškienė, Paulius Slepavicius, Limas Kupcinskas declare that there are no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Laimas Jonaitis, MD, PhD, Department of Gastroenterology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50009 Kaunas,

Lithuania. laimasj@takas.lt
Telephone: +370-37326264
Fax: +370-37331458

Received: April 14, 2016
Peer-review started: April 18, 2016
First decision: May 19, 2016
Revised: June 13, 2016
Accepted: August 11, 2016
Article in press: August 15, 2016
Published online: October 16, 2016

Abstract

Plexiform angiomyxoid myofibroblastic tumor (PAMT) is a rare benign mesenchymal tumor of stomach. Rarity of this kind of tumors and scarce review articles may cause underrecognition of this entity and pose a real diagnostic challenge to gastroenterologists, pathologists and surgeons when encountering such patients and differentiating PAMT from other gastric intramural tumors. We report a case of 28-year-old woman, who presented with epigastric pain after meals, iron-deficiency anaemia and weight loss. Upper gastrointestinal endoscopy revealed submucosal tumor-like elevated lesion in the anterior wall of the antrum with intact overlying mucosa. Endoscopic ultrasound showed a 3-cm hypoechoic homogenous mass, originating from the third layer of the gastric wall. Endoscopic ultrasound-guided fine needle aspiration was not informative. Endoscopic buttonhole biopsy was performed to obtain specimens. Following this, the unexpected prolapse of the tumor occurred into the lumen of the stomach, causing gastric outlet obstruction - the biopsy was obtained. Pathomorphological features suggested the diagnosis of PAMT. Gastric resection of the Billroth I type was performed. Diagnosis was confirmed by histological analysis of the surgical specimen.

Key words: Plexiform angiomyxoid myofibroblastic tumor; Intramural; Mesenchymal; Submucosal; Antrum

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Plexiform angiomyxoid myofibroblastic tumor is a rare benign mesenchymal tumor of stomach. Rarity of this kind of tumors and scarce review articles may cause underrecognition of this entity and pose a real diagnostic challenge, when differentiating between various intramural lesions. Clinical signs and symptoms are nonspecific or absent, radiological features often overlap, upper gastrointestinal endoscopy has a limited role because of intramural location. Endoscopic ultrasound yields opportunity to visualize and biopsy the tumor. Definite diagnosis requires histological and immunohistochemical analysis.

Jonaitis L, Kiudelis M, Slepavicius P, Poskienė L, Kupcinskas L. Plexiform angiomyxoid myofibroblastic tumor of stomach: A rare case. *World J Gastrointest Endosc* 2016; 8(18): 674-678 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/674.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.674>

INTRODUCTION

Plexiform angiomyxoid myofibroblastic tumor (PAMT) is a benign mesenchymal tumor of stomach. To date, only 19 immunohistochemically confirmed cases have been reported in the literature. We report a case of 28-year-old woman with submucosal tumor in the anterior wall of the antrum. After repeated biopsies pathomorphological features of the specimen suggested the diagnosis of PAMT. Gastric resection of the Billroth I type was performed and diagnosis of PAMT was confirmed.

CASE REPORT

A 28-year-old previously healthy Caucasian female was investigated due to epigastric pain, associated with meals, iron-deficiency anaemia and lost 8 kg of weight during the preceding six months. Her previous medical history was unremarkable. Outpatient upper gastrointestinal endoscopy revealed submucosal tumor-like elevated lesion in the anterior wall of the antrum with intact overlying mucosa (Figure 1). Histology from that mucosa showed active chronic *Helicobacter pylori*-positive gastritis with reactive lymphoid hyperplasia.

The endoscopic ultrasound was used to assess the tumor: It showed a 3-cm hypoechoic homogenous mass, originating from the third layer of the gastric wall. Endoscopic ultrasound-guided fine needle aspiration was performed to obtain specimens, but histopathological findings were not informative. Therefore endoscopic buttonhole biopsy was performed, but results were not informative again. After this procedure the patient was discharged home, but hospitalized again 7 d later due to vomiting, nausea and discomfort in the upper

abdomen. The endoscopy revealed that submucosal mass protruded into the gastric lumen and caused gastric outlet obstruction (Figure 2). The biopsies were taken from protruded mass.

This time microscopic features suggested the diagnosis of PAMT. The partial gastrectomy of the Billroth I type has been performed.

Histological examination of resected tumor confirmed the diagnosis: Microscopically, gastric wall showed involvement of submucosa and muscularis propria by a tumor comprising plexiform islands of monomorphic spindle cells accompanied by abundant myxoid stroma, that was rich in small vessels. The surface of tumor was ulcerated with hyperplastic changes found in adjacent mucosa. On immunohistochemical staining, the tumor cells were positive for smooth muscle actin and negative for desmin, CD34 and S100 protein. Mitoses were rarely seen ($< 1/50$ HPF). The vascular endothelial Ki-67 labeling index was approximately 40% (Figure 3).

Recovery after operation was complicated by gastroduodenal anastomosis, which was managed successfully with conservative measures.

We plan to make the follow-up investigations (upper gastrointestinal endoscopy and abdominal ultrasound) for the possible recurrence of tumor after 6 mo and then once a year.

DISCUSSION

PAMT also known as plexiform fibromyxoma of stomach, is an unique benign mesenchymal gastric tumor, originating within the muscularis propria^[1-6]. To date, only 19 immunohistochemically confirmed cases have been reported in the medical literature^[7-9]. According to the reported cases of PAMT, the estimated frequency of this gastric mesenchymal tumor is less than 1/150 compared with that of gastric gastrointestinal stromal tumor (GIST). The patients' ages range from 7 to 75 years (mean, 43 years) and approximate male-to-female ratio is 1:1^[10-13].

The representative signs and symptoms include abdominal pain and discomfort, nausea, vomiting, and weight loss (caused by pyloric obstruction), hematemesis and anemia (associated with upper gastrointestinal bleeding caused by ulceration), palpable abdominal mass. Cystic degeneration, fistulating abscess formation and perforation were also reported^[1,2,12].

Endoscopically, PAMT appears as submucosal mass, which ranges from 1.9 cm to 15 cm (mean, 6.3 cm)^[14]. Tumor is always located in gastric antrum (there are presumptions about the possible origin from cells specifically distributed at this location of muscularis propria layer) though it can extend to the pylorus and duodenal bulb^[15]. The overlying mucosa is often ulcerated.

On computed tomography (CT) scan, the tumor appears relatively small (found in the gastric antrum). There is strong and heterogeneous internal enhancement effect. Small nodules show a strong enhancement

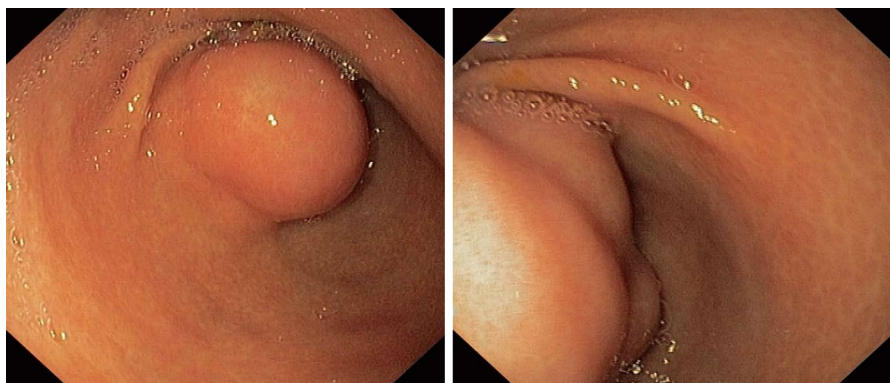


Figure 1 Images from outpatient upper gastrointestinal endoscopy. Submucosal tumor with intact overlying mucosa is located in the anterior wall of the antrum. It partially obstructs the gastric outlet.



Figure 2 Endoscopic images from our case of plexiform angiomyxoid myofibroblastic tumor show multinodular tumor-like mass protruding into the gastric lumen after performed buttonhole biopsy. This mass blocks the pylorus resulting in the stasis of gastric content.

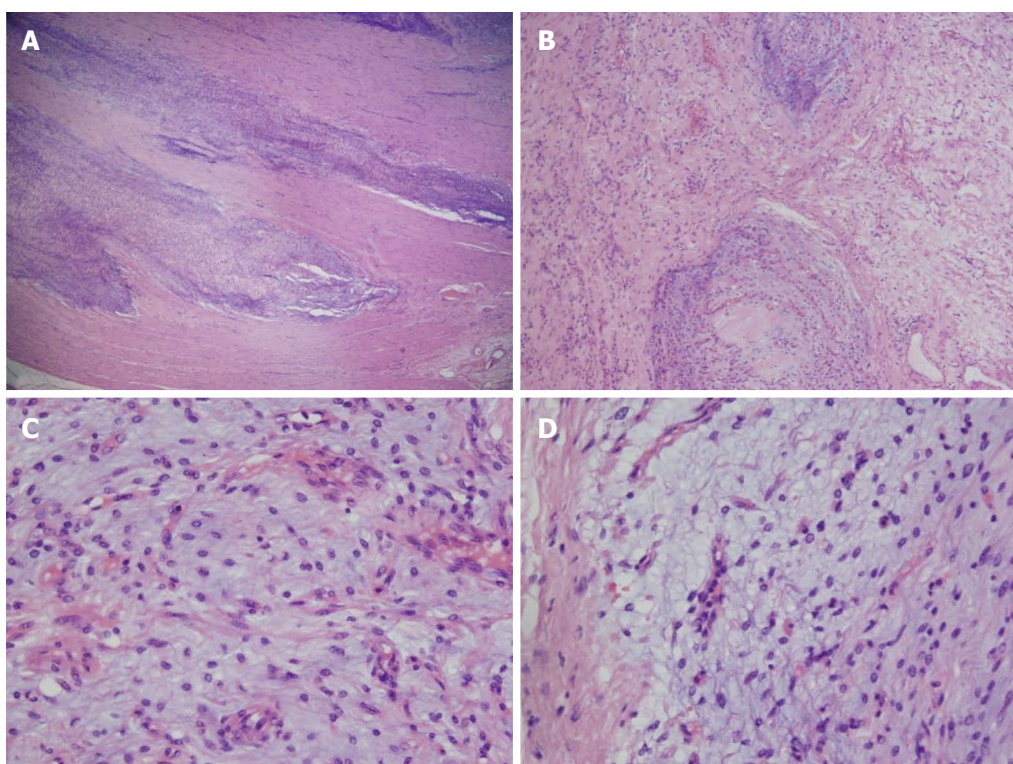


Figure 3 Multinodular plexiform growth pattern (A, B) and monomorphic spindle cells (C, D) accompanied by abundant myxoid stroma.

effect in the rim^[10]. The tumor also shows areas of low attenuation (because of the presence of myxoid tissue) and foci of vascularity. Magnetic resonance (MR) images demonstrate the myxoid stroma as T2-hyperintense lesion with persistent enhancement after administration of contrast material^[3,5].

Histologically, PAMT is characterized by multinodular plexiform growth pattern (except for the extragastric tumor components). Tumor originates within the third layer of stomach wall - the muscularis propria - and may extend into the submucosa and mucosa, causing ulceration (furthermore, gastric content particles may impact into the fistulated tumor, resulting in abscess and pseudocyst formation). Bland-looking spindle tumor cells are separated by an abundant myxoid or fibromyxoid matrix, rich in capillaries. Nuclei of the tumor cells are oval or plump-shaped and cytoplasm is slightly eosinophilic. Nucleoli are small and inconspicuous. Mitoses are rare (usually 0-4/50 HPF). The stroma is positive for Alcian blue stain, occasional collagenization may be observed. Immunohistochemical analysis of PAMT cells shows positivity for actin and vimentin, and negativity for CD34, S100P, KIT, DOG1, cytokeratin, neurofilament, epithelial membrane antigen, ALK. Tumor cells are mostly positive for α -smooth muscle actin (up to 80%), while positivity for desmin, CD10 and caldesmon is variable. Ki-67 usually demonstrates a very low proliferation index (1%-2%). Genetic studies show no mutations in KIT and PDGFRA^[1,2,6,7,9,14].

Differential diagnoses of PAMT include GIST, which accounts for the majority of intramural gastric tumors, also inflammatory fibroid polyp, plexiform neurofibroma, myxoid leiomyoma, leiomyosarcoma, desmoid fibromatosis, gastric schwannoma, solitary fibrous tumor, inflammatory myofibroblastic tumor^[4,8].

As mentioned before, differentiating between various intramural lesions may be difficult - clinical signs and symptoms are nonspecific or absent, radiological features often overlap, upper gastrointestinal endoscopy has a limited role because of intramural location. Endoscopic ultrasound yields opportunity to visualize and biopsy the tumor. Definite diagnosis requires histological and immunohistochemical analysis^[11,16]. According to the described cases PAMT has good prognosis, no cases of local recurrence or metastasis had been reported.

As gastric PAMT is so rare in clinical practice, special attention is necessary to recognise this entity and avoid misdiagnosis. Although absence of confirmed recurrences or metastases suggests that PAMT of stomach is benign^[12], larger number of cases must be reported and analysed in order to specify its clinical significance, outcome and prognosis.

COMMENTS

Case characteristics

A 28-year-old previously healthy Caucasian female presented with epigastric pain, associated with meals, iron-deficiency anaemia and loss of weight during the preceding six months.

Clinical diagnosis

Submucosal tumor-like elevated lesion in the anterior wall of the antrum.

Differential diagnosis

Gastrointestinal stromal tumor, inflammatory fibroid polyp, plexiform neurofibroma, myxoid leiomyoma, leiomyosarcoma, desmoid fibromatosis, gastric schwannoma, solitary fibrous tumor, inflammatory myofibroblastic tumor.

Laboratory diagnosis

Iron-deficiency anaemia.

Imaging diagnosis

The endoscopic ultrasound showed a 3-cm hypoechoic homogenous mass, originating from the third layer of the gastric wall.

Pathological diagnosis

Plexiform angiomyxoid myofibroblastic tumor (PAMT).

Treatment

Partial gastrectomy of the Billroth I type.

Related reports

PAMT also known as plexiform fibromyxoma of stomach, is an unique benign mesenchymal gastric tumor, originating within the muscularis propria. To date, only 19 immunohistochemically confirmed cases have been reported in the medical literature.

Experiences and lessons

Differentiating between various intramural lesions may be difficult - clinical signs and symptoms are nonspecific or absent, radiological features often overlap, upper gastrointestinal endoscopy has a limited role because of intramural location. Definite diagnosis requires histological and immunohistochemical analysis.

Peer-review

The paper Plexiform angiomyxoid myofibroblastic tumor of stomach: A rare case is an interesting description of a rare condition of tumor. The case presented here shows that surgical intervention under is successful.

REFERENCES

- 1 Takahashi Y, Suzuki M, Fukusato T. Plexiform angiomyxoid myofibroblastic tumor of the stomach. *World J Gastroenterol* 2010; **16**: 2835-2840 [PMID: 20556828 DOI: 10.3748/wjg.v16.i23.2835]
- 2 Lee PW, Yau DT, Lau PP, Chan JK. Plexiform fibromyxoma (plexiform angiomyxoid myofibroblastic tumor) of stomach: an unusual presentation as a fistulating abscess. *Int J Surg Pathol* 2014; **22**: 286-290 [PMID: 23794494 DOI: 10.1177/1066896913492198]
- 3 Kang HC, Menias CO, Gaballah AH, Shroff S, Taggart MW, Garg N, Elsayes KM. Beyond the GIST: mesenchymal tumors of the stomach. *Radiographics* 2013; **33**: 1673-1690 [PMID: 24108557 DOI: 10.1148/rg.336135507]
- 4 Stanford Medicine. Gastric Plexiform Fibromyxoma. Differential Diagnosis. Available from: URL:<http://surgpathercriteria.stanford.edu/gitumors/gastric-plexiform-fibromyxoma/differential-diagnosis.html>
- 5 Sakamoto K, Hirakawa M, Atsumi K, Mimori K, Shibata K, Tobo T, Yamamoto H, Honda H. A case of gastric plexiform fibromyxoma: radiological and pathological findings. *Jpn J Radiol* 2014; **32**: 431-436 [PMID: 24744134 DOI: 10.1007/s11604-014-0315-z]
- 6 Miettinen M, Makhoulouf HR, Sobin LH, Lasota J. Plexiform fibromyxoma: a distinctive benign gastric antral neoplasm not to be confused with a myxoid GIST. *Am J Surg Pathol* 2009; **33**: 1624-1632 [PMID: 19675452 DOI: 10.1097/PAS.0b013e3181ae666a]
- 7 Wang FH, Chen ZR, Niu HL, Zeng RX, Xia JQ. Plexiform fibromyxoma of stomach: a distinctive benign tumor of gastric antrum.

- Zhonghua Binglixue Zazhi* 2012; **41**: 190-191 [PMID: 22800485]
- 8 **Sing Y**, Subrayan S, Mqadi B, Ramdial PK, Reddy J, Moodley MS, Bux S. Gastric plexiform angiomyxoid myofibroblastic tumor. *Pathol Int* 2010; **60**: 621-625 [PMID: 20712648 DOI: 10.1111/j.1440-1827.2010.02569.x]
- 9 **Lu B**, Ye W, Liu H. A Rare Gastric Tumor in a Young Woman. Gastric Plexiform Angiomyxoid Myofibroblastic Tumor. *Gastroenterology* 2015; **149**: 294-295 [PMID: 26119799 DOI: 10.1053/j.gastro.2015.03.050]
- 10 **Ikemura M**, Maeda E, Hatao F, Aikou S, Seto Y, Fukayama M. Plexiform angiomyxoid myofibroblastic tumor (PAMT) of the stomach. A case report focusing on its characteristic growth pattern. *Int J Clin Exp Pathol* 2014; **7**: 685-689 [PMID: 24551290]
- 11 **Rau TT**, Hartmann A, Dietmaier W, Schmitz J, Hohenberger W, Hofstaedter F, Katenkamp K. Plexiform angiomyxoid myofibroblastic tumour: differential diagnosis of gastrointestinal stromal tumour in the stomach. *J Clin Pathol* 2008; **61**: 1136-1137 [PMID: 18820104 DOI: 10.1136/jcp.2008.059162]
- 12 **Schulz T**, Drgac J, Chmelar C, Höhler T, Agaimy A, Vieth M. Plexiform angiomyxoid myofibroblastic tumour of the stomach. *Pathologe* 2012; **33**: 65-69 [PMID: 22293792 DOI: 10.1007/s00292-011-1548-6]
- 13 **Kim A**, Bae YK, Shin HC, Choi JH. Plexiform angiomyxoid myofibroblastic tumor of the stomach: a case report. *J Korean Med Sci* 2011; **26**: 1508-1511 [PMID: 22065909 DOI: 10.3346/jkms.2011.26.11.1508]
- 14 **Li P**, Yang S, Wang C, Li Y, Geng M. Presence of smooth muscle cell differentiation in plexiform angiomyxoid myofibroblastic tumor of the stomach: a case report. *Int J Clin Exp Pathol* 2014; **7**: 823-827 [PMID: 24551311]
- 15 **Banerjee N**, Gupta S, Dash S, Ghosh S. Plexiform angiomyxoid myofibroblastic tumour of the duodenum: a rare entity. *BMJ Case Rep* 2015; **2015**: pii: bcr2015210004 [PMID: 26216925 DOI: 10.1136/bcr-2015-210004]
- 16 **Wang LM**, Chetty R. Selected unusual tumors of the stomach: a review. *Int J Surg Pathol* 2012; **20**: 5-14 [PMID: 22134628 DOI: 10.1177/1066896911429300]

P- Reviewer: Bae YK, Shen H, Tomazic A **S- Editor:** Qiu S
L- Editor: A **E- Editor:** Wu HL



Balloon-assisted enteroscopy for suspected Meckel's diverticulum and indefinite diagnostic imaging workup

Guilherme Francisco Gomes, Eduardo Aimore Bonin, Rafael William Noda, Leandro Totti Cavazzola, Thiago Ferreira Bartholomei

Guilherme Francisco Gomes, Eduardo Aimore Bonin, Rafael William Noda, Thiago Ferreira Bartholomei, Endoscopy Unit, Nossa Senhora das Graças Hospital, Curitiba 81830, Brazil

Leandro Totti Cavazzola, Universidade Federal do Rio Grande do Sul, Porto Alegre 91740, Brazil

Author contributions: Gomes GF, Bonin EA and Bartholomei TF acquired the data and wrote and revised the manuscript; Noda RW and Cavazzola LT contributed to writing and revising the manuscript.

Institutional review board statement: This case report is exempt from Institutional review board standards.

Informed consent statement: The patients involved in this study gave written informed consent authorizing use and disclosure of their protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Guilherme Francisco Gomes, MD, Endoscopy Unit, Nossa Senhora das Graças Hospital, Rua Mon Ivo Zanlorenzi, 1850 CEP 81210000, Curitiba 81830, Brazil. guilfgomes@gmail.com
Telephone: +55-41-32406505
Fax: +55-41-32068090

Received: April 27, 2016
Peer-review started: April 27, 2016
First decision: June 12, 2016

Revised: July 13, 2016

Accepted: August 27, 2016

Article in press: August 29, 2016

Published online: October 16, 2016

Abstract

Meckel's diverticulum (MD) is estimated to affect 1%-2% of the general population, and it represents a clinically silent finding of a congenital anomaly in up to 85% of the cases. In adults, MD may cause symptoms, such as overt occult lower gastrointestinal bleeding. The diagnostic imaging workup includes computed tomography scan, magnetic resonance imaging enterography, technetium 99m scintigraphy (99mTc) using either labeled red blood cells or pertechnetate (known as the Meckel's scan) and angiography. The preoperative detection rate of MD in adults is low, and many patients ultimately undergo exploratory laparoscopy. More recently, however, endoscopic identification of MD has been possible with the use of balloon-assisted enteroscopy *via* direct luminal access, which also provides visualization of the diverticular ostium. The aim of this study was to review the diagnosis by double-balloon enteroscopy of 4 adults with symptomatic MD but who had negative diagnostic imaging workups. These cases indicate that balloon-assisted enteroscopy is a valuable diagnostic method and should be considered in adult patients who have suspected MD and indefinite findings on diagnostic imaging workup, including negative Meckel's scan.

Key words: Double-balloon enteroscopy; Meckel's diverticulum; Diagnosis

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Meckel's diverticulum (MD) is estimated to affect 1%-2% of the general population and has 4%-6%

risk of causing symptoms during a lifetime. In adults, it may cause occult massive bleeding and the preoperative detection rate is low; patients with undiagnosed MD ultimately undergo exploratory laparoscopy. More recently, however, endoscopic identification of MD has been possible with the use of balloon-assisted enteroscopy *via* direct luminal access, providing visualization of the diverticular ostium. We report here the use of double-balloon enteroscopy for diagnosing 4 adults with symptomatic MD who had negative diagnostic imaging workup.

Gomes GF, Bonin EA, Noda RW, Cavazzola LT, Bartholomei TF. Balloon-assisted enteroscopy for suspected Meckel's diverticulum and indefinite diagnostic imaging workup. *World J Gastrointest Endosc* 2016; 8(18): 679-683 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i18/679.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i18.679>

INTRODUCTION

Meckel's diverticulum (MD) is a congenital true diverticulum that develops from a patent omphalo-mesenteric duct^[1]. It is estimated to affect 1%-2% of the general population and has 4%-6% risk of causing symptoms during a lifetime^[2,3]. Surgical resection is not mandatory for cases of MD that are found incidentally. Any MD > 2 cm in length and with palpable abnormal tissue within the diverticulum, however, is associated with a higher lifetime risk for complication for male patients of ages under 50 years^[4], and should be considered for resection. Although MD represents a clinically silent finding of a congenital anomaly in up to 85% of cases^[4], patients who develop a complication may suffer from the lack of diagnosis and subsequent delayed initiation of appropriate treatment. When symptoms occur, they usually include melena/hematochezia from a bleeding vessel or abdominal pain from intussusception or adhesions. Confirmation of MD relies on identifying a true diverticulum, usually located within 100 cm from the ileocecal valve. Rarely, a source of bleeding, such as an ulcer, can be found inside its lumen.

In adults, any patient presenting with documented bleeding in the lower gastrointestinal tract and negative findings on upper endoscopy and colonoscopy should be suspected of having a symptomatic MD. The routine diagnostic imaging workup includes computed tomography (CT) scan, magnetic resonance imaging (MRI) enterography, technetium 99m scintigraphy (99mTc) using either labeled red blood cells or pertechnetate (known as the Meckel's scan) and angiography. More recently, however, endoscopic identification of MD has been possible with the use of balloon-assisted enteroscopy *via* direct luminal access, providing visualization of the diverticular ostium^[5].

Herein, we report the use of double-balloon enteros-

copy (DBE) for diagnosing 4 adults with symptomatic MD who had negative diagnostic imaging workup.

CASE REPORT

Between January 2007 and December 2015, 114 patients underwent DBE at Nossa Senhora das Graças Hospital (Curitiba, Brazil). For most patients, the indication for DBE was obscure gastrointestinal bleeding. All patients underwent clinical evaluation by the examiner before the procedure. MD was clinically suspected in young patients with episodes of overt rectal bleeding and negative diagnostic imaging workup. MD was found in 4 patients with obscure gastrointestinal bleeding, including overt rectal bleeding in 3 and with abdominal pain in 1. The patients included 3 males and 1 female, ranging in age from 16-year-old to 45-year-old (mean, 22-year-old).

MD diagnosis was made by retrograde (per anus) DBE for all 4 patients, with 1 of the patients having first undergone an unsuccessful approach by antegrade (per mouth). The typical endoscopic feature of MD in these cases was diverticular ostium and lumen in the ileum, found after exhaustive active search (Figure 1). All diverticula were located between 70 cm and 90 cm from the ileocecal valve, and none had stigmata of recent or active bleeding. All patients underwent endoscopic submucosal ink injection (tattooing) of the peridiverticular region, which facilitated a later elective laparoscopic resection (Figure 2).

The equipment used was the Fujinon EN-450P DBE system (Fuji, Tokyo, Japan). All procedures were performed under deep sedation that was established using intravenous propofol.

Cases 1 and 2

These two patients had similar symptoms, and as such will be described jointly. Diagnosis occurred at 17-years-old (case 1) and 27-years-old (case 2). Both patients had history of multiple episodes of bleeding with hematochezia, melena and blood transfusion. In both patients, upper and lower endoscopy and red blood cell-labeled scintigraphy gave negative findings. Both patients also had a previous negative Meckel's scan. Case 2 had experienced an episode of hematochezia with hemodynamic instability, for which an angiography was performed but did not reveal a source of bleeding. Both patients underwent a retrograde DBE, which revealed MD in the ileum.

Case 3

This 17-year-old male presented to our institution with a history of three episodes of hematochezia, each requiring blood transfusion. He underwent upper endoscopy and colonoscopy, which showed blood clots in the colon but revealed no source of bleeding. A subsequent upper and lower endoscopy, followed by Meckel's scan and small bowel video capsule exam, provided no additional findings. At admission, hemoglobin and hematocrit

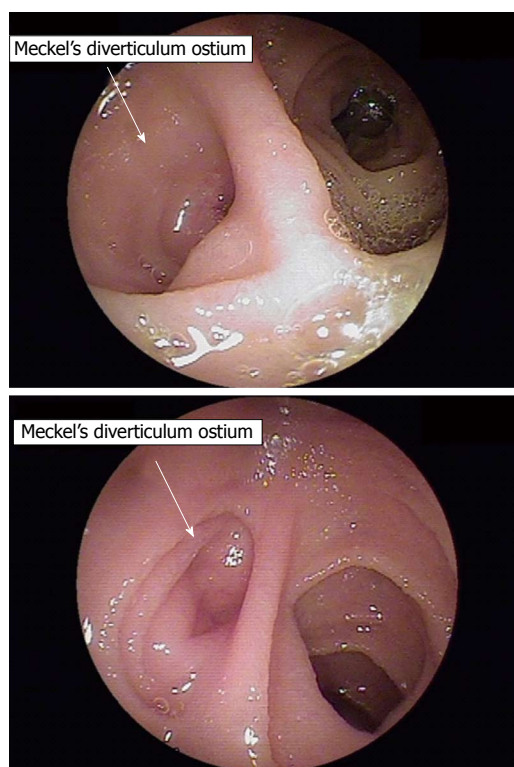


Figure 1 The typical endoscopic feature of Meckel's diverticulum in these cases was diverticular ostium and lumen in the ileum, found after exhaustive active search. The two images represent the different depths of the Meckel's diverticulum in different cases.

were within normal range. Three weeks later, the patient had a new episode of rectal bleeding and was re-hospitalized. A DBE was performed orally until the jejuno-ileal region was reached, which showed normal findings. We then decided to carry out another DBE, this time rectally, and MD was visualized in the ileum at 90 cm from the ileocecal valve. There was no evidence of active bleeding or ulcers around the diverticulum.

Case 4

This 45-year-old female presented with severe abdominal pain associated with bloating. She had been hospitalized twice within a 2-wk period, and presented clinically with abdominal distension; however, no abdominal mass was palpable. White and red blood cell counts and platelets were normal. An abdominal CT scan was performed and demonstrated thickening of the distal ileum region of about 10 cm in length, which was suspected as obstructive inflammatory bowel disease. A DBE was then performed and showed MD, with no signs of ulceration or obstruction. The patient underwent laparoscopy, which showed MD attached to a mesodiverticular band and determined obstruction of the ileum, located approximately 80 cm from the ileocecal valve.

Treatment

All patients underwent elective laparoscopic resection

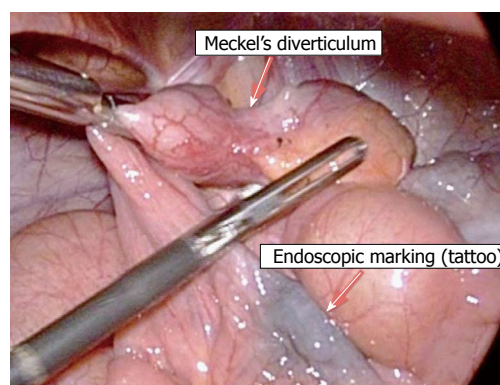


Figure 2 All patients underwent endoscopic submucosal ink injection (tattooing) of the peridiverticular region, which facilitated a later elective laparoscopic resection.

of a segment of the small bowel that contained the diverticulum, with end-to-end anastomosis. The treatment was successful in all cases.

DISCUSSION

MD is considered a true diverticulum, which by definition contains all layers of the intestinal wall. It is located in the ileum, with reported average distances from the ileocecal valve varying according to age: 34 cm in children > 2-year-old; 46 cm in patients between 3-year-old and 21-year-old; 67 cm in adults 21-year or older^[6]. MD may have gastric, duodenal, colon, mucosal and pancreatic rests, which originate from multipotent cells within the omphalo-mesenteric duct wall.

A wide array of imaging techniques are available for detecting MD, such as Meckel's scan, balloon-assisted enteroscopy, capsule endoscopy, CT scan (with or without enterography), MRI enterography and mesenteric catheter angiography. MD diagnosis is more difficult in adults, for whom Meckel's scan MD's most accurate diagnostic modality is less accurate, as compared to children^[1]. In adults, MD should be suspected in cases of occult gastrointestinal bleeding with no evidence of vascular malformation or of unexplained abdominal pain with an abnormal imaging finding in the ileum. In cases of occult bleeding, the preoperative detection rate is low; adult patients may end up having undiagnosed MD and ultimately undergo exploratory laparoscopy^[1].

CT scan is considered the first-line diagnostic method for any adult patient with suspected MD. The sensitivity of CT scan for diagnosing MD has increased over the years, owing to development of the multidetector scan technique (MDCT). This technology provides visualization of the small bowel in various planes, and adding oral contrast (enterography) improves MD imaging^[7]. Furthermore, CT is very useful in diagnosing and assessing complications associated with MD, particularly for intra-abdominal abscess formation, obstruction, perforation and associated tumors, which is crucial in acute abdomen cases. MDCT may also detect

active extravasation of intravenous contrast medium in cases with active intestinal hemorrhage.

Meckel's scan is a valuable non-invasive test, in which radioactive tracers are used to locate the presence of functioning ectopic gastric mucosa. In children, it has a sensitivity of 80%-90%, specificity of 95% and accuracy of 90%^[2]. In contrast, in adults, the sensitivity is 62.5%, specificity is 9% and accuracy is 46%^[8]. According to the guideline recently published by the Society of Nuclear Medicine and Molecular Imaging^[8], "the indication for Meckel scintigraphy is to localize ectopic gastric mucosa in a Meckel diverticulum as the source of unexplained gastrointestinal bleeding. Meckel scintigraphy should be used when the patient is not actively bleeding... Even in young children, active bleeding is best studied by radiolabeled red blood cell scintigraphy". False-positive results are due to the presence of ectopic gastric mucosa elsewhere in the gastrointestinal tract, to enteric duplication and to inflammatory processes. A false-negative result may occur in cases of brisk gastrointestinal bleeding, small gastric ectopic mucosa (< 1.8 cm²) and a "wandering diverticulum". In our series, all patients had a negative Meckel's scan. Despite its low accuracy in adults, though, it remains widely used for confirming MD in our geographic region, given its nature of being a non-invasive diagnostic method.

Mesenteric catheter angiography is another diagnostic modality, but it is useful only in cases of ongoing bleeding and for patients with counterindications to a Meckel's scan. The usual minimum required bleeding rate is of 0.5 mL/min; however, lower bleeding rates can be detected when the digital subtraction angiography technique is applied. This procedure can be useful in locating an overt bleeding vessel and applying embolization treatment; however, it may require super-selective catheterization of the mid- and distal ileal arteries^[9].

Diagnosis of small bowel diseases has evolved dramatically over the past decade, particularly since the advent of capsule endoscopy and balloon-assisted enteroscopy. Both procedures enable endoscopic access to the entire small bowel. Capsule endoscopy is a simple, non-invasive technique to examine the small bowel by ingesting a wireless "pill" camera. Although capsule endoscopy has been used for diagnosing MD, its diagnostic yield is limited and there is a risk of capsule retention within the diverticulum^[10]. For these reasons, we tend not to use capsule endoscopy for patients with suspected MD.

Balloon-assisted enteroscopy consists of using a single- or a double-balloon method for inserting a flexible endoscope for visualization, biopsy and treatment of the entire small bowel. The first case of MD that was diagnosed by DBE was described in 2005, and since then it has been considered a safe and effective method for diagnosing MD, with a low complication rate in adults^[5]. In a recent study by He *et al.*^[11], the overall diagnostic yield of DBE for MD before surgery

was 86%, which was significantly higher compared to that of capsule endoscopy. Compared to Meckel's scan, its accuracy is higher for adult patients with suspected symptomatic MD. Admittedly, such results are based upon limited data, but it seems that DBE is becoming a pivotal diagnostic modality for confirming suspected MD in adults. Fukushima *et al.*^[5], based on their experience with 10 patients, recommends that dynamic MDCT scan followed by retrograde DBE be applied to stable patients to perform the initial diagnostic workup in adults with suspected MD. In addition, anterograde DBE is recommended as the initial approach for patients with overt, ongoing bleeding, and capsule endoscopy and mesenteric angiography are also suggested for such cases.

DBE offers some advantages over other methods for allowing direct observation of the diverticular ostium, access to the entire small bowel, repeated examinations of the region and intraluminal therapy (*i.e.* injection, coagulation)^[12,13]. Finding another potential source of bleeding may aid in establishing the correct diagnosis, since MD may coexist with several other lesions. Endoscopic tattooing is advised for locating the site of the lesion, whenever an endoscopic revision is needed. In our case series, tattooing also aided in locating the affected segment laparoscopically for subsequent resection. DBE may also reveal unusual MD presentations, such as an inverted MD - a rare condition in which the diverticulum is completely inverted intraluminally and mimics a large subepithelial lesion^[12]. Intradiverticular polyps and tumors can be also found through direct visualization inside the MD lumen^[5].

Apart from diagnosis, DBE can also provide a minimally invasive endoscopic approach for treatment of symptomatic MD^[13,14]. Identifying and treating a bleeding vessel within the MD using DBE^[13] can help to avoid an emergency operation. Bleeding control can be accomplished by endoscopic injection, coagulation and clipping. Since rebleeding is a concern, it is advised in such cases to proceed to elective MD resection. Successful cases of intradiverticular MD polypectomy and resection of an inverted MD through DBE have also been reported^[14].

In our experience, DBE has emerged over the years as a useful diagnostic modality of adult patients with suspected MD and indefinite findings on diagnostic imaging workup.

COMMENTS

Case characteristics

The authors describe 4 cases of Meckel's diverticulum being diagnosed using double-balloon enteroscopy.

Clinical diagnosis

Adult patients presenting with overt rectal bleeding or abdominal pain and without diagnosis despite extensive imaging workup.

Differential diagnosis

Gastrointestinal vascular malformations.

Laboratory diagnosis

Anemia due to bleeding.

Imaging diagnosis

Findings from upper endoscopy, lower endoscopy, Meckel's scan and computed tomography scan were all negative for source of symptoms.

Pathological diagnosis

Meckel's diverticulum.

Treatment

Complete laparoscopic surgical excision of the diverticulum.

Related reports

Meckel's diverticulum may cause occult massive bleeding in adult patients and the preoperative detection rate is low. Endoscopic identification of Meckel's diverticulum is possible with the use of balloon-assisted enteroscopy via direct luminal access, providing visualization of the diverticular ostium.

Term explanation

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract. It is estimated to affect 1%-2% of the general population and has 4%-6% risk of causing symptoms during a lifetime. Double-balloon enteroscopy is an endoscopic procedure that allows investigation and treatment of small bowel lesions.

Experiences and lessons

Balloon-assisted enteroscopy is a valuable diagnostic method and should be considered for use in adult patients with suspected Meckel's diverticulum and indefinite diagnostic imaging workup, including negative technetium 99m pertechnetate scintigraphy (known as the Meckel's scan).

Peer-review

The manuscript is well written. The most common cause of obscure gastrointestinal bleeding is gastrointestinal vascular malformation. Meckel's diverticulum, however, is a clinically important condition. Of 114 patients who underwent double-balloon enteroscopy, 4 cases of Meckel's diverticulum were diagnosed and are described by this study.

REFERENCES

- 1 **Sagar J**, Kumar V, Shah DK. Meckel's diverticulum: a systematic review. *J R Soc Med* 2006; **99**: 501-505 [PMID: 17021300 DOI: 10.1258/jrsm.99.10.501]
- 2 **Soltero MJ**, Bill AH. The natural history of Meckel's Diverticulum and its relation to incidental removal. A study of 202 cases of diseased Meckel's Diverticulum found in King County, Washington, over a fifteen year period. *Am J Surg* 1976; **132**: 168-173 [PMID: 952346 DOI: 10.1016/0002-9610(76)90043-X]
- 3 **Cullen JJ**, Kelly KA, Moir CR, Hodge DO, Zinsmeister AR, Melton LJ. Surgical management of Meckel's diverticulum. An epidemiologic, population-based study. *Ann Surg* 1994; **220**: 564-568; discussion 568-569 [PMID: 7944666]
- 4 **Park JJ**, Wolff BG, Tollefson MK, Walsh EE, Larson DR. Meckel diverticulum: the Mayo Clinic experience with 1476 patients (1950-2002). *Ann Surg* 2005; **241**: 529-533 [PMID: 15729078 DOI: 10.1097/01.sla.0000154270.14308.5f]
- 5 **Fukushima M**, Kawanami C, Inoue S, Okada A, Imai Y, Inokuma T. A case series of Meckel's diverticulum: usefulness of double-balloon enteroscopy for diagnosis. *BMC Gastroenterol* 2014; **14**: 155 [PMID: 25175823 DOI: 10.1186/1471-230X-14-155]
- 6 **Ymaguchi M**, Takeuchi S, Awazu S. Meckel's diverticulum. Investigation of 600 patients in Japanese literature. *Am J Surg* 1978; **136**: 247-249 [PMID: 308325]
- 7 **Paulsen SR**, Huprich JE, Fletcher JG, Booya F, Young BM, Fidler JL, Johnson CD, Barlow JM, Earnest F. CT enterography as a diagnostic tool in evaluating small bowel disorders: review of clinical experience with over 700 cases. *Radiographics* 2006; **26**: 641-657; discussion 657-662 [PMID: 16702444 DOI: 10.1148/rg.263055162]
- 8 **Spottswood SE**, Pfluger T, Bartold SP, Brandon D, Burchell N, Delbeke D, Fink-Bennett DM, Hodges PK, Jolles PR, Lassmann M, Maurer AH, Seabold JE, Stabin MG, Treves ST, Vljakovic M. SNMMI and EANM practice guideline for meckel diverticulum scintigraphy 2.0. *J Nucl Med Technol* 2014; **42**: 163-169 [PMID: 24948825 DOI: 10.2967/jmmt.113.136242]
- 9 **Kotha VK**, Khandelwal A, Saboo SS, Shanbhogue AK, Virmani V, Marginean EC, Menias CO. Radiologist's perspective for the Meckel's diverticulum and its complications. *Br J Radiol* 2014; **87**: 20130743 [PMID: 24611767 DOI: 10.1259/bjr.20130743]
- 10 **Tanaka Y**, Motomura Y, Akahoshi K, Nakama N, Osogawa T, Kashiwabara Y, Chaen T, Higuchi N, Kubokawa M, Nishida K, Yukaya T, Oya M, Nakamura K. Capsule endoscopic detection of bleeding Meckel's diverticulum, with capsule retention in the diverticulum. *Endoscopy* 2010; **42** Suppl 2: E199-E200 [PMID: 20845270 DOI: 10.1055/s-0030-1255696]
- 11 **He Q**, Zhang YL, Xiao B, Jiang B, Bai Y, Zhi FC. Double-balloon enteroscopy for diagnosis of Meckel's diverticulum: comparison with operative findings and capsule endoscopy. *Surgery* 2013; **153**: 549-554 [PMID: 23305600 DOI: 10.1016/j.surg.2012.09.012]
- 12 **Huang TY**, Liu YC, Lee HS, Chu HC, Chen PJ, Weng JW, Fu CK, Hsu KF. Inverted Meckel's diverticulum mimicking an ulcerated pedunculated polyp: detection by single-balloon enteroscopy. *Endoscopy* 2011; **43** Suppl 2 UCTN: E244-E245 [PMID: 21837594 DOI: 10.1055/s-0030-1256603]
- 13 **Olafsson S**, Yang JT, Jackson CS, Barakat M, Lo S. Bleeding Meckel's diverticulum diagnosed and treated by double-balloon enteroscopy. *Avicenna J Med* 2012; **2**: 48-50 [PMID: 23210023 DOI: 10.4103/2231-0770.99166]
- 14 **Fukushima M**, Suga Y, Kawanami C. Successful endoscopic resection of inverted Meckel's diverticulum by double-balloon enteroscopy. *Clin Gastroenterol Hepatol* 2013; **11**: e35 [PMID: 23022701 DOI: 10.1016/j.cgh.2012.09.023]

P- Reviewer: Chung DKV, Figueiredo PN, Vija L
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 November 16; 8(19): 684-722





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herreras Gutierrez, *Sevilla*

ASSOCIATE EDITORS

Chisato Hamashima, *Tokyo*

GUEST EDITORIAL BOARD MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmann, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Dimitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *Udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Naoki Hotta, *Nagoya*

Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurionhoj*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iruru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satohiro Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Nosho, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *UiJeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornnotin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentis, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *Albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciaccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

MINIREVIEWS

- 684** Gastrointestinal tract access for urological natural orifice transluminal endoscopic surgery
Miakicheva O, Hamilton Z, Beksac AT, Berquist SW, Hassan AE, Holden M, Derweesh IH
- 690** Microvasculature of the esophagus and gastroesophageal junction: Lesson learned from submucosal endoscopy
Maselli R, Inoue H, Ikeda H, Onimaru M, Yoshida A, Santi EG, Sato H, Hayee B, Kudo SE

ORIGINAL ARTICLE

Observational Study

- 697** Patients presenting for colonoscopy: A great opportunity to screen for sleep apnea
Harvin G, Ali E, Raina A, Leland W, Abid S, Vahora Z, Movahed H, Kachru S, Tee R
- 701** Information seeking and anxiety among colonoscopy-naïve adults: Direct-to-colonoscopy vs traditional consult-first pathways
Silvester JA, Kalkat H, Graff LA, Walker JR, Singh H, Duerksen DR

Prospective Study

- 709** Post-endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity
El Nakeeb A, El Hanafy E, Salah T, Atef E, Hamed H, Sultan AM, Hamdy E, Said M, El Geidie AA, Kandil T, El Shobari M, El Ebidy G

Randomized Controlled Trial

- 716** Vonoprazan 20 mg vs lansoprazole 30 mg for endoscopic submucosal dissection-induced gastric ulcers
Takahashi K, Sato Y, Kohisa J, Watanabe J, Sato H, Mizuno K, Hashimoto S, Terai S

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 19 November 16, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Timothy D Kane, MD, Professor, Surgeon, Division Pediatric General and Thoracic Surgery, Childrens National Medical Center, Washington, DC 20010-2970, United States

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Dan Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Shui Qiu*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com>

www.wjgnet.com/1948-5190/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
Fang-Fang Ji, Vice Director
World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
November 16, 2016

COPYRIGHT
© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

Gastrointestinal tract access for urological natural orifice transluminal endoscopic surgery

Olga Miakicheva, Zachary Hamilton, Alp T Beksac, Sean W Berquist, Abd-elrahman Hassan, Marc Holden, Ithaar H Derweesh

Olga Miakicheva, Zachary Hamilton, Alp T Beksac, Sean W Berquist, Abd-elrahman Hassan, Marc Holden, Ithaar H Derweesh, Department of Urology, UC San Diego School of Medicine, La Jolla, CA 92093-0987, United States

Author contributions: All authors contributed to this paper with conception and design of study, literature review, drafting, critical revision and editing and approval of the final version.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Ithaar H Derweesh, Department of Urology, UC San Diego School of Medicine, 3855 Health Sciences Drive, La Jolla, CA 92093-0987, United States. iderweesh@gmail.com
Telephone: +1-858-8226187
Fax: +1-858-8226188

Received: April 27, 2016

Peer-review started: April 28, 2016

First decision: July 20, 2016

Revised: August 8, 2016

Accepted: September 13, 2016

Article in press: September 18, 2016

Published online: November 16, 2016

transluminal endoscopic surgery (NOTES), focusing on urologic procedures with gastrointestinal tract access, to update on the development of this novel surgical approach. As part of the methods, a comprehensive electronic literature search for NOTES was conducted using PubMed and Cochrane Library from March 2002 to February 2016 for papers reporting urologic procedures performed utilizing gastrointestinal tract access. A total of 11 peer-reviewed studies examining utility of gastrointestinal access for NOTES urologic procedures were noted, with the first report in 2007. The procedures reported in the studies were total/radical nephrectomy, partial nephrectomy, adrenalectomy, and prostatectomy. The transgastric approach was identified in five studies examining total/radical nephrectomy ($n = 2$), partial nephrectomy ($n = 1$), partial cystectomy ($n = 1$), and adrenalectomy ($n = 1$). Six studies evaluated transrectal approach for NOTES, describing total/radical nephrectomy ($n = 3$), partial nephrectomy ($n = 1$), robotic nephrectomy with adrenalectomy ($n = 1$) and prostatectomy ($n = 1$). Feasibility was reported in all studies. Most studies were preclinical and acute, and limited by concerns regarding restricted instrumentation and infection risk. We concluded that gastrointestinal access for urologic NOTES demonstrates promise as described by outlined feasibility studies in preclinical models. Nonetheless, clinical application awaits further advancements in surgical technology and concerns regarding infectious potential.

Key words: Gastrointestinal tract; Transrectal; Urology; Natural orifice transluminal endoscopic surgery

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Gastrointestinal (transgastric and transrectal) access is technically feasible for natural orifice transluminal endoscopic surgery (NOTES) in a number of major urological procedures, and is an attractive alterna-

Abstract

We conducted a literature review of natural orifice

tive with similar outcomes and distinct advantages compared to transvaginal NOTES. The recent adaptation of robotic technology to transrectal NOTES points the way toward future horizons. Further testing and device development is required prior to clinical application.

Miakicheva O, Hamilton Z, Beksac AT, Berquist SW, Hassan AE, Holden M, Derweesh IH. Gastrointestinal tract access for urological natural orifice transluminal endoscopic surgery. *World J Gastrointest Endosc* 2016; 8(19): 684-689 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/684.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.684>

INTRODUCTION

The introduction of minimally invasive urologic surgery has ushered in a new era of surgical advancements that aim to improve surgical outcomes such as decreasing morbidity, expediting patient recovery, and minimizing scars^[1]. Procedures which were initially laparoscopic, progressed to single-site and robotically assisted minimally invasive techniques and are now made possible *via* natural orifice transluminal endoscopic surgery (NOTES)^[2,3].

Indeed, the promise of NOTES has been the next quantum leap of minimally invasive surgery to further decrease wound morbidity and to further diminish the surgical footprint has outcomes associated with traditional laparoscopic surgery. The past ten plus years have seen a dizzying array of feasibility experiments in general surgical, urological and gynecologic natural orifice procedures, with more limited clinical applications. Nonetheless, NOTES currently remains on the margins of surgical practice, restricted to an "avant-garde" of surgical innovators. In urologic practice, NOTES applications have been mostly transvaginal, though given the substantial male patient population, a need to consider alternative points has been imperative. As such, the gastrointestinal tract may present an alternative with greater applicability to the urologic patient population. We conducted a systematic review of the utilization of gastrointestinal tract access in the performance of urological procedures.

MATERIALS AND METHODS

A systemic electronic literature search was conducted to identify any publications relating to gastrointestinal tract access for urological NOTES using PubMed (<http://www.pubmed.gov/>) and Cochrane Library (<http://www.cochranelibrary.com/>) from March 2002 to February 2016. Several combinations of the following search terms were used to identify pertinent publications: "Natural Orifice Transluminal Endoscopic Surgery", "transrectal", "trans anal", "transgastric", "gastrointestinal tract access", "urology", "NOTES", "nephrectomy", "cystectomy", "adrenalectomy", and "prostatectomy". Only peer-reviewed published series of urological NOTES procedures were included in the analysis of current state

of gastrointestinal tract access urological NOTES. We excluded reviews, editorials, and abstracts.

Historical context

The coining of NOTES as the exact term was agreed on by the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Working Group in 2005^[1]. The first pre-clinical example of natural orifice surgery in urology was completed in 2002 by Gettman *et al*^[4] when a transvaginal laparoscopic nephrectomy in a porcine model was completed. Since that time, various procedures in urology have been proven possible by NOTES, including partial and radical nephrectomy, cystectomy and prostatectomy^[5]. Transoral, transgastric, transvaginal, transvesical and transrectal routes have been utilized^[5-7]. Additionally, NOTES has included various surgical approaches, including laparoscopic and robotic assisted techniques^[5-7]. Initial barriers to NOTES, outlined by the SAGES/ASGE Working Group^[1], included: Access to peritoneal cavity, gastric (intestinal) closure, prevention of infection, development of suturing and anastomotic devices, spatial orientation, development of a multitasking platform to accomplish procedures, management of intraperitoneal complications, physiologic untoward events, compression syndromes, and training. Gastrointestinal tract access NOTES for urologic procedures still remains firmly in pre-clinical research stages; however, there is great potential in extending the availability of NOTES to a greater clinical context. A total of 11 pre-clinical studies utilizing gastrointestinal tract access for NOTES urologic procedures were identified (Tables 1 and 2).

TRANSGASTRIC UROLOGICAL NOTES

Five studies were identified that investigated utility of transgastric approach for urologic NOTES. Two studies demonstrated feasibility of total nephrectomy, one for partial nephrectomy, partial cystectomy, and adrenalectomy, respectively (Table 1).

Transgastric nephrectomy and partial nephrectomy

In 2007 Lima *et al*^[8] first demonstrated feasibility of transgastric access in urologic NOTES for total nephrectomy. This porcine acute study utilized a combined transgastric and transvesical approach *via* an ureteroscope and a gastroscope to successfully perform nephrectomy in all planned procedures ($n = 6$), with median operative time of 120 min. The initial two procedures were notable for mild hemorrhage after renal vessel ligation; however, this was avoided in remaining operations by the application of surgical clips prior to ultrasonic ligation of the vessels. The findings of the study were limited by a lack of closure of gastrotomy due to absence of endoscopic suturing devices and lack of specimen extraction^[8].

Isariyawongse *et al*^[9] investigated utility of NOTES nephrectomy utilizing a hybrid transgastric and trans-

Table 1 Transgastric gastrointestinal tract access urological natural orifice transluminal endoscopic surgery

Ref.	Access	Procedures	Model	Summary
Lima <i>et al</i> ^[8] , 2007	Transgastric; transvesical	Nephrectomy (<i>n</i> = 6)	Porcine	Initial mild hemorrhage appropriately corrected in remaining group
Isariyawongse <i>et al</i> ^[9] , 2008	Transgastric; transvaginal	Nephrectomy (<i>n</i> = 1)	Porcine	Successful bilateral nephrectomies achieved with both transvaginal and transgastric approaches
Sawyer <i>et al</i> ^[12] , 2009	Transgastric; transurethral	Partial cystectomy (<i>n</i> = 5)	Porcine	Successful completion of pure transurethral NOTES transurethral (<i>n</i> = 4) and pure transgastric NOTES (<i>n</i> = 1)
Boylu <i>et al</i> ^[10] , 2010	Transgastric; hybrid	Partial nephrectomy (<i>n</i> = 1)	Porcine	Use of thulium laser in successful partial nephrectomy
Fritscher-Ravens <i>et al</i> ^[11] , 2008	Transgastric	Adrenalectomy (<i>n</i> = 10)	Porcine	A comparative study of NOTES alone <i>vs</i> NOTES and endoscopic ultrasound guidance NOTES

NOTES: Natural orifice transluminal endoscopic surgery.

Table 2 Transrectal gastrointestinal tract access urological natural orifice transluminal endoscopic surgery

Ref.	Access	Procedures	Model	Summary
Bazzi <i>et al</i> ^[13] , 2011	Transrectal hybrid	Nephrectomy (<i>n</i> = 3)	Porcine	First report of transrectal hybridized NOTES
Bazzi <i>et al</i> ^[15] , 2012	Transrectal hybrid	Nephrectomy (<i>n</i> = 4)	Cadaver	Successful nephrectomy in a cadaveric model with intact specimen extraction
Eyraud <i>et al</i> ^[18] , 2013	Transrectal hybrid	Robot assisted nephrectomy and adrenalectomy (<i>n</i> = 1)	Cadaver	First investigation of robotic nephrectomy and adrenalectomy. Successful adaptation of robot to NOTES platform
Bazzi <i>et al</i> ^[17] , 2013	Transrectal hybrid; Transvaginal hybrid	Partial nephrectomy (<i>n</i> = 10)	Porcine	No significant in access or operative times for transrectal or transvaginal approaches to partial nephrectomy
Park <i>et al</i> ^[16] , 2014	Transvaginal; transrectal; Conventional laparoscopy	Nephrectomy (<i>n</i> = 15)	Porcine	Survival model; no difference in evidence of infection or injury at necropsy; no difference in inflammatory markers
Akça <i>et al</i> ^[19] , 2015	Transrectal	Prostatectomy (<i>n</i> = 1)	Cadaver	Proof of principle for transrectal approach for NOTES prostatectomy

NOTES: Natural orifice transluminal endoscopic surgery.

vaginal approach. Successful bilateral nephrectomy was performed by first visualizing the abdominal cavity *via* a transgastric endoscope and using the transgastric endoscope to establish a transvaginal NOTES port. Total operative time was 40 min for the right nephrectomy and 20 min for the left. The combined transgastric-transvaginal approach allowed for excellent visualization, multitude of readily available instruments to perform basic surgical tasks, and successful specimen extraction through a transvaginal route^[9].

Boylu *et al*^[10] successfully demonstrated the feasibility of transgastric NOTES partial nephrectomy hemostasis in the porcine model. The procedure utilized a therapeutic gastroscope (Olympus GIF-2T160, Melville, NY, United States) combined with a thulium laser (RevoLix; AllMed Systems, Pleasanton, CA, United States) to gain access to the peritoneum, visualize and complete excision the left kidney's upper pole without additional hemostatic measures. The specimen was extracted using an endoscopic wire loop *via* the stomach and the gastrostomy was closed with metal clips. Total operative time was 240 min. Limitations described by the authors included excess smoke produced by the thulium laser as well as lack of appropriate entrapment sacks for safe specimen removal *via* a gastroscope^[10].

Transgastric adrenalectomy

Fritscher-Ravens *et al*^[11] demonstrated adrenal gland removal in pigs using NOTES alone or with endoscopic ultrasound guidance (EUS). The study showed that

adrenal gland removal failed in all NOTES-only procedures (*n* = 4) in which it was attempted while it was successful in six NOTES-EUS (*n* = 6) cases. The NOTES-only cases of adrenalectomy were halted due to lack of safe access to the organ and bleeding during attempted access. Successful adrenalectomy was achieved in the NOTES-EUS group without complication with a mean duration of 78 min. In addition to successful adrenalectomy in the combined NOTES-EUS approach, the study demonstrated successful closing of the gastrostomy using an endoscopic suturing system^[11].

Transgastric partial cystectomy

NOTES partial cystectomy in a porcine model was described by Sawyer *et al*^[12]. The study outlined both two approaches: Transgastric with a urethral assist port and pure transurethral. Both approaches allowed for the completion of successful partial cystectomy with specimen excision and defect reapproximation with endoscopic clips. Transgastric partial cystectomy was performed in one porcine model with an operative time of 93 min. The authors noted that despite being more invasive, the transgastric approach offered better visualization of target anatomy and ability to sample lymph nodes for malignant pathology^[12].

TRANSRECTAL UROLOGIC NOTES

Six studies investigated utility of transrectal NOTES for urologic procedures. Three studies demonstrated

feasibility of total nephrectomy, one for partial nephrectomy, total nephrectomy and adrenalectomy, and prostatectomy, respectively (Table 2).

Transrectal NOTES nephrectomy

Bazzi *et al.*^[13] described the first transrectal NOTES nephrectomy in an acute porcine model utilizing a transrectal access technique described by Ramamoorthy *et al.*^[14]. This form of access involved creation of a submucosal tunnel in the anus, and dissection along the posterior rectal wall and access into the retroperitoneum, which was monitored by a transumbilical port which was also used for additional retraction, thus fitting into the “hybrid” NOTES model. Three cases of transrectal hybrid NOTES nephrectomy were successfully completed without conversion to conventional laparoscopic or open surgery and without significant intra-abdominal bleeding. Median operative time was 180 min and estimated blood loss was < 50 mL for all cases. The setting of a transrectal access with nephrectomy provided the advantages of a larger access point for instruments and specimen retrieval, easier closure of the access site compared to the transgastric approach, and the ability for application of the approach in both sexes, compared to transvaginal access. The success of this initial report provided proof-of-principle for the transrectal approach as an alternative to the primary transvaginal approach^[13].

Bazzi *et al.*^[15] described feasibility of transrectal hybrid NOTES nephrectomy in four human cadavers. Similar to prior work, the hybrid approach utilized a periumbilical transabdominal laparoscopic port. All four cases were performed successfully with a mean operative time of 175 min and no conversions of operative approach. The periumbilical port was utilized for guidance of transrectal access, assistance in renal mobilization, and in deployment of the stapler. However, more than 75% of the procedure was performed *via* instrumentation inserted *via* the transrectal access^[15].

Park *et al.*^[16] compared feasibility and safety of transrectal ($n = 5$), transvaginal ($n = 5$) and conventional laparoscopic ($n = 5$) total nephrectomy in a survival porcine model, and examined inflammatory cytokines between the groups. They noted that all procedures were successfully completed without conversion, and while operative time was longer for transrectal and transvaginal approaches (84 min vs 61 min vs 24 min, respectively, $P < 0.001$), there were no signs of visceral injury or peritonitis on postmortem examination at the 1 wk mark. Furthermore, none of the laboratory parameters, including white blood cell count, tumor necrosis factor- α , interleukin (IL)-1, and IL-6 differed among the groups during the entire experimental period^[16].

Transrectal NOTES partial nephrectomy

Bazzi *et al.*^[17] compared transrectal ($n = 5$) and transvaginal ($n = 5$) approaches for hybrid NOTES partial nephrectomy in an acute porcine model. In this study, 10 porcine models (5 transrectal, 5 transvaginal) un-

derwent partial nephrectomy. Following transrectal and transvaginal access, the SPIDER (Transenterix, Morrisville, NC, United States) articulating dissecting and suturing platform, was deployed. The procedure was completed successfully in all 10 cases without need for conversion. There were no significant differences when comparing transrectal and transvaginal approaches for access time (29.2 min vs 29.6 min, $P = 0.944$), operative time (196 min vs 183 min, $P = 0.631$) or estimated blood loss (59 mL vs 54 mL, $P = 0.631$)^[17].

Transrectal NOTES robotic nephrectomy and adrenalectomy

Eyraud *et al.*^[18] demonstrated feasibility of robotic (Da Vinci SI, Intuitive Surgical, Sunnyvale, CA, United States) assisted hybrid transrectal NOTES nephrectomy and adrenalectomy in a male cadaver. Transrectal access was achieved by a submucosal tunnel followed by placement of a robotic 8 mm-trocar. This was followed by placement of periumbilical 12 mm and 8 mm robotic ports, and a transrectal 8 mm robotic ports. The procedure was successfully completed with an operative time of 145 min, of which 20 min was for access/robotic docking and 20 min was for rectal closure^[18].

Transrectal NOTES prostatectomy

Akca *et al.*^[19] described transrectal NOTES prostatectomy in a cadaveric model. The cadaver was placed in an exaggerated lithotomy position, the anterior rectal wall was incised, and a single port device (GelPOINT®, Applied Medical, Santa Margarita, CA, United States) was deployed, through which all working and camera ports were inserted through. The authors reported ease of exposure of the posterior surface of the prostate and seminal vesicles with intact specimen extraction, and pointed the way for further testing with respect to feasibility of lymph node dissection using the transrectal route^[19].

FUTURE DIRECTIONS

In order for transrectal NOTES to evolve into a clinically viable option, advances in device development and addressing concerns regarding infection risk with outcomes comparable to conventional laparoscopy must be demonstrated^[20]. Single port surgery can lead to reduced maneuverability and difficult laparoscopic suturing skills, thus further developments will likely incorporate robotic platforms to overcome these limitations^[21]. Transrectal NOTES has continued to gain influence in the setting of colorectal surgery, and further advancement in urology will require emulation of this field^[22]. From this foundation of colorectal procedures, urologic applications can continue to advance.

Robotic assistance in NOTES has been suggested as a way to increase surgical feasibility and procedure applicability^[23]. As the robotic platform continues to expand in its scope of utilization in urologic surgery,

applications of robotics in NOTES may follow. As robotic technology continues to evolve in the direction of decreased instrument profile and flexible articulation, haptic feedback and improved optics, robotic NOTES may reach that critical tipping point of fusion of technical feasibility, adoption, desirability by patients and ultimately, acceptance by medical and surgical establishments to enter the mainstream of the surgical armamentarium.

Concerns regarding infectious potential of transiting viscera have been a significant hindrance to acceptance and application of NOTES, and this is especially true with the transrectal approach. Given high bacterial prevalence in the gastrointestinal tract, post-operative infections continue to be a major concern regarding transrectal NOTES^[24]. Device innovation is working to decrease this risk as well. Recently, Senft *et al.*^[25] demonstrated the efficacy of ColoShield (A.M.I., Feldkirch, Austria), a colon occlusion device, in reducing peritoneal contamination in transrectal NOTES. The occlusion device is inserted 15-20 cm above the anus, inflated to ensure a tight seal with the colonic wall, and maintained in the position through the duration of the surgery. The device acts as a physical impediment in the colon to prevent any unwanted fecal contamination. Device innovations such as this will certainly play a role in the future of transrectal NOTES.

CONCLUSION

Transvaginal NOTES, although feasible for urologic procedures, has limited applicability to the female population^[26]. The introduction and exploration of gastrointestinal tract as a urological NOTES entry site opens up the realm of the minimally invasive technique to a much larger population. Urologic transrectal and transgastric NOTES has thus far included nephrectomy, partial nephrectomy, adrenalectomy, and prostatectomy, as well as robotic-assisted techniques. Future pre-clinical survival studies are requisite to determine the potential of urologic transrectal NOTES, with emphasis on improved instrumentation, robotic assistance, and avoidance of infection.

REFERENCES

- 1 ASGE; SAGES. ASGE/SAGES Working Group on Natural Orifice Transluminal Endoscopic Surgery White Paper October 2005. *Gastrointest Endosc* 2006; **63**: 199-203 [PMID: 16427920]
- 2 Harrell AG, Heniford BT. Minimally invasive abdominal surgery: lux et veritas past, present, and future. *Am J Surg* 2005; **190**: 239-243 [PMID: 16023438 DOI: 10.1016/j.amjsurg.2005.05.019]
- 3 Swain P. Nephrectomy and natural orifice transluminal endoscopy (NOTES): transvaginal, transgastric, transrectal, and transvesical approaches. *J Endourol* 2008; **22**: 811-818 [PMID: 18419222 DOI: 10.1089/end.2007.9831]
- 4 Gettman MT, Lotan Y, Napper CA, Cadeddu JA. Transvaginal laparoscopic nephrectomy: development and feasibility in the porcine model. *Urology* 2002; **59**: 446-450 [PMID: 11880100 DOI: 10.1016/S0090-4295(01)01568-0]
- 5 Auyang ED, Santos BF, Enter DH, Hungness ES, Soper NJ. Natural orifice transluminal endoscopic surgery (NOTES®): a technical review. *Surg Endosc* 2011; **25**: 3135-3148 [PMID: 21553172 DOI: 10.1007/s00464-011-1718-x]
- 6 Tyson MD, Humphreys MR. Urological applications of natural orifice transluminal endoscopic surgery (NOTES). *Nat Rev Urol* 2014; **11**: 324-332 [PMID: 24818850 DOI: 10.1038/nrurol.2014.96]
- 7 Autorino R, Cadeddu JA, Desai MM, Gettman M, Gill IS, Kavoussi LR, Lima E, Montorsi F, Richstone L, Stolzenburg JU, Kaouk JH. Laparoendoscopic single-site and natural orifice transluminal endoscopic surgery in urology: a critical analysis of the literature. *Eur Urol* 2011; **59**: 26-45 [PMID: 20828918 DOI: 10.1016/j.eururo.2010.08.030]
- 8 Lima E, Rolanda C, Pêgo JM, Henriques-Coelho T, Silva D, Osório L, Moreira I, Carvalho JL, Correia-Pinto J. Third-generation nephrectomy by natural orifice transluminal endoscopic surgery. *J Urol* 2007; **178**: 2648-2654 [PMID: 17945287 DOI: 10.1016/j.juro.2007.07.117]
- 9 Isariyawongse JP, McGee MF, Rosen MJ, Cherullo EE, Ponsky LE. Pure natural orifice transluminal endoscopic surgery (NOTES) nephrectomy using standard laparoscopic instruments in the porcine model. *J Endourol* 2008; **22**: 1087-1091 [PMID: 18419337 DOI: 10.1089/end.2007.0404]
- 10 Boylu U, Oommen M, Joshi V, Thomas R, Lee BR. Natural orifice transluminal endoscopic surgery (NOTES) partial nephrectomy in a porcine model. *Surg Endosc* 2010; **24**: 485-489 [PMID: 19585068 DOI: 10.1007/s00464-009-0610-4]
- 11 Fritscher-Ravens A, Ghanbari A, Cumming T, Kahle E, Niemann H, Koehler P, Patel K. Comparative study of NOTES alone vs. EUS-guided NOTES procedures. *Endoscopy* 2008; **40**: 925-930 [PMID: 19009485 DOI: 10.1055/s-2008-1077732]
- 12 Sawyer MD, Cherullo EE, Elmunzer BJ, Schomisch S, Ponsky LE. Pure natural orifice transluminal endoscopic surgery partial cystectomy: intravesical transurethral and extravesical transgastric techniques in a porcine model. *Urology* 2009; **74**: 1049-1053 [PMID: 19758685 DOI: 10.1016/j.urolgy.2009.03.057]
- 13 Bazzi WM, Wagner O, Stroup SP, Silberstein JL, Belkind N, Katagiri T, Paleari J, Duro A, Ramamoorthy S, Talamini MA, Horgan S, Derweesh IH. Transrectal hybrid natural orifice transluminal endoscopic surgery (NOTES) nephrectomy in a porcine model. *Urology* 2011; **77**: 518-523 [PMID: 21376997 DOI: 10.1016/j.urolgy.2010.10.057]
- 14 Ramamoorthy SL, Fischer LJ, Jacobsen G, Thompson K, Wong B, Spivack A, Cullen J, Talamini MA, Horgan S. Transrectal endoscopic retrorectal access (TERA): a novel NOTES approach to the peritoneal cavity. *J Laparoendosc Adv Surg Tech A* 2009; **19**: 603-606 [PMID: 19715485 DOI: 10.1089/lap.2009.0071]
- 15 Bazzi WM, Stroup SP, Cohen SA, Dotai T, Kopp RP, Colangelo C, Raheem OA, Ramamoorthy S, Talamini M, Horgan S, Kane CJ, Derweesh IH. Feasibility of transrectal hybrid natural orifice transluminal endoscopic surgery (NOTES) nephrectomy in the cadaveric model. *Urology* 2012; **80**: 590-595 [PMID: 22925236 DOI: 10.1016/j.urolgy.2012.06.026]
- 16 Park YH, Kim KT, Bae JB, Kim HH. Transvaginal and transrectal natural orifice transluminal endoscopic surgery nephrectomy in a porcine survival model: comparison with conventional laparoscopic nephrectomy. *J Endourol* 2015; **29**: 351-356 [PMID: 25350081 DOI: 10.1089/end.2014.0309]
- 17 Bazzi WM, Stroup SP, Cohen SA, Sisul DM, Liss MA, Masterson JH, Kopp RP, Gudeman SR, Leeflang E, Palazzi KL, Ramamoorthy S, Kane CJ, Horgan S, Derweesh IH. Comparison of transrectal and transvaginal hybrid natural orifice transluminal endoscopic surgery partial nephrectomy in the porcine model. *Urology* 2013; **82**: 84-89 [PMID: 23676357 DOI: 10.1016/j.urolgy.2013.03.007]
- 18 Eyraud R, Laydner H, Autorino R, Hillyer S, Long JA, Panumattasamee K, Khalifeh A, Stein RJ, Haber GP, Kaouk JH. Robot-assisted transrectal hybrid natural orifice transluminal endoscopic surgery nephrectomy and adrenalectomy: initial investigation in a cadaver model. *Urology* 2013; **81**: 1090-1094 [PMID: 23490523 DOI: 10.1016/j.urolgy.2012.11.006]
- 19 Akça O, Zargar H, Autorino R, Brandao LF, Gürler AS, Avşar A, Horuz R, Albayrak S. The transrectal single port laparoscopic

- radical prostatectomy in a cadaver model. *Turk J Urol* 2015; **41**: 78-82 [PMID: 26328206 DOI: 10.5152/tud.2015.40336]
- 20 **Shin EJ**, Kalloo AN. Transcolonic NOTES: Current experience and potential implications for urologic applications. *J Endourol* 2009; **23**: 743-746 [PMID: 19405815 DOI: 10.1089/end.2009.0217]
 - 21 **Haber GP**, White MA, Autorino R, Escobar PF, Kroh MD, Chalikhonda S, Khanna R, Forest S, Yang B, Altunrende F, Stein RJ, Kaouk JH. Novel robotic da Vinci instruments for laparoendoscopic single-site surgery. *Urology* 2010; **76**: 1279-1282 [PMID: 20980046 DOI: 10.1016/j.urology.2010.06.070]
 - 22 **Wolthuis AM**, de Buck van Overstraeten A, D'Hoore A. Laparoscopic natural orifice specimen extraction-colectomy: a systematic review. *World J Gastroenterol* 2014; **20**: 12981-12992 [PMID: 25278692 DOI: 10.3748/wjg.v20.i36.12981]
 - 23 **Rane A**, Autorino R. Robotic natural orifice transluminal endoscopic surgery and laparoendoscopic single-site surgery: current status. *Curr Opin Urol* 2011; **21**: 71-77 [PMID: 20962649 DOI: 10.1097/MOU.0b013e32833fd602]
 - 24 **Costantino FA**, Diana M, Wall J, Leroy J, Mutter D, Marescaux J. Prospective evaluation of peritoneal fluid contamination following transabdominal vs. transanal specimen extraction in laparoscopic left-sided colorectal resections. *Surg Endosc* 2012; **26**: 1495-1500 [PMID: 22179455 DOI: 10.1007/s00464-011-2066-6]
 - 25 **Senft JD**, Carstensen B, Mischnik A, Warschkow R, Müller-Stich BP, Linke GR. Endolumenal colon occlusion reduces peritoneal contamination during a transrectal NOTES procedure: a controlled porcine survival study. *Surg Endosc* 2016; **30**: 2946-2950 [PMID: 26487201 DOI: 10.1007/s00464-015-4582-2]
 - 26 **Bazzi WM**, Raheem OA, Cohen SA, Derweesh IH. Natural orifice transluminal endoscopic surgery in urology: Review of the world literature. *Urol Ann* 2012; **4**: 1-5 [PMID: 22346092 DOI: 10.4103/0974-7796.91611]

P- Reviewer: Neri V S- Editor: Gong ZM L- Editor: A
E- Editor: Li D



Microvasculature of the esophagus and gastroesophageal junction: Lesson learned from submucosal endoscopy

Roberta Maselli, Haruhiro Inoue, Haruo Ikeda, Manabu Onimaru, Akira Yoshida, Esperanza Grace Santi, Hiroki Sato, Bu'Hussain Hayee, Shin-Ei Kudo

Roberta Maselli, Haruhiro Inoue, Haruo Ikeda, Manabu Onimaru, Akira Yoshida, Esperanza Grace Santi, Hiroki Sato, Bu'Hussain Hayee, Shin-Ei Kudo, Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama 224-8503, Japan

Roberta Maselli, Department of "Paride Stefanini" Surgical, Umberto I° General Hospital, Sapienza University of Rome, 00161 Rome, Italy

Bu'Hussain Hayee, King's College Hospital NHSFT, London WC2R 2LS, United Kingdom

Author contributions: Maselli R and Inoue H contributed to conception and design; Maselli R contributed to drafting of the article; Ikeda H, Onimaru M, Yoshida A and Sato H contributed to data collection, analysis and interpretation of the data; Santi EG contributed to analysis and interpretation of the data; Hayee B contributed to clinical revision; Kudo S contributed to clinical revision and final approval.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Roberta Maselli, MD, Digestive Disease Center, Showa University Northern Yokohama Hospital, 35-1 Chigasaki-cho, Tsuzuki-ku, Yokohama 224-8503, Japan. roberta.maselli.md@gmail.com
Telephone: +81-45-9497000

Received: April 28, 2015

Peer-review started: May 5, 2015

First decision: October 26, 2015

Revised: October 10, 2016

Accepted: October 22, 2016

Article in press: October 24, 2016

Published online: November 16, 2016

Abstract

Advanced therapeutic endoscopy, in particular endoscopic mucosal resection, endoscopic submucosal dissection, per-oral endoscopic myotomy, submucosal endoscopic tumor resection opened a new era where direct esophageal visualization is possible. Combining these information with advanced diagnostic endoscopy, the esophagus is organized, from the luminal side to outside, into five layers (epithelium, lamina propria with lamina muscularis mucosa, submucosa, muscle layer, adventitia). A specific vascular system belonging to each layer is thus visible: Mucosa with the intra papillary capillary loop in the epithelium and the sub-epithelial capillary network in the lamina propria and, at the lower esophageal sphincter (LES) level with the palisade vessels; submucosa with the drainage vessels and the spindle veins at LES level; muscle layer with the perforating vessels; peri-esophageal veins in adventitia. These structures are particularly important to define endoscopic landmark for the gastro-esophageal junction, helpful in performing submucosal therapeutic endoscopy.

Key words: Microvasculature; Esophageal anatomy; Submucosal endoscopy; Per-oral endoscopic myotomy; Advanced imaging

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In the last years advanced endoscopic technology and techniques allowed the possibility to *in vivo* evaluate the esophageal vasculature. We aimed to

review the endoscopic endoluminal and transluminal appearance of the esophageal vascular structures. This paper will allow the reader to deeply understand mucosal, submucosal and muscular layer vessels by a direct endoscopic visualization. The authors' knowledge of the characteristic changes in health and disease, as well as descriptions of anatomical landmarks, will serve to inform the practice of endoscopic surgery in the future.

Maselli R, Inoue H, Ikeda H, Onimaru M, Yoshida A, Santi EG, Sato H, Hayee B, Kudo SE. Microvasculature of the esophagus and gastroesophageal junction: Lesson learned from submucosal endoscopy. *World J Gastrointest Endosc* 2016; 8(19): 690-696 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/690.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.690>

INTRODUCTION

Flexible endoscopes were first introduced in 1950s and since that time physicians have been able visualize the gastrointestinal tract. In the past 10 years endoscopy benefited from several technologies such as high-definition television, high-resolution endoscopy, magnification and narrow band imaging (NBI)^[1]. Results from the anatomical *ex-vivo* studies have informed the approach to endoscopic examination, but these technologies herald a new era of observation, where the direct visualization of living tissue can confirm, and add to, the observations of the past.

In this article we aimed to review the endoscopic endoluminal and transluminal appearance of the esophageal vascular structures, with particular attention to the state-of-the-art endoscopic equipment and techniques now available.

Advanced diagnostic endoscopy: Magnification endoscopy and NBI

Magnification endoscopy up to 80x (GIF-H260, Olympus Medical Systems Co. Tokyo, Japan) is an excellent tool for the visualization of the normal esophageal mucosa and in the diagnosis of early esophageal cancer^[2]. Using magnification, one can begin to visualize the esophageal microvasculature, with the surface capillaries displaying a looped configuration^[3]: The intra-papillary capillary loops (IPCLs).

NBI is a relatively recent modality employing narrow-bandwidth filters [red-green-blue (R/G/B) sequential system]^[4], to increase the contrast between the mucosal surface and the underlying vascular pattern^[5]. The depth of penetration, and thus the color seen in the screen, depends on the wavelength used: It is superficial for the blue band, deep for the red band and intermediate for the green band. The blue filter in particular has been designed to be similar to the peak absorption of hemoglobin, in order to emphasize capillary vessels at

the mucosal surface^[6]. Magnification endoscopy with NBI (M-NBI), therefore, has been developed for two distinct applications: The analysis of the architecture of the epithelium (or microsurface) and analysis of the microvasculature^[7].

Advanced diagnostic endoscopy: Endocytoscopy and Endomicroscopy

New optical imaging modalities to enable *in vivo* characterization of suspicious lesions involves both endogenous optical contrast as well as the use of contrast agents targeted against biomarkers that are associated with early and superficial neoplasias^[8].

Recently the confocal laser endomicroscopy (CLE) has been studied in the evaluation of the gastrointestinal (GI) tract. Fluorescence diagnosis can be achieved by measuring the tissue fluorescence following administration of an agent (usually fluorescein).

The typical resolution achievable with CLE is on the order of 1-2 μm with a field of view of approximately 500-700 μm^2 . It allows for the immediate evaluation of the superficial GI layers and can be used for morphological diagnosis because of the recognition of morphological changes in cells and nuclei^[9].

Several studies have compared the performance of confocal microendoscopy to white light endoscopy examination and NBI in the esophagus and colon. In particular in the esophageal field, most of these papers were focused on Barrett Esophagus changes.

More recently the endocytoscopy was introduced. A prototype gastroscope (Olympus Medical Systems Corp., Tokyo, Japan) with a high-power magnifying endocytoscope (450 × magnification) was used to compare the size and appearance of nuclei and cytoplasm ratio, without the need of a contrast agent. In the esophagus the endocytoscopic images has been classified into five grades of endocytoscopic atypia (ECA) from healthy squamous epithelium (ECA 1) to lesion recognized as malignant (ECA 5)^[10].

Advanced therapeutic endoscopy

Advanced operative endoscopy, ranging from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), per-oral endoscopic myotomy (POEM), submucosal endoscopic tumor resection (SET), has open the door to the direct view of the submucosal virtual space and its anatomy. If with diagnostic endoscopy the interest was related only in understanding "superficial" findings and in wondering the submucosal subsequent meanings, the current procedures let the physician to watch from "inside" with his/her eyes a real, true anatomy of submucosal space, until now only imagined by both diagnostic endoscopists and surgeons. EMR and ESD are performed as indicated by local clinical guidelines for early esophageal cancers, POEM for esophageal achalasia^[11-15] and SET for subepithelial tumors^[16]. These procedures enable clear and direct visualization of the layers of the esophageal wall, as therapy progresses.

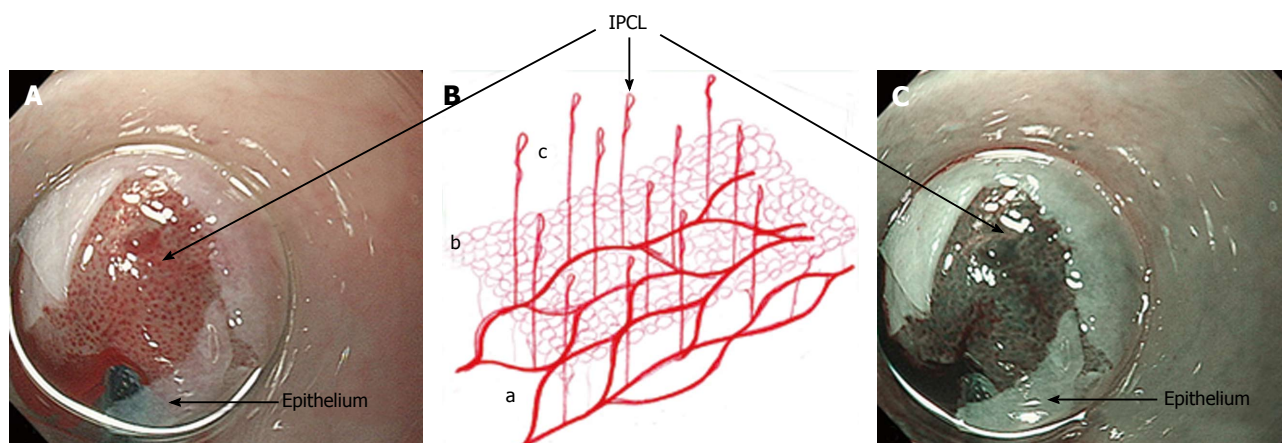


Figure 1 Mucosal vessels. A and C: Endoscopic images during per-oral endoscopic myotomy procedure (high magnification images); after unintentional removal of the epithelium (white layer), top half of epithelium was peeled off, and IPCLs were exposed. IPCLs appear as regularly-arranged, red dots (A: White light) or dark green spots (C: NBI); B: A schematic representation of the vascular network of esophageal mucosa: a: Branching vessels; b: SECN; c: IPCL. IPCL: Intrapapillary capillary loop; SECN: Sub epithelial capillary network; NBI: Narrow band imaging.

Esophageal vasculature: Endoscopic appearance

Combining the information gained from the therapeutic endoscopy, the esophageal wall is organized, from the lumen to outside, in five different layers: Epithelium, lamina propria with lamina muscularis mucosa, submucosa, muscle layer, adventitia. Different vascular system are recognize, belonging to each layer and connecting each other: In the mucosal layer we can find IPCL in the epithelium and sub-epithelial capillary network (SECN) in the lamina propria (Figure 1); at the lower esophageal sphincter (LES) level, we can recognize palisade vessels running in this layer; in the submucosa we find drainage vessels and the spindle veins just under the LES; in the muscle layer are present perforating vessels and peri-esophageal veins in Adventitia. In particular, considering the vasculature by each layer we can find the following structures (Figure 2)^[16].

Mucosa: IPCLs and the SECN can be visualized laying all along the esophagus, from the upper esophageal sphincter (UES) to the LES (Figure 3). IPCLs are terminal vessels laying in the epithelial papilla and they drain into the branching vessels located within the lamina propria; they can be clearly demonstrated with M-NBI, although they are visible even with magnification alone. The branching vessels finally drain into the submucosal drainage vessels.

Submucosa: It is a connective “space” between the mucosa and the muscle layer. In this layer drainage vessels can be found running in the entire esophageal length; at the esophagogastric junction (GEJ) level the drainage veins become elongated.

Muscle layer: It is a double layer composed by muscular fibers running circularly in the inner layer and longitudinally in outer part. It is crossed by a venous network running in the intramuscular space. The muscle

layer is also crossed by additional perforating vessels, large veins connecting the submucosal drainage veins/arteries with the main longitudinal arteries and veins of the adventitia, the outer esophageal layer.

Adventitia: It is the outermost connective tissue layer, enclosing the esophagus in all its length. The peri-esophageal vessels are clearly demonstrated during submucosal endoscopy for POEM, after the myotomy.

From the early 90s several studies focused on IPCL changes relevant to malignant tumors^[2]. These studies led to the development of the IPCL classification^[1]: IPCLs show characteristic changes in carcinoma *in situ* (irregular caliber, weaving, dilatation and different shape of IPCL). Analyzing grades of IPCL changes, the mucosa can be differentiated from normal (Type I) to carcinoma (Type V). By this classification, infiltration depth of the esophageal lesion can also be evaluated.

ESOPHAGEAL VASCULATURE ON HISTOLOGY

The immunohistochemical analysis on non-pathological esophageal specimens using CD34, specific for the vascular endothelium, and D2-40, specific for lymphatics, shows a high expression of CD34 in the areas corresponding to the IPCLs, SECN and branching vessels (Figure 4). IPCLs and SECN stained with CD34, but they are negative for D2-40 staining.

GEJ: ENDOSCOPIC LANDMARKS

The GEJ is usually endoscopically defined as that area where the palisade vessels encounter gastric longitudinal mucosal folds^[17-19]. These structures can be directly seen by entering in the submucosal space: From this internal point of view, on the mucosal side, the branching vessels appears neighboring with palisade vessels, running in the

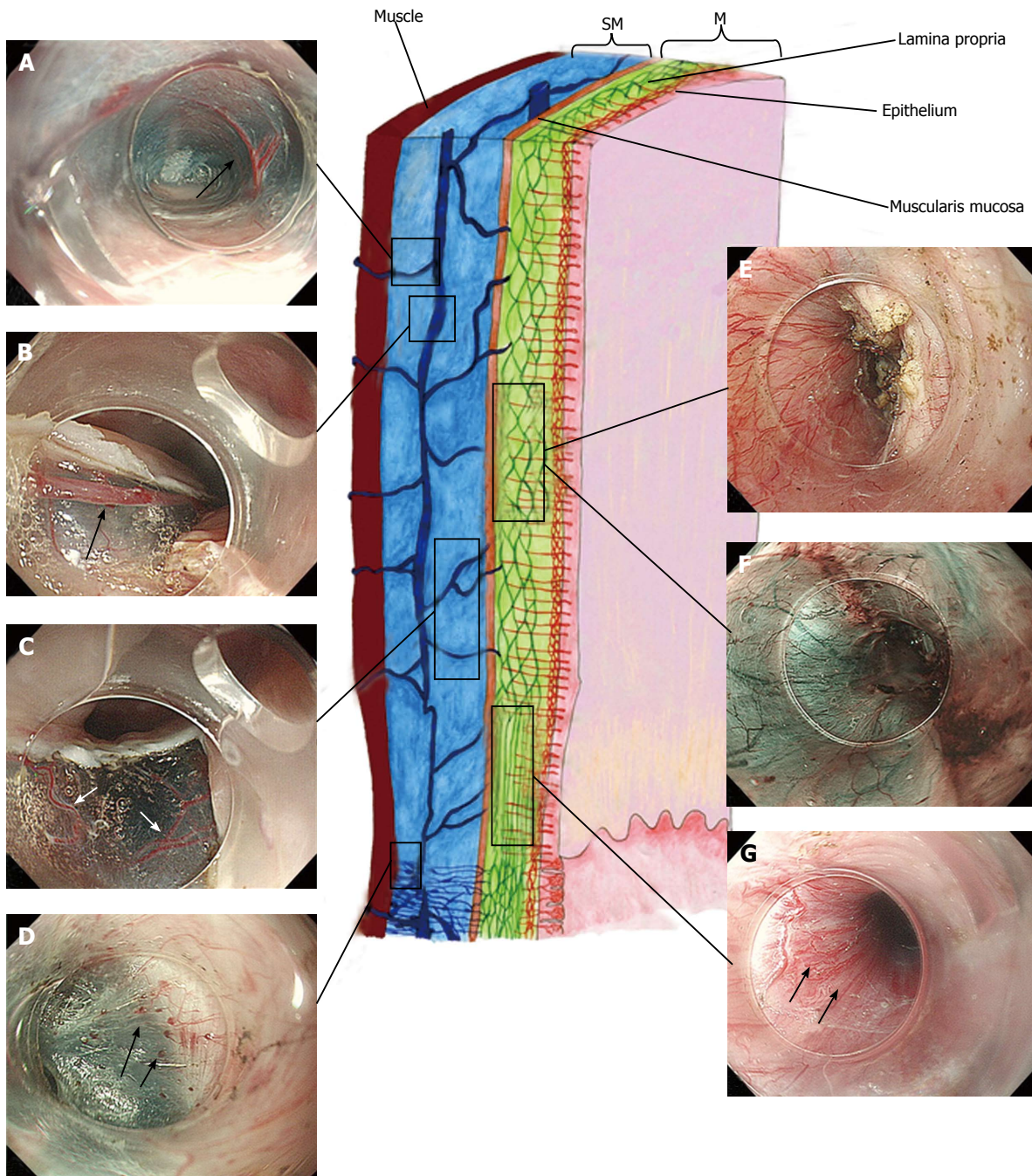


Figure 2 Esophageal wall and esophago-gastric junction vasculature: Schematic illustration and endoscopic corresponding images (high magnification images). Black arrow indicates vessels. This image was originally published in "Treatment Strategies Gastroenterology"^[28]. A: Perforating vessels from the outer esophagus to the submucosal vessel; image captured during tunnelization in POEM (bottom side muscle layer, left side submucosal lifting); B: Submucosal drainage vessel (mucosal layer lifted on during ESD). These veins can become esophageal varices in portal hypertension; C: Submucosal vessels connecting the drainage veins to the mucosal branching vessels (in the lamina propria); D: Spindle veins immediately below the GEJ (in left side of the image, in blue, the submucosa and in the right side the muscle); E and F: Whitet light and NBI of the branching vessels (seen from inside the submucosal tunnel). Backside of the mucosa on the left; muscle-already cut-on the right; G: Passage between lower esophagus and GEJ. In the image is possible to recognize, in different planes, all the vessel of the submucosa and lamina propria (palisade vessels). POEM: Per-oral endoscopic myotomy; ESD: Endoscopic submucosal dissection; GEJ: Esophagogastric junction; NBI: Narrow band imaging; M: Mucosa; SM: Submucosa.

same plane, just above the muscularis mucosae.

In the submucosal layer, immediately below the GEJ, small veins are laying, running regularly and parallel to each other, perpendicularly to the muscular layer, found in most of the patients (Figure 5). These "spindle veins" can be considered a reliable landmark of the GEJ already been passed through.

DISCUSSION

The first descriptions of the esophageal vasculature and its connection with the portal system span from Vesalius in 1543 to Bartholin in 1673 and Dionis in 1703. In 1951 Butler recorded a more detailed description, categorizing the intramural esophageal vessels into intrinsic veins,

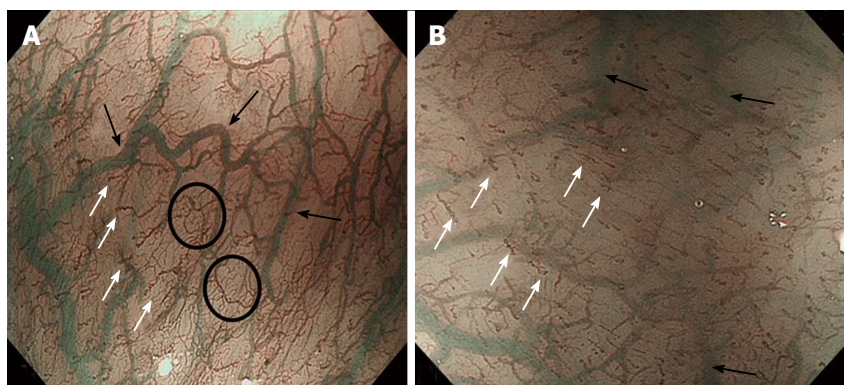


Figure 3 High magnifying narrow band imaging image of normal esophageal mucosa (luminal side). A: Soft pressure of the endoscope distal attachment ("hood") onto the mucosal surface demonstrates SECN, hard pressure onto the mucosa compresses horizontal vessels, allowing clear observation of IPCLs; B: In the circle the SECN located at the top layer of lamina propria mucosae, just beneath the epithelium. The black arrows indicate the branching vessels into the lower lamina propria; white arrows indicate the IPCL located in the epithelial papilla, which is a projection of lamina propria mucosae into the epithelium. SECN: Sub-epithelial capillary network; IPCL: Intrapapillary capillary loop.

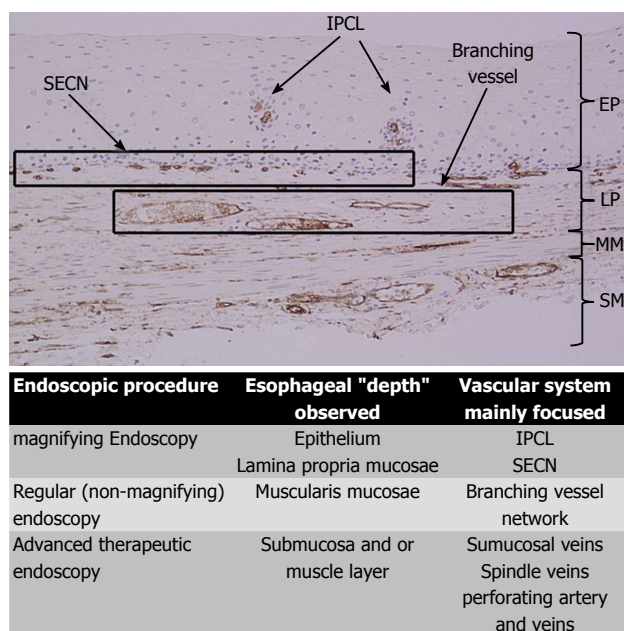


Figure 4 The figure shows the histology of a non-pathologic esophageal specimen. The vessels' wall has been colored by CD34, showing superficially the IPCLs (upper part of the lamina propria, arising the epithelium) and the SECN; deeply in the lamina propria the branching vessels. In the sumucosal layer also the drainage veins are evident. The table summarizes the vascular system observed and its own esophageal layer according to the different endoscopic procedure performed. SECN: Sub-epithelial capillary network; IPCL: Intrapapillary capillary loop; EP: Epithelium; LP: Lamina propria; MM: Muscularis mucosa; SM: Submucosa.

venae comitantes of the vagus and extrinsic veins^[20].

Subsequent descriptions have concentrated largely on abnormalities due to esophageal varices, but these were limited to post-mortem, *ex vivo* analysis, frequently employing the corrosion-cast technique, or scanning electron microscopy (visualizing vessels down to 200 μm)^[21]. These studies demonstrated the existence of a SECN, a draining submucosal venous plexus, and the anastomoses between these two.

Advanced therapeutic endoscopy allows, for the first time, the direct *in vivo* observation of the deeper

layers of the esophageal wall. Many of these structures are of interest and key importance to endoscopists undertaking advanced therapeutic procedures.

Previous studies of the esophageal vasculature have yielded conflicting observations. Palisade vessels were first described using microangiography, then in 1984 endoscopically identified as "sudare-like veins"^[19]. In 1987 Vianna *et al*^[22] performed a study on the normal esophageal venous circulation and defined in particular the palisade zone located at the gastroesophageal junction. The veins in this zone were distributed uniformly, running longitudinally and parallel to each other. The submucosal veins of the gastric zone were described as piercing the muscularis mucosae at the GEJ, running in the lamina propria, with the exception of a small number which seemed to remain in the submucosal space^[22]. In contrast, Aharinejad *et al*^[23] demonstrated that submucosal veins maintain their general longitudinal course when passing through the GEJ. Using M-NBI, Kumagai and colleagues observations of the GEJ and its vessels corresponded to the *ex vivo* description of Kagaries and Butler: They described in the lamina propria a longitudinal plexus of small vessels and in the submucosa at the GEJ, the palisade vessels, with a caliber of 150-170 μm . They demonstrated that the density of palisade vessels is highest near the squamo-columnar junction and that starting from their proximal ends they gradually increase in thickness and become confluent^[24]. Using M-NBI, our endoscopic findings, approaching the submucosal space, correspond most closely to those of Aharinejad, with the palisade vessels at the GEJ lying in the lamina propria. In other words, the palisade vessels are continuations of the branching vessels, but we postulate that the vessels appear elongated as a result of the high pressure forces present at the GEJ. This is supported by the presence of similar vessels at the UES level (Figure 6).

The GEJ has previously been divided into four distinct zones (the first two immediately below and the second two above the "Z" line). In zone 1, the most caudally zone directly connected with the gastric side, a complex

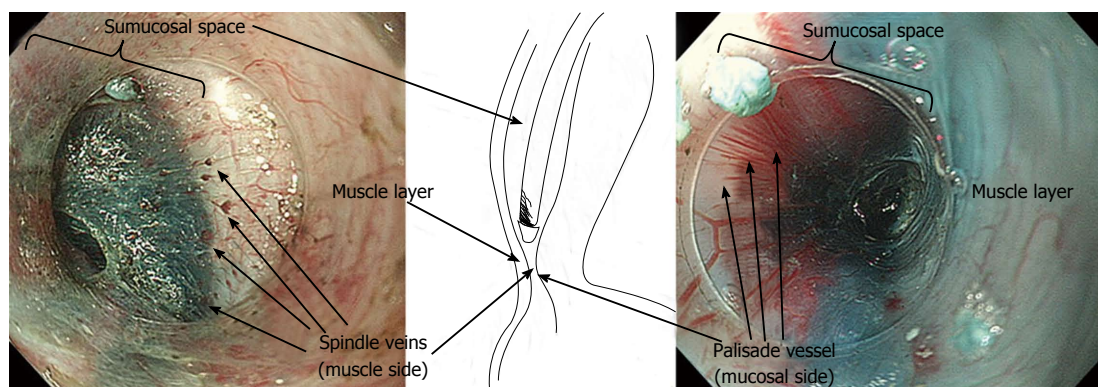


Figure 5 In the center a scheme of the submucosal view at the gastro-esophageal junction during per-oral endoscopic myotomy. At the muscle side (left endoscopic image) the spindle vein are clearly visible; at the mucosal side (seen on its backside, right endoscopic image) the palisade vessel are recognized. High magnification images.

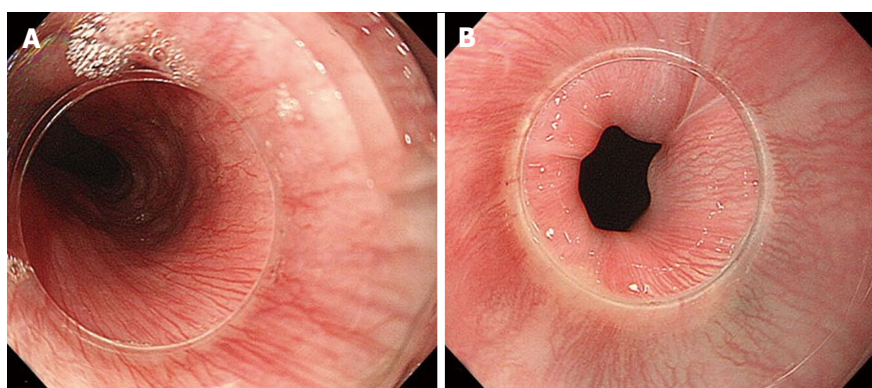


Figure 6 Palisade vessels at the esophageal sphincter. A: Palisade vessels at the upper esophageal sphincter; B: In the lower esophageal sphincter, the vessels, located in the lamina propria, are continuation of the branching vessels, "stretched" by the high pressure present in the area. High magnification images.

of small twisted veins, with circumscribed, ampullar bulges^[21] - has been found. These veins correspond to the so-called "spindle veins", found in more than 70% of the total cases of our personal series and clearly visible during submucosal endoscopy.

The architecture of IPCLs has been evaluated *ex vivo* in the normal esophagus, with microfilm^[19]; comparing these stereoscopic microscopic images with magnifying endoscopic images, at a magnification of approximately 80 times, small vessels coming up from the mucosal vessels could be seen originating and running obliquely upward toward the epithelium and then toward to the intrapapillary capillaries. At a magnification of more than 100 × each intrapapillary capillary can be observed as a single distinct loop^[25].

As endoscopists have become more familiar with M-NBI, it became apparent that characteristic morphological changes were associated with the development of malignancy^[26]. These observations finally led to the development of the IPCL classification^[1,27].

Esophageal vasculature is now *in vivo* evaluable with advanced endoscopic technology and techniques. Our knowledge of the characteristic changes in health and disease, as well definition of anatomical landmarks, will serve to the practice of endoscopic diagnostics and treatment in the future.

REFERENCES

- 1 **Inoue H.** Magnification endoscopy in the esophagus and stomach. *Digest Endosc* 2001; **13**: S40-S41 [DOI: 10.1111/j.1443-1661.2001.0116b.x]
- 2 **Inoue H, Honda T, Nagai K, Kawano T, Yoshino K, Takeshita K, Endo M.** Ultra-high magnification endoscopic observation of carcinoma in situ of the esophagus. *Dig Endosc* 1997; **9**: 16-18 [DOI: 10.1111/j.1443-1661.1997.tb00453.x]
- 3 **Inoue H, Honda T, Yoshida T, Nishikage T, Nagahama T, Yano K, Nagai K, Kawano T, Yoshino K, Tani M, Takeshita K, Endo M.** Ultra-high magnification endoscopy of the normal esophageal mucosa. *Dig Endosc* 1996; **8**: 134-138 [DOI: 10.1111/j.1443-1661.1996.tb00429.x]
- 4 **Tajiri H, Matsuda K, Fujisaki J.** What can we see with the endoscope? Present status and future perspectives. *Dig Endosc* 2002; **14**: 131-137 [DOI: 10.1046/j.0915-5635.2002.00191.x]
- 5 **Gheorghe C.** Narrow-band imaging endoscopy for diagnosis of malignant and premalignant gastrointestinal lesions. *J Gastrointest Liver Dis* 2006; **15**: 77-82 [PMID: 16680239]
- 6 **Sambongi M, Igarashi M, Obi T.** Analysis of spectral reflectance of mucous membrane for endoscopic diagnosis. *Med Phys* 2000; **27**: 1396-1398
- 7 **Kiesslich R, Jung M.** Magnification endoscopy: does it improve mucosal surface analysis for the diagnosis of gastrointestinal neoplasias? *Endoscopy* 2002; **34**: 819-822 [PMID: 12244505 DOI: 10.1055/s-2002-34259]
- 8 **Carns J, Keahey P, Quang T, Anandasabapathy S, Richards-Kortum R.** Optical molecular imaging in the gastrointestinal tract. *Gastrointest Endosc Clin N Am* 2013; **23**: 707-723 [PMID: 23735112 DOI: 10.1016/j.giec.2013.03.010]

- 9 **Wong Kee Song LM**, Wilson BC. Endoscopic detection of early upper GI cancers. *Best Pract Res Clin Gastroenterol* 2005; **19**: 833-856 [PMID: 16338645 DOI: 10.1016/j.bpg.2005.04.006]
- 10 **Inoue H**, Sasajima K, Kaga M, Sugaya S, Sato Y, Wada Y, Inui M, Satodate H, Kudo SE, Kimura S, Hamatani S, Shiokawa A. Endoscopic in vivo evaluation of tissue atypia in the esophagus using a newly designed integrated endocytoscope: a pilot trial. *Endoscopy* 2006; **38**: 891-895 [PMID: 16981105 DOI: 10.1055/s-2006-944667]
- 11 **Huang Q**. Definition of the esophagogastric junction: a critical mini review. *Arch Pathol Lab Med* 2011; **135**: 384-389 [PMID: 21366465 DOI: 10.1043/2010-0162-RA.1]
- 12 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382 DOI: 10.1055/s-2007-966764]
- 13 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
- 14 **Inoue H**, Tianle KM, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Minami H, Kudo SE. Peroral endoscopic myotomy for esophageal achalasia: technique, indication, and outcomes. *Thorac Surg Clin* 2011; **21**: 519-525 [PMID: 22040634 DOI: 10.1016/j.thorsurg.2011.08.005]
- 15 **von Renteln D**, Inoue H, Minami H, Werner YB, Pace A, Kersten JF, Much CC, Schachschal G, Mann O, Keller J, Fuchs KH, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: a prospective single center study. *Am J Gastroenterol* 2012; **107**: 411-417 [PMID: 22068665 DOI: 10.1038/ajg.2011.388]
- 16 **Shiwaku H**, Inoue H, Beppu R, Nakashima R, Minami H, Shiroshita T, Yamauchi Y, Hoshino S, Yamashita Y. Successful treatment of diffuse esophageal spasm by peroral endoscopic myotomy. *Gastrointest Endosc* 2013; **77**: 149-150 [PMID: 22482919 DOI: 10.1016/j.gie.2012.02.008]
- 17 **Inoue H**, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Eleftheriadis N, Maselli R, Kudo S. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. *Endoscopy* 2012; **44**: 225-230 [PMID: 22354822 DOI: 10.1055/s-0031-1291659]
- 18 **Hoshihara Y**, Kogure T. What are longitudinal vessels? Endoscopic observation and clinical significance of longitudinal vessels in the lower esophagus. *Esophagus* 2006; **3**: 145-150 [DOI: 10.1007/s10388-006-0096-2]
- 19 **Noda T**. Angioarchitectural study of esophageal varices. With special reference to variceal rupture. *Virchows Arch A Pathol Anat Histopathol* 1984; **404**: 381-392 [PMID: 6437071 DOI: 10.1007/BF00695222]
- 20 **Butler H**. The veins of the oesophagus. *Thorax* 1951; **6**: 276-296 [PMID: 14884140 DOI: 10.1136/thx.6.3.276]
- 21 **Ferraz-de-Carvalho CA**, Liberti EA, Fujimura I, Nogueira JO. Scanning electron microscope study of the veins at the human esophago-gastric junction. *Rev Hosp Clin Fac Med Sao Paulo* 1994; **49**: 49-52 [PMID: 7817091]
- 22 **Vianna A**, Hayes PC, Moscoso G, Driver M, Portmann B, Westaby D, Williams R. Normal venous circulation of the gastroesophageal junction. A route to understanding varices. *Gastroenterology* 1987; **93**: 876-889 [PMID: 3623028 DOI: 10.1016/0016-5085(87)90453-7]
- 23 **Aharinejad S**, Böck P, Lametschwandner A. Scanning electron microscopy of esophageal microvasculature in human infants and rabbits. *Anat Embryol (Berl)* 1992; **186**: 33-40 [PMID: 1514702 DOI: 10.1007/BF00710400]
- 24 **Kumagai Y**, Yagi M, Aida J, Ishida H, Suzuki S, Hashimoto T, Amanuma Y, Kusano M, Mukai S, Yamazaki S, Iida M, Ochiai T, Matsuura M, Iwakiri K, Kawano T, Hoshihara Y, Takubo K. Detailed features of palisade vessels as a marker of the esophageal mucosa revealed by magnifying endoscopy with narrow band imaging. *Dis Esophagus* 2012; **25**: 484-490 [PMID: 22098187 DOI: 10.1111/j.1442-2050.2011.01283.x]
- 25 **Kumagai Y**, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. *Endoscopy* 2002; **34**: 369-375 [PMID: 11972267 DOI: 10.1055/s-2002-25285]
- 26 **Arima H**, Arima M, Tada T. Microvascular Patterns Of Esophageal Micro Squamous Cell Carcinoma On Magnifying Endoscopy. *Digest Endosc* 2008; **20**: 6-11 [DOI: 10.1111/j.1443-1661.2007.00765.x]
- 27 **Yoshida T**, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. *Gastrointest Endosc* 2004; **59**: 288-295 [PMID: 14745410 DOI: 10.1016/S0016-5107(03)02532-X]
- 28 **Maselli R**, Inoue H, Ikeda H, Onimaru M, Yoshida A, Santi EG, Sato H, Kaga M, Hayee B, Kudo S. In vivo Observation of the Esophagus by Intraluminal and Transmural Endoscopy: Anatomical Lessons from Advanced Endoscopy. *Treatment Strategies - Gastroenterology* 2013; **2**: P48-49 Available form: URL: <http://viewer.zmags.com/publication/69da19a6#/69da19a6/48>

P- Reviewer: Lirici MM, Teoh AY **S- Editor:** Kong JX

L- Editor: A **E- Editor:** Li D



Observational Study

Patients presenting for colonoscopy: A great opportunity to screen for sleep apnea

Glenn Harvin, Eslam Ali, Amit Raina, William Leland, Sabeen Abid, Zahid Vahora, Hossein Movahed, Sumyra Kachru, Rick Tee

Glenn Harvin, Eslam Ali, Amit Raina, William Leland, Brody School of Medicine at East Carolina University, Greenville, NC 27834, United States

Sabeen Abid, Zahid Vahora, Hossein Movahed, Sumyra Kachru, Rick Tee, Vidant Medical Center, Greenville, NC 27834, United States

Author contributions: All the authors contributed to the manuscript.

Institutional review board statement: The study was reviewed and approved by the East Carolina University and Vidant Medical Center Institutional Review Board.

Informed consent statement: Written informed consent was obtained from all the patients prior to study inclusion.

Conflict-of-interest statement: The authors have no potential conflict of interest.

Data sharing statement: Informed consent was not obtained for data sharing, and no additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Glenn Harvin, MD, Assistant Professor, Brody School of Medicine at East Carolina University, 521 Moye Boulevard, Greenville, NC 27834, United States. harving@ecu.edu
Telephone: +1-252-7445681
Fax: +1-252-8160801

Received: June 7, 2016

Peer-review started: June 12, 2016

First decision: July 11, 2016

Revised: July 29, 2016

Accepted: September 6, 2016

Article in press: September 8, 2016

Published online: November 16, 2016

Abstract

AIM

To discover the prevalence and the feasibility of screening for obstructive sleep apnea (OSA) in patients presenting for routine colonoscopy.

METHODS

Adult patients having a colonoscopy for routine indications at our outpatient endoscopy center were eligible if they did not carry a diagnosis of OSA or had not had a prior sleep study. All patients were administered the Berlin questionnaire prior to the procedure. Mallampati, neck circumference, height, weight, and BMI were obtained for each patient. Patients were observed for any drops in oxygen saturation < 92% or the presence of snoring for > 10 s. Patients were determined to be high-risk if they met at least 2 of the 3 symptom categories for the Berlin questionnaire.

RESULTS

A total of 60 patients were enrolled and completed the study; mean age was 56 years (range 23-72 year). Twenty-six patients had a positive Berlin questionnaire (43.3%), 31 patients had a negative Berlin questionnaire (51.6%) and 3 patients had an equivocal result (5.0%). Patients with a positive Berlin questionnaire were more likely to be of increased weight (mean 210.5 lbs vs mean 169.8 lbs, $P = 0.003$), increased BMI (33.0 kg/m² vs 26.8 kg/m², $P = 0.0016$), and have an increased neck circumference (38.4 cm vs 35.5 cm, $P = 0.012$).

Patients with a positive Berlin questionnaire were more likely to have a drop in oxygen saturation < 92% (76.9% *vs* 36.4%, $P = 0.01$). Patients with snoring were more likely to have a positive Berlin questionnaire (8/9 patients *vs* 1/31 patients with negative Berlin questionnaire; $P = 0.0045$).

CONCLUSION

Risk for OSA is extremely common in a population presenting for a routine colonoscopy, and screening at the time of a colonoscopy offers an excellent opportunity to identify these patients.

Key words: Colonoscopy; Obstructive sleep apnea; Berlin questionnaire; Sedation; Screening

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We sought to determine the prevalence of patients at risk for obstructive sleep apnea (OSA) and the feasibility of screening patients for sleep apnea presenting for a routine colonoscopy to our outpatient endoscopy facility. All patients were screened for OSA with the Berlin questionnaire prior to the procedure. Overall, screening patients for sleep apnea at the time of a colonoscopy offers a unique opportunity not only to screen for colon cancer but also to identify patients at high risk for OSA who should undergo further testing.

Harvin G, Ali E, Raina A, Leland W, Abid S, Vahora Z, Movahed H, Kachru S, Tee R. Patients presenting for colonoscopy: A great opportunity to screen for sleep apnea. *World J Gastrointest Endosc* 2016; 8(19): 697-700 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/697.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.697>

INTRODUCTION

Obstructive sleep apnea (OSA) is extremely common and affects 2%-4% of the population^[1], yet around 92% of females and 82% males with OSA are undiagnosed^[2]. OSA has been associated with an increased cardiovascular mortality and risk for stroke^[3,4], and some studies have shown an increased perioperative morbidity and mortality^[5]. Various screening tools to identify patients at risk for OSA have been utilized including the Berlin questionnaire, the STOP questionnaire, the ASA checklist, and STOP-BANG^[6,7]. The Berlin Questionnaire has been determined to be one of the best methods for identifying patients likely to have OSA, and has been shown to be helpful in surgical patients in detecting patients at high risk of OSA^[6]. In one study, patients in the high risk group on the Berlin questionnaire predicted a respiratory disturbance index of greater than 5 with a sensitivity of 86% and a specificity of 77% with a positive predictive value of 89%^[8]. One study showed that of patients who snored greater than 10 s during their

screening colonoscopies, all were noted to have OSA^[9]. We sought to determine the prevalence of patients at risk for OSA and the feasibility of screening patients for sleep apnea presenting for a routine colonoscopy to our outpatient endoscopy facility.

MATERIALS AND METHODS

Adult patients having a colonoscopy only for routine indications at the East Carolina University Outpatient Endoscopy Center between the dates November 3, 2014 and February 12, 2015 were eligible to participate in the study if they did not carry a diagnosis of sleep apnea and had not had a prior sleep study. The study was approved by the East Carolina University and Vidant Medical Center Institutional Review Board. Written informed consent was obtained from all the patients. Enrollment was limited to days with additional personnel present to help enroll patients. Exclusion criteria included our standard exclusion criteria for the outpatient endoscopy center: BMI > 52, age < 18, home oxygen use, cardiac defibrillator, and ASA class 4 patients.

All patients had a determination of their height, weight, BMI, Mallampati score, neck circumference, and whether they had a history of hypertension. The Mallampati was calculated by both the gastroenterologist and the nurse anesthetist, and a consensus was reached prior to performing the procedure. All patients were administered the Berlin questionnaire prior to the procedure by either the attending or the research fellow. Patients were determined to be high-risk if they met at least 2 of the 3 symptom categories for the Berlin questionnaire. If the patient was negative by category 2 or 3, and if they were not aware whether they snored, they were given an equivocal result. The group determined to have a high likelihood of sleep-disordered breathing based upon a positive result on the Berlin questionnaire were recommended to follow-up with the primary care physician to consider a sleep study per standard medical care.

The colonoscopy was performed under standard monitoring for all patients to include blood pressure and continuous heart rate and oxygen saturation monitoring with 2 L of oxygen per nasal cannula. Nurse anesthetist-administered propofol was used for all cases. Patients were given a bolus of propofol by the nurse anesthetist with additional injections every few minutes titrated to a moderate sedation level. Any drops in oxygen saturation < 92% were noted, and patients were also observed for the presence of snoring for > 10 s.

Statistics analysis

Data were entered manually, and statistical analysis was performed using SAS Version 9.1 (SAS Institute, Cary, NC). Statistical review was performed by a biomedical statistician. Descriptive statistics were performed using standard methods. χ^2 test and Fischer's exact test were used to test direct association between drop in oxygen saturation < 92% with the results of the Berlin

Table 1 Patient measurements

	Mean	Std Dev	Minimum	Maximum
Age	55.8	10.8	23.0	72.0
Height (inches)	66.7	4.1	55.0	74.0
Weight (lbs)	189.3	50.4	90.0	335.0
BMI (kg/m ²)	29.9	7.3	17.0	52.0
Neck circumference (cm)	36.7	4.3	27.0	48.0

BMI: Body mass index.

questionnaire and snoring and with the results of the Berlin questionnaire. A two sample *t*-test was used to test direct association between height, weight, BMI, neck circumference, and the Berlin questionnaire.

RESULTS

A total of 60 patients were enrolled and completed the study; mean age was 56 (range 23-72 year). The baseline demographics are listed in Table 1. The ASA classification results were as follows: ASA class 1-10 patients (16.7%); ASA class 2-30 patients (50.0%); ASA class 3-20 patients (33.3%). There were no ASA class 4 patients as they were not eligible for our outpatient endoscopy facility.

The indications for the procedures included screening for colon cancer (34 patients), history of colon polyps (10 patients), rectal bleeding (4 patients), inflammatory bowel disease surveillance (3 patients), change in bowel function (2 patients), heme-positive stools (2 patients), diarrhea (2 patients), abdominal pain (2 patients), and a history of colon cancer (1 patient). The baseline Mallampati results can be seen in Table 2.

Twenty-six patients had a positive Berlin questionnaire (43.3%), 31 patients had a negative Berlin questionnaire (51.6%) and 3 patients had an equivocal result (5.0%). The patients with the equivocal Berlin questionnaire results were excluded from the analysis. Nine of the 57 patients had snoring > 10 s (15.8%), and 13 of the 57 patients (22.8%) had a drop in oxygen saturation < 92%.

Patients with a positive Berlin questionnaire were more likely to have an increased neck circumference (38.4 cm vs 35.5 cm, $P = 0.012$), increased weight (mean 210.5 lbs vs mean 169.8 lbs, $P = 0.003$), and have an increased BMI (33.0 kg/m² vs 26.8 kg/m², $P = 0.0016$). Patients with snoring were more likely to have a positive Berlin questionnaire (8/9 patients vs 1/31 patients with negative Berlin questionnaire, $P = 0.0045$). Patients with a positive Berlin questionnaire were more likely to have a drop in oxygen saturation < 92% (76.9% vs 36.4%, $P = 0.01$).

DISCUSSION

In our study, 43% of patients had a positive Berlin questionnaire, and thus were considered to be at high risk for OSA. This demonstrates the reality that many patients with sleep apnea are not being identified, and

Table 2 Mallampati

Mallampati	Frequency	%
1	10	16.67
2	30	50.0
3	18	30.0
4	2	3.3

this underscores the need to develop novel methods to identify patients at risk for OSA. Making screening for OSA routine at the time of a screening colonoscopy would greatly increase the screening of the population for OSA and ensure that a large portion of the population is screened at the age of 50. This is similar to the rationale for screening patients for hepatitis C during the visit for a routine colonoscopy that has been suggested by some^[10]. Screening patients for OSA with the Berlin questionnaire at the time of the procedure is less labor-intensive than screening for viral hepatitis and involves a simple questionnaire.

Forty-three percent of patients in our study had a positive Berlin questionnaire. This is similar to results observed by Mehta *et al*^[11] in which 48% had a positive score on the STOP-BANG questionnaire administered at the Cleveland Clinic. In the study by Cote, 43% of patients presenting to a tertiary medical center for endoscopic retrograde cholangiopancreatography or endoscopic ultrasound had a positive score on the STOP-BANG test^[12] and were more likely to have hypoxemia or require the need for airway maneuvers. Mador *et al*^[13] also showed that 39% of patients at a Veterans Affairs outpatient endoscopy center identified as high-risk for OSA as defined by the Berlin questionnaire. Our study illustrates that a large portion of patients presenting to our university-based outpatient endoscopy center are likely to have undiagnosed OSA. This agrees with the results of other studies showing that many patients with OSA are not being screened and identified. Screening patients for OSA at the time of their colonoscopy offers a unique opportunity to increase the screening rate for OSA as we also strive to increase the screening rate for colorectal cancer. With rising obesity rates, undiagnosed OSA is likely to increase^[11].

Snoring during a colonoscopy has been noted to be a strong predictor of OSA. In the study by Sharara *et al*^[9] all the patients investigated who snored during conscious sedation for their colonoscopy were diagnosed with OSA, with 70% of these found to have moderate to severe OSA. In our study, patients with snoring > 10 s were more likely to have a positive Berlin questionnaire. Endoscopists should monitor their patients closely for the presence of snoring > 10 s during colonoscopy. If this is noted, these patients should be referred for further sleep testing as there is a very strong likelihood that they have OSA.

We found patients with a positive Berlin questionnaire were more likely to have a drop in oxygen saturation. Some other studies have also noted more oxygen

desaturations in patients with high risk for OSA^[12], although Khiani and Mador did not find an increased risk^[13, 14]. However, in the study by Mehta *et al.*^[11] patients with undiagnosed sleep apnea undergoing routine upper endoscopy or colonoscopy with propofol sedation were not noted to have an increased risk of "sedation-rated adverse events". Mador *et al.*^[13] noted a similar finding in that patients with OSA undergoing endoscopic procedures with conscious sedation did not have an increased risk of cardiopulmonary complications.

Endoscopists carefully evaluate the airway of each patient who undergoes sedation for gastrointestinal procedures, including colonoscopy. They are responsible for the sedation of large numbers of patients and offer a select group of physicians with the skill and experience to carefully evaluate patients at risk for OSA. Overall, screening patients for sleep apnea at the time of a colonoscopy offers a unique opportunity not only to screen for colon cancer but also to identify patients at high risk for OSA who should undergo further testing.

ACKNOWLEDGMENTS

Special thanks to Dr. Sherif El-Behiry who assisted with the design of the study and Dr. Qiang Wu who performed the statistical analysis.

COMMENTS

Background

Obstructive sleep apnea (OSA) is extremely common and affects 2%-4% of the population, yet many patients with OSA are undiagnosed or never undergo screening for OSA.

Research frontiers

Sharara *et al* noted that of patients who snored greater than 10 s during their screening colonoscopies, all were noted to have OSA. The authors sought to determine the prevalence of OSA and the feasibility of screening these patients with the Berlin questionnaire at the time of their routine colonoscopy.

Innovations and breakthroughs

Endoscopists carefully evaluate the airway of each patient who undergoes sedation for gastrointestinal procedures, including colonoscopy. Screening patients for sleep apnea at the time of a colonoscopy offers a unique opportunity not only to screen for colon cancer but also to identify patients at high risk for OSA who should undergo further testing and adds little overall time to the procedure.

Applications

Screening patients for sleep apnea at the time of a screening colonoscopy is not only feasible but adds little time to the overall procedure, and offers a unique opportunity to screen patients for OSA that otherwise may never be screened.

Peer-review

This is an interesting study of screening for patients for sleep apnoea during colonoscopy. The paper is well written and presents a convincing proposal which may not have been addressed before as it crosses a field not handled

normally by gastroenterologists.

REFERENCES

- 1 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; **328**: 1230-1235 [PMID: 8464434 DOI: 10.1056/NEJM199304293281704]
- 2 Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997; **20**: 705-706 [PMID: 9406321]
- 3 Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkilä K, Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. *Br Med J (Clin Res Ed)* 1987; **294**: 16-19 [PMID: 3101779]
- 4 Poceta JS, Loube DI, Kellgren EL, Bizik K, Mitler MM. Mortality in Obstructive Sleep Apnea: Association with Impaired Wakefulness. *Sleep Breath* 1999; **3**: 3-8 [PMID: 11898096 DOI: 10.1007/s11325-999-0003-x]
- 5 Gupta RM, Parvizi J, Hanssen AD, Gay PC. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: a case-control study. *Mayo Clin Proc* 2001; **76**: 897-905 [PMID: 11560300 DOI: 10.4065/76.9.897]
- 6 Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology* 2008; **108**: 822-830 [PMID: 18431117 DOI: 10.1097/ALN.0b013e31816d91b5]
- 7 Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008; **108**: 812-821 [PMID: 18431116 DOI: 10.1097/ALN.0b013e31816d83e4]
- 8 Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999; **131**: 485-491 [PMID: 10507956]
- 9 Sharara AI, El Zahabi L, Maasri K, Hashash JG, Mansour N, Skoury A, Kanafani Z, Bou-Khalil P, Husari A. Persistent snoring under conscious sedation during colonoscopy is a predictor of obstructive sleep apnea. *Gastrointest Endosc* 2010; **71**: 1224-1230 [PMID: 20304398 DOI: 10.1016/j.gie.2009.11.049]
- 10 Sears DM, Cohen DC, Ackerman K, Ma JE, Song J. Birth cohort screening for chronic hepatitis during colonoscopy appointments. *Am J Gastroenterol* 2013; **108**: 981-989 [PMID: 23511461 DOI: 10.1038/ajg.2013.50]
- 11 Mehta PP, Kochhar G, Kalra S, Maurer W, Tetzlaff J, Singh G, Lopez R, Sanaka MR, Vargo JJ. Can a validated sleep apnea scoring system predict cardiopulmonary events using propofol sedation for routine EGD or colonoscopy? A prospective cohort study. *Gastrointest Endosc* 2014; **79**: 436-444 [PMID: 24219821 DOI: 10.1016/j.gie.2013.09.022]
- 12 Coté GA, Hovis CE, Hovis RM, Waldbaum L, Early DS, Edmundowicz SA, Azar RR, Mullady DK, Jonnalagadda SS. A screening instrument for sleep apnea predicts airway maneuvers in patients undergoing advanced endoscopic procedures. *Clin Gastroenterol Hepatol* 2010; **8**: 660-665.e1 [PMID: 20580942 DOI: 10.1016/j.cgh.2010.05.015]
- 13 Mador MJ, Abo Khamis M, Nag N, Mreyoud A, Jallu S, Mehboob S. Does sleep apnea increase the risk of cardiorespiratory complications during endoscopy procedures? *Sleep Breath* 2011; **15**: 393-401 [PMID: 20461471 DOI: 10.1007/s11325-010-0346-3]
- 14 Khiani VS, Salah W, Maimone S, Cummings L, Chak A. Sedation during endoscopy for patients at risk of obstructive sleep apnea. *Gastrointest Endosc* 2009; **70**: 1116-1120 [PMID: 19660748 DOI: 10.1016/j.gie.2009.05.036]

P- Reviewer: Gutierrez JMH, Seow-Choen F, Souza JLS

S- Editor: Qiu S L- Editor: A E- Editor: Li D



Observational Study

Information seeking and anxiety among colonoscopy-naïve adults: Direct-to-colonoscopy vs traditional consult-first pathways

Jocelyn A Silvester, Harmandeep Kalkat, Lesley A Graff, John R Walker, Harminder Singh, Donald R Duerksen

Jocelyn A Silvester, Harmandeep Kalkat, Lesley A Graff, John R Walker, Harminder Singh, Donald R Duerksen, Faculty of Health Sciences, College of Medicine, University of Manitoba, Winnipeg, MB R2H 2A6, Canada

Jocelyn A Silvester, Celiac Research Program, Boston Children's Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, United States

Author contributions: Silvester JA and Kalkat H collected data; Silvester JA, Kalkat H, Graff LA, Walker JR, Singh H and Duerksen DR contributed to data analysis, editing of manuscript and approval of the final version as submitted; Silvester JA, Graff LA, Walker JR, Singh H and Duerksen DR conceived and designed the study.

Supported by Health Sciences Centre Medical Staff Council Resident Research Award.

Institutional review board statement: This study was reviewed and approved by the Research Ethics Board at the University of Manitoba.

Informed consent statement: All study participants were informed about the purpose of the study verbally and in writing. Submission of a completed survey constituted informed consent to participate in the study.

Conflict-of-interest statement: Harminder Singh has been a consultant to Pendopharm; the other authors have no conflicts of interest to declare.

Data sharing statement: No other data available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Donald R Duerksen, MD, FRCPC, Associate Professor of Medicine, Faculty of Health Sciences, College of Medicine, University of Manitoba, St Boniface Hospital, C5120 - 409 Tache Avenue, Winnipeg, MB R2H 2A6, Canada. dduerkse@sbgh.mb.ca
Telephone: +1-204-2372796
Fax: +1-2042337154

Received: March 29, 2016

Peer-review started: April 4, 2016

First decision: May 23, 2016

Revised: July 7, 2016

Accepted: July 20, 2016

Article in press: July 22, 2016

Published online: November 16, 2016

Abstract

AIM

To investigate the effects of direct to colonoscopy pathways on information seeking behaviors and anxiety among colonoscopy-naïve patients.

METHODS

Colonoscopy-naïve patients at two tertiary care hospitals completed a survey immediately prior to their scheduled outpatient procedure and before receiving sedation. Survey items included clinical pathway (direct or consult), procedure indication (cancer screening or symptom investigation), telephone and written contact from the physician endoscopist office, information sources, and pre-procedure anxiety. Participants reported pre-procedure anxiety using a 10 point scale anchored by "very relaxed" (1) and "very nervous" (10). At least three months following the procedure, patient medical records were reviewed to determine sedative dose, procedure indications and any adverse events.

The primary comparison was between the direct and consult pathways. Given the very different implications, a secondary analysis considering the patient-reported indication for the procedure (symptoms or screening). Effects of pathway (direct *vs* consult) were compared both within and between the screening and symptom subgroups.

RESULTS

Of 409 patients who completed the survey, 34% followed a direct pathway. Indications for colonoscopy were similar in each group. The majority of the participants were women (58%), married (61%), and internet users (81%). The most important information source was family physicians (Direct) and specialist physicians (Consult). Use of other information sources, including the internet (20% *vs* 18%) and Direct family and friends (64% *vs* 53%), was similar in the Direct and Consult groups, respectively. Only 31% of the 81% who were internet users accessed internet health information. Most sought fundamental information such as what a colonoscopy is or why it is done. Pre-procedure anxiety did not differ between care pathways. Those undergoing colonoscopy for symptoms reported greater anxiety [mean 5.3, 95%CI: 5.0-5.7 (10 point Likert scale)] than those for screening colonoscopy (4.3, 95%CI: 3.9-4.7).

CONCLUSION

Procedure indication (cancer screening or symptom investigation) was more closely associated with information seeking behaviors and pre-procedure anxiety than care pathway.

Key words: Direct access colonoscopy; Colonoscopy/ utilization; Information seeking behavior; Referral and consultation; Health care delivery; Anxiety

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Direct access colonoscopy pathways are increasingly common, yet there has been relatively little scrutiny of how this practice impacts patients. This study examines the relationships among endoscopy pathway (direct *vs* traditional consult first), colonoscopy indication (cancer screening *vs* symptom investigation), information seeking behavior and pre-procedure anxiety. Patients undergoing their first colonoscopy completed questionnaires immediately prior to the procedure, before receiving sedation. The finding that direct-to-colonoscopy did not impact patient pre-procedure anxiety is reassuring. Analysis of information seeking behaviors underscores the crucial role of the family physician for referred patients who follow a direct-to-endoscopy pathway.

INTRODUCTION

As demands for prompt diagnostic and therapeutic colonoscopy have increased, direct to colonoscopy pathways have become common in many centers in North America^[1]. Direct to colonoscopy, also referred to as "open access colonoscopy", allows for provision of a colonoscopy without clinical consultation with the endoscopist prior to the day of the procedure. In an era of lengthy consultation waitlists and limited clinic resources^[2], this pathway has potential to facilitate expedited clinical care for many patients. Timely access is critical because delays in diagnostic colonoscopy may result in significant delays in cancer diagnosis^[3,4].

Despite being an increasingly common practice associated with appropriate utilization and diagnostic yield^[5-7], there is a paucity of data regarding how direct to colonoscopy pathways affect patients. It is essential for the success of the procedure that patients receive adequate information prior to the colonoscopy, including information about bowel preparation, and risks and benefits related to the procedure^[8]. Studies performed during the 1990s showed that direct to colonoscopy pathways were associated with receiving significantly less of this information prior to the procedure^[9]. Since then, using the internet to access health information has become a much more common practice^[10], and there are many other potential sources of information available to patients in addition to the specialist clinics. It is unknown whether the internet is commonly searched by patients prior to undergoing their first colonoscopy, what information they look for or how they use the information.

Persons undergoing an endoscopic procedure for the first time often experience heightened anxiety^[11]. It is not known if patients who do not have an opportunity to address issues of concern directly during a specialist consultation experience greater anxiety or if they are more likely to seek information from other sources.

The aims of this naturalistic study were to compare information seeking behavior (including use of the internet), pre-procedure preparation and anxiety level between patients following the direct pathway and patients undergoing colonoscopy after clinical consultation with an endoscopist (consult pathway). We hypothesized that patients who follow a direct to endoscopy pathway are more likely to use the internet to obtain information regarding their procedure and may have heightened pre-procedure anxiety compared to those whose endoscopy referral pathway includes a pre-procedure consultation with the endoscopist. The implications of a colonoscopy for colon cancer screening and a colonoscopy triggered by symptoms are very different; therefore, we performed a secondary analysis considering the patient-reported indication for the procedure (symptoms or screening). An understanding of these factors will help to optimize patient preparation for their procedure and their

Silvester JA, Kalkat H, Graff LA, Walker JR, Singh H, Duerksen DR. Information seeking and anxiety among colonoscopy-naïve adults: Direct-to-colonoscopy *vs* traditional consult-first pathways. *World J Gastrointest Endosc* 2016; 8(19): 701-708 Available from: URL: <http://www.wjgnet.com/1948-5190/full/>

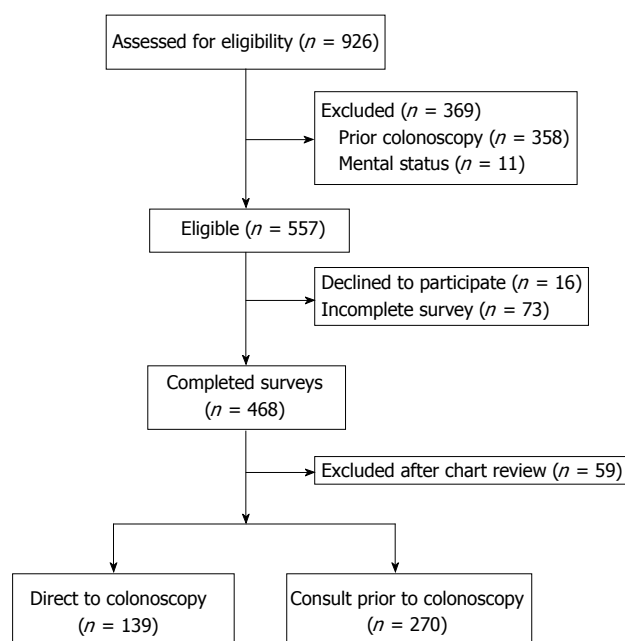


Figure 1 Participant recruitment. Recruitment and exclusions of patients participating in study.

colonoscopy experience, particularly for those following a direct to colonoscopy pathway.

MATERIALS AND METHODS

From May 2011 to August 2012, consecutive adults presenting for elective outpatient colonoscopy at the two largest hospitals in Winnipeg, Canada (serving a population of 800000) were invited to complete a pre-endoscopy survey. As this was a naturalistic study, assignment of patients to direct to colonoscopy or pre-procedure consultation was not randomized. Rather, assignment followed the usual practice of the endoscopist reviewing the information provided by the referring physician to determine the appropriate care pathway. This information typically includes patient sex, date of birth and a brief description of the symptoms prompting gastrointestinal consultation. Exclusion criteria were: (1) prior endoscopy; (2) concurrent gastroscopy and colonoscopy; and (3) unable to complete the survey due to language or cognitive difficulties. The study protocol was approved by the Research Ethics Board at the University of Manitoba.

Sample size was estimated assuming a 2:1 allocation to the consult and direct pathways. Assuming a standard deviation of 264 in the Direct group and 128 in the Consult group are needed to detect a 1 point difference in self-reported anxiety with a type I error rate of 5% and power of 80%.

Colonoscopies were performed by a physician endoscopist (gastroenterologist or surgeon). Written information was provided to patients in advance with modest differences in content and detail between clinics. Patient information included: A description of the procedure and use of sedation; a description of the post-procedure

process and follow-up; a list of potential adverse events, and instructions regarding the bowel preparation, diet, and medication use prior to the procedure.

Patients completed the survey after registering and prior to receiving sedation for their colonoscopy. The survey included items related to: (1) demographic characteristics; (2) sources of information about the colonoscopy (written information, internet, friends and family, appointment with endoscopist, telephone contact - yes/no response); (3) ranking of the three most important sources of information about the colonoscopy (10 sources listed); (4) internet use to learn about aspects of the colonoscopy (8 questions, yes/no response); (5) whether they had seen a video of a colonoscopy (yes/no response); and (6) details of type of bowel preparation used, whether they took time off work and if they completed the preparation successfully. Anxiety about the procedure was assessed with the question "how do you feel about your endoscopy today?" using a 10-item numerical rating scale, anchored by (1) very relaxed and (10) very nervous. For analysis, anxiety was characterized as "low" (a rating of 1 to 4), "moderate" (5 to 7) or "high" (8-10). Participants identified whether the colonoscopy was for cancer screening or for symptoms.

Hospital medical records of all participants were reviewed at least 3 mo after the procedure to document procedure-related processes, including indication for the colonoscopy, dose of sedative agents used, findings at colonoscopy and any adverse events.

Data were analyzed using SPSS version 15.0. Patients in the direct to colonoscopy (Direct) pathway were compared with patients who had received a pre-procedure consultation with the endoscopist who subsequently performed the procedure (consult pathway). Means and 95%CI or standard deviation were calculated for all variables as appropriate. The implications of a colonoscopy for colon cancer screening and a colonoscopy triggered by symptoms are very different; therefore, we performed a secondary analysis considering the patient-reported indication for the procedure (symptoms or screening). The effects of pathway (direct vs consult) were compared both within and between the screening and symptom subgroups. The 95%CIs around the estimates (mean or proportions) were used to make comparisons and the differences were considered significant if there was no overlap of 95%CIs or 95%CI around calculated differences did not cross zero.

RESULTS

Of the 926 patients screened for study participation, 409 fulfilled study criteria and completed the pre-procedure survey (Figure 1). The most common reason for exclusion was prior endoscopy. A further 59 were excluded when chart review identified a previous endoscopy or concurrent gastroscopy. The mean age of participants was 55 years (SD 8.6). The majority of the participants were women (58%), married (61%), and internet users (81%). The demographic characteristics

Table 1 Background characteristics of patients and colonoscopy processes comparing direct to colonoscopy and pre-procedure consult

	Direct (<i>n</i> = 139) % (95%CI)	Consult (<i>n</i> = 270) % (95%CI)
Highest level of education		
High school or less	35 (27-43)	37 (31-43)
Trade or non-university certificate	29 (21-37)	35 (29-41)
University	36 (28-44)	28 (23-33)
Marital status - married	60%	62%
Internet user	81%	81%
Used internet to learn about colonoscopy	29%	32%
Patient indication screening	<i>n</i> = 76	<i>n</i> = 117
% of screening high risk	60 (48-72)	49 (40-58)
Patient indication symptoms	<i>n</i> = 63	<i>n</i> = 153
Bloating	86 (77-95)	78 (70-86)
Diarrhea	78 (68-88)	68 (60-76)
Abdominal cramps and/or pain	76 (65-87)	72 (64-80)
Constipation	54 (42-66)	61 (52-70)
Blood in stool	50 (38-62)	37 (28-46)
Nausea or vomiting	35 (23-47)	35 (26-44)
Weight loss	30 (19-41)	36 (27-45)
Pre-procedure information		
Telephone contact	69 (58-80)	48 (39-57)
Written information	94%	96%
Age in years mean (IQR)	56 (54-58)	54 (53-56)
Sex - female	59%	57%

Bolded values indicate pairs for which confidence intervals do not overlap. IQR: Interquartile range.

Table 2 Most important sources of information for learning about colonoscopy comparing direct to colonoscopy and pre-procedure consult care pathways

	Most important		Among top three most important	
	Direct % (95%CI)	Consult % (95%CI)	Direct % (95%CI)	Consult % (95%CI)
Any physician	51 (43-59)	69 (63-75)	81 (75-88)	89 (85-93)
Family physician	37 (29-45)	26 (21-31)	59 (51-67)	39 (33-45)
Specialist physician	14 (8-20)	43 (37-49)	22 (15-29)	50 (44-56)
Family and friends	13 (7-19)	10 (6-14)	64 (56-72)	53 (47-59)
Internet	7 (3-11)	4 (2-6)	20 (13-27)	18 (13-23)
Other	3 (0-6)	3 (1-5)	20 (13-27)	13 (9-17)

Bolded values indicate pairs for which CI do not overlap. Note: Participants reviewed 10 potential sources of information and ranked the three most important.

of those in the direct and consult groups were similar (Table 1). Virtually all patients in both groups reported receiving written information about their procedure.

A greater proportion of patients in the Direct group received a pre-procedure telephone call from the physician's office with relevant pre-procedure preparation information (Direct 69% vs Consult 48%; Table 1). Receiving a pre-procedure telephone call was not associated with pre-procedure anxiety, sedation use, or information-seeking behavior (data not shown).

Ranking of the importance of information sources that were accessed to learn more about colonoscopy is described in Table 2. Both groups identified physicians as the most important source of information. Family and friends were also an important source of information for both groups, with 64% (56%-72%) in the direct group and 53% (47%-59%) in the Consult group rating them among the three most important sources of information.

As expected, those following the direct pathway obtained information from a specialist physician less often, and were more likely to rate information from a family physician among the top three most important information sources [59% (51%-67%) vs 39% (33%-45%)]. The use and importance of other information sources, including the internet, did not differ between the two groups.

The rate of general internet use was 81% in both groups (*n* = 301), with about 30% reporting they used the internet to learn more about colonoscopy. The pattern of responses shown in Table 3 suggests that among the respondents who used the internet to obtain information about colonoscopy (*n* = 301), there was interest in a wide range of questions which did not differ between care pathways. Considering the indication for colonoscopy, those referred for symptoms accessed internet health information more often than those in the screening group [48% (40%-56%) vs 28% (20%-36%)]. Despite the

Table 3 Use of the internet to answer questions about colonoscopy by regular internet users (*n* = 301) comparing care pathway and indication

	Care pathway		Indication	
	Direct (<i>n</i> = 104) % (95%CI)	Consult (<i>n</i> = 197) % (95%CI)	Screening (<i>n</i> = 166) % (95%CI)	Symptoms (<i>n</i> = 135) % (95%CI)
What is a colonoscopy	29 (20-38)	32 (26-39)	23 (16-31)	38 (31-46)
How to prepare for colonoscopy	16 (8-23)	24 (17-30)	15 (9-22)	26 (19-33)
What happens during colonoscopy	20 (12-28)	26 (19-32)	17 (10-24)	30 (22-37)
How much time does a colonoscopy take	13 (6-19)	20 (14-26)	14 (8-20)	21 (15-28)
What to expect after colonoscopy	11 (5-18)	18 (12-24)	12 (6-18)	19 (13-26)
Why colonoscopy is done	30 (21-40)	28 (22-35)	19 (12-26)	37 (29-45)
Risks of colonoscopy	19 (11-27)	22 (16-28)	16 (10-23)	25 (18-32)
What is a biopsy	11 (5-18)	14 (9-19)	9 (4-14)	17 (11-23)
Saw video of colonoscopy	24 (15-33)	17 (11-22)	19 (12-25)	20 (13-26)

Bolded values indicate pairs for which confidence interval do not overlap.

Table 4 Bowel preparation, time off work and sedation used for colonoscopy comparing direct to colonoscopy and pre-procedure consult pathways

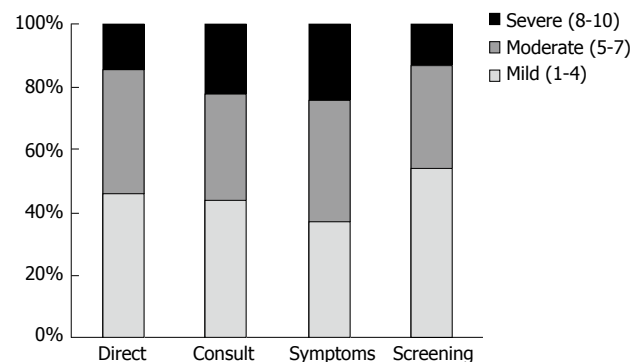
	Direct (<i>n</i> = 139) % (95%CI)	Consult (<i>n</i> = 270) % (95%CI)
Bowel prep		
Picosulfate and magnesium oxide	69 (60-76)	71 (65-77)
Polyethylene glycol	17 (11-24)	14 (10-18)
Other	14 (8-20)	15 (11-19)
Completion of bowel prep	98%	98%
Time off work for bowel prep		
Full-time workers (<i>n</i> = 188)	56 (43-69)	64 (56-72)
Part-time workers (<i>n</i> = 52)	42 (20-64)	50 (29-71)
Sedation		
Midazolam (mg)	5.6 (5.2-5.9)	4.7 (4.5-4.9)
Fentanyl (μg)	106 (100-111)	93 (89-97)

Bolded values indicate pairs for which confidence intervals do not overlap.

wealth of information available on the internet, including well-produced videos, only 1 in 6 patients had seen a video of a colonoscopy prior to the procedure.

There was no difference in the type of bowel preparation used or the self-reported completion of bowel preparation between the two groups (Table 4). Most respondents took time off work to complete bowel preparation, but there was no difference between the Direct and Consult care pathways.

Overall, 20% of participants reported high pre-procedure anxiety. In both care pathways, females reported significantly higher pre-procedure anxiety than males [overall females 5.3 (5.0-5.7), males 4.3 (3.9-4.7); 95%CI for difference 0.76-1.9]. There were no differences in the pre-procedure anxiety levels among individuals in the Direct group compared with the Consult group [mean 4.7 (95%CI: 4.3-5.2) vs 5.0 (95%CI: 4.6-5.3)]. Similarly, there was no statistical differences in proportions reporting low, moderate or high pre-procedure anxiety, comparing the Direct and Consult groups (Figure 2). Mean pre-procedure anxiety was lower among those undergoing screening colonoscopy, but the difference was significant only within the Consult group (males 4.2 vs females 5.4; 95%CI for difference

**Figure 2** Anxiety levels comparing clinical pathway and indication for colonoscopy. Anxiety levels comparing care pathway and indication for colonoscopy. Anxiety ratings on a 10 point Likert scale were categorized as mild (1-4), moderate (5-7) or high (8-10).

0.5-2.0). There were 311 participants for whom the self-reported indication matched the indication documented in the medical record. In sensitivity analysis, the relationship between procedure indication and pre-procedure anxiety was observed among this group for both care pathways (Direct 4.4 vs 5.4; Consult 4.1 vs 5.5). Mean anxiety levels among those for whom the patient-reported and documented indication were discordant were similar to the population mean. In the Direct group, the relationship between pre-procedure anxiety and indication was attenuated (screening 4.2, non-screening 4.6). Among the Consult group, the relationship was reversed, with higher anxiety levels reported by those undergoing screening colonoscopy (5.1 vs 4.8). This difference persisted even when those identified as high-risk were excluded from the analysis (data not shown).

Patients in the Direct group received more midazolam (5.4 mg vs 4.6 mg, 95%CI: 0.41-1.2 mg) and fentanyl (105 μg vs 93 μg; 95%CI: 5-20 μg). This association between direct pathway and midazolam use was also observed within the screening and symptom sub-groups (data not shown). Midazolam and fentanyl doses were unrelated to self-rated pre-procedure anxiety, indication for the procedure or duration of the procedure (data not shown). There were no sedation or procedure related

adverse events reported, based on the chart review.

DISCUSSION

This observational study clarifies the real-world effects of referral pathway upon the behaviors and experiences of colonoscopy-naïve patients. We hypothesized that those in the direct (open access) pathway would display more information seeking behaviors and may experience more anxiety related to the procedure given that they did not have the benefit of a consultation with the physician endoscopist prior to the day of their procedure. We found that information seeking behaviors and anxiety were more closely associated with the indication for the procedure (colon cancer screening vs for diagnosis of symptoms) than by the referral pathway. This illustrates the intricacy of designing referral pathways to optimize the utilization of scarce clinical and endoscopy resources while providing care which meets the needs of the patient. It also underscores the importance of primary care physicians in the continuum of care.

The pattern of information seeking behavior did not differ between the two care pathways. Even with the plethora of electronic and other resources available, the patient-physician relationship was paramount for obtaining information regarding colonoscopy. Patients following a direct pathway received this information from a primary care physician, while patients in the Consult group received this information from an endoscopist.

This study was conducted in Canada where there is one of the highest rates of internet penetration^[12] and the majority of the population has used the internet to access health information^[10]. Over 80% of patients in our study were internet users; however, only 30% of them used the internet to learn more about colonoscopy. Patients who accessed internet health information sought to answer fundamental questions related to what a colonoscopy is and why is it done, with fewer reporting having delved more deeply into details such as biopsy or the risks of colonoscopy. This observation is concerning given a narrative review of the relationships between lower endoscopy and clinical outcomes which concluded that providing written information and reminders improve adherence to procedures, but that a large proportion of patients have poor comprehension of the risks, benefits and alternatives to colonoscopy^[13]. The general nature of information sought by participants in our study indicates a need for additional educational initiatives to increase patient knowledge about the procedure which encompasses more than instruction for achieving a quality bowel preparation.

The role of the internet in educating patients about colonoscopy prior to their procedure has not been studied. Given that over 80% of patients in this study were internet users, there is opportunity to develop internet resources or more proactively use appropriate existing resources to support physicians in preparing patients for endoscopic procedures. Advantages of the internet

are that it is accessible for most people, can present video materials easily, and allows the user to choose how much material to review, depending on information preferences and previous knowledge. Video materials have the advantage that they can present information vividly and may impart information about the procedure more easily than text-based information. There are currently resources on the internet that provide realistic and positive depictions of the patient experience before and during a colonoscopy^[14,15], but they do not appear to be widely used by patients preparing for their first colonoscopy.

We hypothesized that increased pre-procedure anxiety might be an unintended and unrecognized consequence of direct to colonoscopy pathways. However, in our study of colonoscopy-naïve individuals, pre-procedure anxiety was similar regardless of referral pathway. There were a significant minority (20%) who reported high pre-procedure anxiety, with higher anxiety levels reported by women than by men. There is one other report of the relationship between direct to colonoscopy pathway and pre-procedure anxiety^[11]. That study was also an observational study, but included patients who had previously undergone an endoscopic procedure as well as patients undergoing gastroscopy. Nevertheless, similar to our study, the direct to colonoscopy pathway was not associated with increased pre-procedure anxiety^[11]. We found, understandably, that participants undergoing colonoscopy for symptom investigation reported greater pre-procedure anxiety than participants whose endoscopy was for colorectal cancer screening. Among the entire group, the majority of participants reported moderate or high anxiety related to their procedure, irrespective of the pathway or indication.

Clearly, allaying pre-procedure anxiety may be helpful in optimizing the experience of patients undergoing a colonoscopy, yet there have been few studies which have evaluated interventions to decrease pre-procedure anxiety^[16-18]. For colonoscopy-naïve patients, education has been found to effectively decrease anxiety when delivered either as a ten minutes video at the pre-procedure visit^[17] or as a detailed information pamphlet about colonoscopy^[19] in addition to standard written information. Provision of written instruction and information was associated with decreased pre-procedure anxiety in a cohort of patients who had undergone a previous endoscopic procedure^[18].

The content of the information provided is also relevant to pre-procedure anxiety. Provision of a colonoscopy pamphlet developed by the American Gastroenterology Association which explained all aspects of colonoscopy and why it is done in addition to "standard colonoscopy preparation instructions" (which focused primarily on the details of the bowel prep) may decrease pre-procedure anxiety^[19]. Interestingly, in a randomized study in which participants were invited to watch an informational video in addition to receiving standard information, offering the choice did not result in a reduction in pre-procedure anxiety, yet all patients who viewed the video

experienced less pre-procedure anxiety^[17].

An unexpected finding of our study was that patients following the direct pathway received higher doses of sedative medications than patients who had a pre-procedure consult. This was not significantly associated with self-reported pre-procedure anxiety, indication for the procedure, or duration of the procedure. While the lack of association between pre-procedure anxiety and sedation requirements during colonoscopy has been reported^[20], referral pathway has not previously been identified as a risk factor for increased sedation requirement. The relationship between referral pathway and sedation use during colonoscopy merits further study, not only to improve our limited understanding of the complex factors contributing to sedation requirements^[21-23], but also to determine whether inclusion of this variable would enhance clinical scoring systems to prospectively identify patients with high sedation requirements^[23].

A potential consequence of direct to colonoscopy is inadequate instruction regarding the bowel preparation required for the procedure. Adequacy of bowel preparation is considered a quality indicator in colonoscopy^[24] and is particularly relevant for screening for colorectal cancer, the most common indication for colonoscopy in our patient sample, and in most endoscopy units. Self-reported successful completion of bowel preparation was similar in both care pathways. The quality of bowel preparation was not evaluated because this was not systematically recorded by the endoscopists. The work of other investigators suggests that open access does not compromise the bowel preparation with up to 96% of patients achieving adequate bowel preparation using a split-dose regimen^[25].

The primary strength of this study is the use of a naturalistic design to explore a topic about which relatively little is known. This provides insight into patient experiences and behaviors in a real-world scenario reflective of clinical practice.

The use of an observational design is also a limitation. There were multiple endoscopists involved who used several similar, non-identical, pre-procedure information pamphlets. Assignment to the direct to endoscopy pathway was a decision made by the endoscopist without reference to pre-determined standardized criteria or as part of a randomized study design. This may have introduced bias into the study; however, it reflects clinical practice and the distribution of patients between the two pathways was similar at the two study sites. Although the difference was relatively small (11%), there were more patients undergoing screening in the Direct to colonoscopy group compared to the Consult group. This is not unexpected given that age is indicated on the referral and is an indication for screening colonoscopy. Nevertheless, there were no major differences in the demographic characteristics of the two patient groups and the relative differences in pre-procedure anxiety and information seeking behaviors between those who were undergoing colonoscopy for unexplained symptoms and those who were undergoing screening colonoscopy were

similar in both care pathways.

In conclusion, our findings demonstrate that the ramifications of open access colonoscopy encompass far more than improved efficiency and cost savings. Patients in the direct pathway relied upon their family doctor to obtain information about their procedure. In an era of open access colonoscopy, it may be especially important that primary care physicians can provide accurate and relevant information regarding colonoscopy to their patients. This includes specifics about the procedure, the preparation, the risks and the rationale for its use, which is the information that patients were most likely to seek using the internet. Preparation for endoscopy is a complex and multifactorial process which involves more than ensuring an adequate bowel preparation. The value of primary care counseling is underscored by a study in which those who received primary care counseling had greater participation in a colon cancer screening program and required less sedation during their procedure^[26].

Colonoscopy-naïve patients who were assigned to a direct to colonoscopy pathway demonstrated similar information seeking behavior, use of the internet as an information source, completion of the bowel prep and levels of pre-procedure anxiety as those who had a pre-procedure outpatient consultation. However, there was a relevant minority of patients with high pre-procedure anxiety which was higher in women and in individuals undergoing a colonoscopy for symptom investigation. Future studies should address ways of optimizing preparation of patients for the colonoscopy and reducing pre-procedure anxiety.

ACKNOWLEDGMENTS

We thank all the patients who participated in this study and the endoscopy unit staff who assisted with recruiting them. As well, we thank the Health Sciences Center Medical Staff Council who provided funding for this study.

COMMENTS

Background

Direct access colonoscopy pathways are increasingly common as health care systems strive to expedite care and control costs. This is associated with appropriate use and diagnostic yield, but other impacts have not been well-described.

Research frontiers

This study of colonoscopy-naïve patients investigates information use and anxiety in patients undergoing direct access colonoscopy and compares this with patients who have an initial consult prior to their colonoscopy procedure.

Innovations and breakthroughs

Open access colonoscopy has ramifications beyond efficiency gains and cost savings. Physicians play a key role in informing patients about colonoscopy and primary care physicians play an especially important role in an open access pathway. Pre-procedure anxiety is more closely associated with patient reported indication for the procedure than with referral pathway.

Applications

This study supports the practice of direct access colonoscopy. Patients

undergoing direct access colonoscopy do not have increased anxiety and access information about their procedure similar to patients having a specialist consult prior to the procedure. Referral pathways must be responsive to the needs of patients and attentive to the role of referring clinicians to ensure adequately informed and prepared patients.

Peer-review

This is an interesting study looking at difference in anxiety between open access and consult first pathways to colonoscopy. The research is well-designed and the overall structure of the manuscript is complete.

REFERENCES

- 1 **Pike IM.** Open-access endoscopy. *Gastrointest Endosc Clin N Am* 2006; **16**: 709-717 [PMID: 17098617 DOI: 10.1016/j.giec.2006.08.012]
- 2 **Leddin D,** Bridges RJ, Morgan DG, Fallone C, Render C, Plourde V, Gray J, Switzer C, McHattie J, Singh H, Walli E, Murray I, Nestel A, Sinclair P, Chen Y, Irvine EJ. Survey of access to gastroenterology in Canada: the SAGE wait times program. *Can J Gastroenterol* 2010; **24**: 20-25 [PMID: 20186352 DOI: 10.1155/2010/246492]
- 3 **Singh H,** Khan R, Giardina TD, Paul LW, Daci K, Gould M, El-Serag H. Postreferral colonoscopy delays in diagnosis of colorectal cancer: a mixed-methods analysis. *Qual Manag Health Care* 2013; **21**: 252-261 [PMID: 23011072 DOI: 10.1097/QMH.0b013e31826d1f28]
- 4 **Sey MS,** Gregor J, Adams P, Khanna N, Vinden C, Driman D, Chande N. Wait times for diagnostic colonoscopy among outpatients with colorectal cancer: a comparison with Canadian Association of Gastroenterology targets. *Can J Gastroenterol* 2012; **26**: 894-896 [PMID: 23248790]
- 5 **Gimeno García AZ,** González Y, Quintero E, Nicolás-Pérez D, Adrián Z, Romero R, Alarcón Fernández O, Hernández M, Carrillo M, Felipe V, Díaz J, Ramos L, Moreno M, Jiménez-Sosa A. Clinical validation of the European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) II criteria in an open-access unit: a prospective study. *Endoscopy* 2012; **44**: 32-37 [PMID: 22109649 DOI: 10.1055/s-0031-1291386]
- 6 **Morini S,** Hassan C, Meucci G, Toldi A, Zullo A, Minoli G. Diagnostic yield of open access colonoscopy according to appropriateness. *Gastrointest Endosc* 2001; **54**: 175-179 [PMID: 11474386 DOI: 10.1067/mge.2001.116565]
- 7 **Charles RJ,** Cooper GS, Wong RC, Sivak MV, Chak A. Effectiveness of open-access endoscopy in routine primary-care practice. *Gastrointest Endosc* 2003; **57**: 183-186 [PMID: 12556781 DOI: 10.1067/mge.2003.55]
- 8 **Kazarian ES,** Carreira FS, Toribara NW, Denberg TD. Colonoscopy completion in a large safety net health care system. *Clin Gastroenterol Hepatol* 2008; **6**: 438-442 [PMID: 18304886 DOI: 10.1016/j.cgh.2007.12.003]
- 9 **Staff DM,** Saeian K, Rochling F, Narayanan S, Kern M, Shaker R, Hogan WJ. Does open access endoscopy close the door to an adequately informed patient? *Gastrointest Endosc* 2000; **52**: 212-217 [PMID: 10922093 DOI: 10.1067/mge.2000.107719]
- 10 **Underhill C,** McKeown L. Getting a second opinion: health information and the Internet. *Health Rep* 2008; **19**: 65-69 [PMID: 18457212]
- 11 **Mahajan RJ,** Agrawal S, Barthel JS, Marshall JB. Are patients who undergo open-access endoscopy more anxious about their procedures than patients referred from the GI clinic? *Am J Gastroenterol* 1996; **91**: 2505-2508 [PMID: 8946975]
- 12 **de Argaez E.** Top 50 countries with highest internet penetration rates. Internet World Stats: usage and population statistics. 2014. Available from: URL: <http://www.internetworldstats.com/top25.htm>
- 13 **Coombes JM,** Steiner JF, Bekelman DB, Prochazka AV, Denberg TD. Clinical outcomes associated with attempts to educate patients about lower endoscopy: a narrative review. *J Community Health* 2008; **33**: 149-157 [PMID: 18165928 DOI: 10.1007/s10900-007-9081-5]
- 14 **American Society for Gastrointestinal Endoscopy.** Colonoscopy: What Patients Can Expect. 2009. Available from: URL: <https://www.youtube.com/watch?v=eA1PIMa1ULg>
- 15 **Stand up to Cancer.** Katie Couric's Colonoscopy for SU2C. 2000. Available from: URL: <https://www.youtube.com/watch?v=15JsYZIT-Q>
- 16 **Pearson S,** Maddern GJ, Hewett P. Interacting effects of preoperative information and patient choice in adaptation to colonoscopy. *Dis Colon Rectum* 2005; **48**: 2047-2054 [PMID: 16228834 DOI: 10.1007/s10350-005-0172-z]
- 17 **Luck A,** Pearson S, Maddern G, Hewett P. Effects of video information on precolonoscopy anxiety and knowledge: a randomised trial. *Lancet* 1999; **354**: 2032-2035 [PMID: 10636368]
- 18 **Kutlutürk S,** Görgülü U, Fesci H, Karavelioglu A. The effects of providing pre-gastrointestinal endoscopy written educational material on patients' anxiety: a randomised controlled trial. *Int J Nurs Stud* 2010; **47**: 1066-1073 [PMID: 20181334 DOI: 10.1016/j.ijnurstu.2010.01.007]
- 19 **Shaikh AA,** Hussain SM, Rahn S, Desilets DJ. Effect of an educational pamphlet on colon cancer screening: a randomized, prospective trial. *Eur J Gastroenterol Hepatol* 2010; **22**: 444-449 [PMID: 19940781 DOI: 10.1097/MEG.0b013e328333fca6]
- 20 **Chung KC,** Juang SE, Lee KC, Hu WH, Lu CC, Lu HF, Hung KC. The effect of pre-procedure anxiety on sedative requirements for sedation during colonoscopy. *Anaesthesia* 2013; **68**: 253-259 [PMID: 23167579 DOI: 10.1111/anae.12087]
- 21 **Hazeldine S,** Fritschi L, Forbes G. Predicting patient tolerance of endoscopy with conscious sedation. *Scand J Gastroenterol* 2010; **45**: 1248-1254 [PMID: 20560818 DOI: 10.3109/00365521.2010.497939]
- 22 **Bal BS,** Crowell MD, Kohli DR, Menendez J, Rashti F, Kumar AS, Olden KW. What factors are associated with the difficult-to-sedate endoscopy patient? *Dig Dis Sci* 2012; **57**: 2527-2534 [PMID: 22565338 DOI: 10.1007/s10620-012-2188-2]
- 23 **Braunstein ED,** Rosenberg R, Gress F, Green PH, Lebowitz B. Development and validation of a clinical prediction score (the SCOPE score) to predict sedation outcomes in patients undergoing endoscopic procedures. *Aliment Pharmacol Ther* 2014; **40**: 72-82 [PMID: 24815064 DOI: 10.1111/apt.12786]
- 24 **Rex DK,** Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, Lieb JG, Park WG, Rizk MK, Sawhney MS, Shaheen NJ, Wani S, Weinberg DS. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; **81**: 31-53 [PMID: 25480100 DOI: 10.1016/j.gie.2014.07.058]
- 25 **MacPhail ME,** Hardacker KA, Tiwari A, Vemulapalli KC, Rex DK. Intraprocedural cleansing work during colonoscopy and achievable rates of adequate preparation in an open-access endoscopy unit. *Gastrointest Endosc* 2015; **81**: 525-530 [PMID: 24998464 DOI: 10.1016/j.gie.2014.05.002]
- 26 **Boguradzka A,** Wiszniewski M, Kaminski MF, Kraszewska E, Mazurczak-Pluta T, Rzewuska D, Ptasiński A, Regula J. The effect of primary care physician counseling on participation rate and use of sedation in colonoscopy-based colorectal cancer screening program—a randomized controlled study. *Scand J Gastroenterol* 2014; **49**: 878-884 [PMID: 24797871 DOI: 10.3109/00365521.2014.913191]

P- Reviewer: Chaptini L, Saligram S, Zhang QS S- Editor: Gong ZM

L- Editor: A E- Editor: Li D



Prospective Study

Post-endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity

Ayman El Nakeeb, Ehab El Hanafy, Tarek Salah, Ehab Atef, Hosam Hamed, Ahmad M Sultan, Emad Hamdy, Mohamed Said, Ahmed A El Geidie, Tharwat Kandil, Mohamed El Shobari, Gamal El Ebidy

Ayman El Nakeeb, Ehab El Hanafy, Tarek Salah, Ehab Atef, Hosam Hamed, Ahmad M Sultan, Emad Hamdy, Mohamed Said, Ahmed A El Geidie, Tharwat Kandil, Mohamed El Shobari, Gamal El Ebidy, Gastroenterology Surgical Center, Mansoura University, Mansoura 35516, Egypt

Author contributions: El Nakeeb A designed the research; El Nakeeb A, El Hanafy E, Salah T, Atef E, Hamed H, Sultan AM, Hamdy E, Said M, El Geidie AA, Kandil T, El Shobari M and El Ebidy G performed the research; El Nakeeb A and Said M analyzed data; El Nakeeb A and Hamed H wrote the paper.

Institutional review board statement: This study was approved by the institutional review board of Mansoura University.

Informed consent statement: All patients underwent ERCP after a careful explanation of the nature of the disease and possible complications.

Conflict-of-interest statement: There are no potential conflicts of interest relevant to this article.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Ayman El Nakeeb, Associate Professor, Gastroenterology Surgical Center, Mansoura University, El Gomhouria St, Mansoura 35516, Egypt. elnakeebayman@yahoo.com
Telephone: +2-50-2353430
Fax: +2-50-2243220

Received: June 5, 2016

Peer-review started: June 6, 2016

First decision: July 20, 2016

Revised: July 27, 2016

Accepted: August 27, 2016

Article in press: August 29, 2016

Published online: November 16, 2016

Abstract

AIM

To detect risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and investigate the predictors of its severity.

METHODS

This is a prospective cohort study of all patients who underwent ERCP. Pre-ERCP data, intraoperative data, and post-ERCP data were collected.

RESULTS

The study population consisted of 996 patients. Their mean age at presentation was 58.42 (\pm 14.72) years, and there were 454 male and 442 female patients. Overall, PEP occurred in 102 (10.2%) patients of the study population; eighty (78.4%) cases were of mild to moderate degree, while severe pancreatitis occurred in 22 (21.6%) patients. No hospital mortality was reported for any of PEP patients during the study duration. Age less than 35 years (P = 0.001, OR = 0.035), narrower common bile duct (CBD) diameter (P = 0.0001) and increased number of pancreatic cannulations (P = 0.0001) were independent risk factors for the occurrence of PEP.

CONCLUSION

PEP is the most frequent and devastating complication after ERCP. Age less than 35 years, narrower median CBD diameter and increased number of pancreatic

cannulations are independent risk factors for the occurrence of PEP. Patients with these risk factors are candidates for prophylactic and preventive measures against PEP.

Key words: Pancreatitis; Obstructive jaundice; Endoscopic retrograde cholangiopancreatography

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most devastating and frequent complication after ERCP. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients. Age less than 35 years, narrower median common bile duct diameter and increased number of pancreatic cannulations were identified to be independent risk factors for the occurrence of PEP.

El Nakeeb A, El Hanafy E, Salah T, Atef E, Hamed H, Sultan AM, Hamdy E, Said M, El Geidie AA, Kandil T, El Shobari M, El Ebidy G. Post-endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity. *World J Gastrointest Endosc* 2016; 8(19): 709-715 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/709.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.709>

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases^[1]. However, ERCP is not a procedure without morbidities^[2]. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP^[3]. The reported incidence of PEP is around 5%^[4,5]. This rate may increase up to 20%-40% in high risk patients. Although the majority of PEP cases are of mild degree, it can be severe and life threatening in a substantial proportion of cases^[6].

Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients^[1,7,8]. Being convinced with a number of patient-related risk factors, some gastroenterologists and surgeons prefer adoption of alternative management strategies for ERCP whenever possible in high risk patients. Similarly, some endoscopists try to avoid procedure-related risk factors to increase the safety of the procedure. All these factors make identification of risk factors for PEP be of paramount importance for the practice of ERCP.

Many patient and procedure related factors have been suggested to be associated with increased likelihood of PEP^[8]. The trigger mechanism and pathogenesis for PEP

remain unclear^[9]. The aim of this study was to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Middle East in Egypt.

MATERIALS AND METHODS

This is a prospective cohort study of all patients who underwent ERCP between August 2012 and September 2014. Excluded patients were those who presented with obstructed stent, active pancreatitis, previous endoscopic sphincterotomy, biliary complications after liver transplantation, dye allergy, pregnancy, or mental disability.

Patients were admitted 24 h before the procedure. Baseline laboratory assessment of liver functions, blood count and serum amylase level were done prior to ERCP. No pre-ERCP treatment was used to decrease the risk of PEP. In our center, ERCP is performed under general anesthesia with endotracheal intubation in left semi prone position with monitoring of oxygen saturation, heart rate, and blood pressure. The procedure was performed by experienced endoscopists who had performed at least 1500 ERCPs over the last 10 years. Selective bile duct cannulation was carried out in all patients, but pancreatic duct cannulation was performed when necessary. When three or more attempts were needed due to difficulty in cannulation, precut papillotomy was selectively performed. In addition, endoscopic papillotomy for stone extraction using balloon, basket and mechanical lithotripsy, bile duct placement of either plastic or self-expanding metallic stent, as well as brush cytology and dilation, were performed when indicated. Pancreatic duct stenting was not used to minimize PEP in our practice.

ERCP data were recorded in a standardized manner including all potential risk factors for PEP. Patients were hospitalized for 24 h after the procedure and observed for symptoms and signs of post-ERCP complications. Complete blood picture and serum amylase level were determined routinely after 6 h and 24 h.

PEP was defined and classified according to the consensus definition and grading system^[10]. PEP was defined as new or worsened abdominal pain together with a serum amylase level at least three times normal at more than 24 h after ERCP and necessitating hospitalization for more than one night. PEP was graded according to the length of hospital stay and the need for intervention. Mild PEP required hospitalization for 2-3 nights, moderate PEP required hospitalization for 4-10 nights, and severe pancreatitis required hospitalization for more than 10 d, or required intervention or was complicated by pseudocyst^[10].

Descriptive data are presented as means and standard deviation or medians with range according to the data distribution. Comparison of means was done by χ^2 test for categorical data or Student's *t* test for continuous data. Difference was considered significant when a *P*-value was less than 0.05. Independent risk factors for PEP were assessed by multiple logistic

Table 1 Risk factors for pancreatitis after endoscopic retrograde cholangiopancreatography *n* (%)

	No pancreatitis 894 (89.9)	Pancreatitis 102 (10.2)	<i>P</i> -value
Patient related factors			
Median age (yr)	60	48	0.0001
Age group			
< 35	32 (7.2)	20 (39.2)	0.0001
> 35	415 (92.8)	31 (60.8)	
Sex			
Male	510 (57)	44 (43.1)	0.05
Female	384 (43)	58 (56.9)	
Median serum bilirubin (mg%)	10.6	12.5	0.76
< 2	124 (88.6)	16 (11.4)	
> 2	770 (90)	86 (10)	0.72
Median CBD diameter (mm)	16	10	0.0001
< 10	70 (7.8)	58 (56.9)	
> 10	824 (92.2)	44 (43.1)	0.0001
Indication for ERCP			
Malignant	402 (45)	40 (39.2)	0.43
Benign	492 (55)	62 (60.8)	
Type of papilla			
Normal	540 (60.4)	56 (54.9)	0.01
Atrophic	18 (2)	8 (7.8)	
Pregnant	68 (7.6)	2 (2)	
Tumour	64 (7.2)	4 (3.9)	
Redundant	66 (7.4)	12 (11.8)	
Juxta-divericular	68 (7.6)	16 (15.7)	
Small	60 (6.6)	2 (2)	
Long	10 (1.1)	2 (2)	
Procedure related factors			
Number of cannulation attempts			
< 5	660 (73.9)	58 (56.9)	0.01
≥ 6	234 (26.1)	44 (43.1)	
Number of pancreatic cannulations	0	2	0.0001
< 3 times	864 (96.6)	60 (58.8)	
> 3 times	28 (3.4)	42 (41.2)	0.0001
Method of cannulation			
Conventional	640 (89.4)	76 (10.6)	0.7
Precut	252 (90.6)	26 (9.4)	
Biliary sphincter balloon dilatation			
No	654 (73.2)	86 (84.3)	0.08
Yes	240 (26.8)	16 (15.7)	

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography

regression. Statistical analyses of the data in this study were performed using SPSS software, version 17 (Chicago, IL).

RESULTS

From August 2012 to September 2014, a total of 1296 patients underwent ERCP at Gastrointestinal Surgical Center, Mansoura University, Egypt. The study population consisted of 996 cases after exclusion of those who presented with obstructed stent ($n = 66$), active pancreatitis ($n = 24$), previous endoscopic sphincterotomy ($n = 110$), biliary complications after liver transplantation ($n = 36$), dye allergy ($n = 10$), pregnancy ($n = 14$), or mental disability ($n = 10$).

Indications for ERCP were malignant obstructive

jaundice due to periampullary tumor ($n = 460$, 46.2%) or hilar cholangiocarcinoma ($n = 2$, 0.2%), calcular obstructive jaundice ($n = 512$, 51.4%), benign biliary stricture ($n = 10$, 1.0%), and post-cholecystectomy biliary leakage ($n = 12$, 1.2%). The mean age at presentation was $58.42 (\pm 14.727)$ years. There were 554 male in comparison to 442 female patients, with a male to female ratio of 1.3:1.

Overall, PEP occurred in 102 (10.2%) patients of the study population. Eighty (78.4%) cases were of mild to moderate degree, while severe pancreatitis occurred in 22 (21.6%) patients. The median length of hospital stay in patients with pancreatitis was 3 d (range, 2–15 d). No hospital mortality was reported for any of PEP patients during the study duration. Univariate analysis showed that patient age and narrower CBD diameter are statistically significant patient-related risk factors associated with occurrence and severity of PEP, while increased number of cannulation attempts and pancreatic cannulation more than three times were significant procedure-related risk factors associated with occurrence and severity of PEP. Indication for ERCP was not significantly associated with occurrence of pancreatitis ($P = 0.4$), but it was significantly associated with the severity of PEP ($P = 0.009$) (Tables 1 and 2).

Multivariate analysis after binary logistic regression analysis revealed that patient age less than 35 years ($P = 0.001$, OR = 0.035), narrower median CBD diameter ($P = 0.0001$) and increased number of pancreatic cannulations ($P = 0.0001$) were independent risk factors for the occurrence of PEP (Table 3).

DISCUSSION

PEP is the most common and serious complication after ERCP^[8]. PEP is associated with higher morbidity and mortality beside its effect in increasing the consumption of hospital resources^[11]. Identification of clinical and procedural correlates for PEP is of crucial importance in the practice of ERCP. It affects the medical decision regarding patient choice, adoption of pharmacological prophylactic measures, avoidance of procedural risk factors, and determination of the time of discharge after the procedure^[1,7,8]. Risk factors for PEP have been a matter of controversy and the pathogenesis of PEP is not fully understood yet^[9,11]. This study reports risk factors for PEP according to the experience of a tertiary high volume surgical center in Egypt.

Despite advanced accessories and novel techniques in ERCP, complication rate after ERCP remained unchanged over the last decade^[7,12]. According to previous reports, the incidence of PEP ranges from 5% to 40%. This great discrepancy in the reported rates can be attributed to heterogeneity of the definition of PEP and its grading system, variability in data collection, inclusion of diagnostic ERCP in the study, and difference in expertise among endoscopists^[13]. The incidence of PEP in this cohort was 10.2% with adoption of the consensus definition of PEP^[10]. Mild to moderate PEP occurred in 80

Table 2 Predictors of severity of pancreatitis after endoscopic retrograde cholangiopancreatography *n* (%)

	Mild to moderate pancreatitis (80)	Severe pancreatitis (22)	P-value
Patient related factors			
Median age (yr)	52	30	0.0001
Age			
< 35	26 (32.5)	14 (63.6)	0.0001
> 35	54 (67.5)	8 (36.4)	
Sex			
Male	38 (47.5)	6 (27.3)	0.08
Female	42 (52.5)	16 (72.7)	
Median serum bilirubin (mg%)	14.1	9.9	0.3
< 2	8 (50)	8 (50)	
> 2	72 (85.7)	14 (14.3)	0.07
Median CBD diameter (mm)	10	9	0.0001
< 10	42 (52.5)	16 (72.7%)	
> 10	38 (47.5)	6 (27.3%)	0.0001
Indication for ERCP			
Malignant	39 (97.5)	1 (2.5)	0.009
Benign	41 (66.1)	21 (33.9)	
Type of papilla			
Normal	39	17	0.06
Atrophic	6	2	
Pregnant	0	2	
Tumour	4	0	
Redundant	9	3	
Juxtadiverticular	15	1	
Small	2	0	
Long	2	0	
Procedure related factors			
No. of cannulation attempts			
< 5	46 (57.5)	12 (54.5)	0.03
≥ 6	34 (27.5)	10 (45.5)	
Median number of pancreatic cannulations	2	4	0.0001
< 3 times	58 (72.5)	2 (9.1)	0.0001
> 3 times	22 (52.4)	20 (90.9)	
Method of cannulation			
Conventional	58 (72.5)	18 (81.8)	0.07
Precut	22 (52.4)	4 (18.2)	
Biliary sphincter balloon dilatation			
No	70 (87.5)	16 (72.7)	0.1
Yes	10 (12.5)	6 (27.3)	

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Multivariate logistic regression for analysis of pancreatitis after endoscopic retrograde cholangiopancreatography

Variable	P-value	Odds ratio	95%CI for EXP(B)	
			Lower	Upper
Age group	0.001	0.035	0.005	0.259
Age	0.519	1.012	0.976	1.050
Sex	0.362	0.143	0.075	0.270
CBD diameter below 10 mm	0.609	0.726	0.212	2.481
CBD diameter	0.000	0.612	0.495	0.757
Difficult cannulation	0.207	0.476	0.150	1.506
No. of pancreatic cannulations below 3	0.117	0.219	0.033	1.460
No. of pancreatic cannulations	0.000	5.258	2.665	10.370
Papilla	0.964			

CBD: Common bile duct.

(8%) patients, while severe PEP occurred in 22 (2.2%) patients. These ratios are concordant with data reported by previous studies^[14-16].

Among different patient related risk factors, younger age and non-dilated extrahepatic biliary radicals were independent risk factors for PEP on multivariate analysis

in this study. Also, using a cutoff value of 35 years to divide patients into two groups, the rate of PEP was significantly higher in the younger group by univariate analysis. Younger age has been a subject of controversy regarding its association with PEP^[8]. Many studies reported an insignificant relation between patient age and likelihood of PEP^[2,17]. However, Freeman *et al.*^[18] first reported relatively younger age as a predictor of PEP on multivariate analysis. This finding was confirmed by later studies^[5,16,19]. Higher incidence of PEP in younger age was explained by the aging effect on pancreatic exocrine function, smaller common bile duct diameter and the higher incidence of sphincter of Oddi dysfunction in younger age^[13,16,18].

Management of CBD stones in case of non-dilated extrahepatic biliary system represents a surgical challenge^[20]. Laparoscopic transcholedochal CBD exploration mandates a CBD diameter of at least 6-8 mm^[21-23]. According to many studies including this one, normal caliber CBD is associated with increased difficulty of the ERCP procedure^[24-26]. However, most of recent studies reported absence of association between narrower CBD diameter and PEP^[13]. Laparoscopic management for surgically fit patients with concomitant gall bladder and CBD stones in case of non-dilated CBD through transcystic CBD exploration or laparoendoscopic Rendezvous is better to avoid or minimize the risk of PEP^[21]. In case of isolated choledocholithiasis or in patients who are unfit for surgery, prophylactic measures against PEP should be adopted.

In this cohort, difficult cannulation, denoted by frequent cannulation attempts and pancreatic cannulation more than three times, was associated with a higher risk of PEP. The effect of pancreatic duct injection with contrast dye on PEP could not be evaluated because we did not use the conventional contrast cannulation method. The effect of precut sphincterotomy on PEP is controversial^[11]. Some authors advocate that precut sphincterotomy causes papillary oedema which retains pancreatic secretion resulting in PEP^[8,24]. On the other hand, some authors indicate that precut sphincterotomy is usually preceded by difficult cannulation through the conventional approach and that the later, not the precut sphincterotomy itself, is responsible for the development of PEP^[26]. This is supported by the finding that precut sphincterotomy was not reported as a risk factor for PEP from endoscopists who adopted precut sphincterotomy as a preferred technique from the start not just a salvage procedure after difficult cannulation through conventional cannulation methods^[27]. Early precut leads to more successful cannulation rate without more hazard of morbidity after ERCP^[28-33].

Risk factors for PEP have a synergetic effect^[8]. Jeurnink *et al.*^[1] suggested that development of prognostic models and scoring systems based on various patient and procedure related risk factors will help in defining patients at the highest risk for PEP. According to this cohort, young patients (< 35 years) with narrow CBD (< 10 mm) who had shown evidence of difficult

cannulation (high number of cannulation attempts or pancreatic cannulation more than three times) are candidates for prophylactic and preventive measures against PEP^[28].

Despite the improvement of techniques of ERCP in recent years and increased experiences, the incidence of PEP has not decreased. Therefore, studies to determine risky patients and predict severity of PEP are very important to give the risk factors prophylactic agents for prevention of PEP^[34-37]. Pre-ERCP administration of rectal indometacin reduced the overall occurrence of PEP without increasing risk of bleeding^[34]. Some studies reported that the combination of a temporary prophylactic pancreatic plastic stent placement and rectal non-steroidal anti-inflammatory drugs is recommended for preventing PEP in high-risk cases^[34-36]. Somatostatin can reduce the incidence of PEP but has not been routinely administered in most of centers nor recommended by guidelines as a prophylactic measure for PEP^[36,37]. Patients at high risk of PEP should be also monitored for at least 24 h to avoid occurrence of PEP after early discharge^[1,7].

In conclusion, PEP is the most frequent and devastating complication after ERCP. PEP is associated with higher morbidity and mortality beside its effect in increasing the consumption of hospital resources. Age less than 35 years, narrower median CBD diameter and increased number of pancreatic cannulations are independent risk factors for the occurrence of PEP. Patients with these risk factors are candidates for prophylactic and preventive measures against PEP.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to 20%-40% in high risk patients. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients.

Research frontiers

Many studies have tried to identify the risk factors for pancreatitis after ERCP. Many patient and procedure related factors are suggested to be associated with increased likelihood of PEP. The trigger mechanism and pathogenesis for PEP remain unclear.

Innovations and breakthroughs

ERCP is not a procedure without morbidities. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients.

Applications

The data in this study suggested risk factors for PEP and investigated the predictors of its severity in a tertiary high volume. Furthermore, this study also provided readers with important information regarding the risk factors for PEP.

Terminology

PEP remains the most devastating and frequent complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to

20%-40% in high risk patients.

Peer-review

This is an interesting manuscript with a significant number of patients treating an important topic, and the aim of this study was to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Egypt.

REFERENCES

1. **Jeurnink SM**, Siersema PD, Steyerberg EW, Dees J, Poley JW, Haringsma J, Kuipers EJ. Predictors of complications after endoscopic retrograde cholangiopancreatography: a prognostic model for early discharge. *Surg Endosc* 2011; **25**: 2892-2900 [PMID: 21455806 DOI: 10.1007/s00464-011-1638-9]
2. **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88 [PMID: 19286178 DOI: 10.1016/j.gie.2008.10.039]
3. **Yang D**, Draganov PV. Indomethacin for post-endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis: is it the magic bullet? *World J Gastroenterol* 2012; **18**: 4082-4085 [PMID: 22919238 DOI: 10.3748/wjg.v18.i31.4082]
4. **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M. Risk factors for complication following ERCP: results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801 [PMID: 17703388 DOI: 10.1055/s-2007-966723]
5. **Cheng CL**, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; **101**: 139-147 [PMID: 16405547 DOI: 10.1111/j.1572-0241.2006.00380.x]
6. **Moon SH**, Kim MH. Prophecy about post-endoscopic retrograde cholangiopancreatography pancreatitis: from divination to science. *World J Gastroenterol* 2013; **19**: 631-637 [PMID: 23429236 DOI: 10.3748/wjg.v19.i5.631]
7. **Katsinelos P**, Lazaraki G, Chatzimavroudis G, Gkagkalis S, Vasiliadis I, Papaethimiou A, Terzoudis S, Pilpilidis I, Zavos C, Kountouras J. Risk factors for therapeutic ERCP-related complications: an analysis of 2,715 cases performed by a single endoscopist. *Ann Gastroenterol* 2014; **27**: 65-72 [PMID: 24714755]
8. **Dumonceau JM**, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, Testoni PA. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy* 2010; **42**: 503-515 [PMID: 20506068 DOI: 10.1055/s-0029-1244208]
9. **Tammaro S**, Caruso R, Pallone F, Monteleone G. Post-endoscopic retrograde cholangio-pancreatography pancreatitis: is time for a new preventive approach? *World J Gastroenterol* 2012; **18**: 4635-4638 [PMID: 23002332 DOI: 10.3748/wjg.v18.i34.4635]
10. **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]
11. **Chen JJ**, Wang XM, Liu XQ, Li W, Dong M, Suo ZW, Ding P, Li Y. Risk factors for post-ERCP pancreatitis: a systematic review of clinical trials with a large sample size in the past 10 years. *Eur J Med Res* 2014; **19**: 26 [PMID: 24886445 DOI: 10.1186/2047-783X-19-26]
12. **Freeman ML**. Complications of endoscopic retrograde cholangiopancreatography: avoidance and management. *Gastrointest Endosc Clin N Am* 2012; **22**: 567-586 [PMID: 22748249 DOI: 10.1016/j.giec.2012.05.001]
13. **Testoni PA**, Mariani A, Giussani A, Vailati C, Masci E, Macarri G, Ghezzi L, Familiari L, Giardullo N, Mutignani M, Lombardi G, Talamini G, Spadaccini A, Briglia R, Piazzi L. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. *Am J Gastroenterol* 2010; **105**: 1753-1761 [PMID: 20372116 DOI: 10.1038/ajg.2010.136]
14. **Perney P**, Berthier E, Pageaux GP, Hillaire-Buys D, Roques V, Fabbro-Peray P, Melki M, Hanslik B, Bauret P, Larrey D, Blayac JP, Blanc F. Are drugs a risk factor of post-ERCP pancreatitis? *Gastrointest Endosc* 2003; **58**: 696-700 [PMID: 14595303 DOI: 10.1016/S0016-5107(03)02019-4]
15. **Andriulli A**, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, Leandro G, Leo P, De Maio G, Perri F. Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial. *Gastrointest Endosc* 2002; **56**: 488-495 [PMID: 12297762 DOI: 10.1016/S0016-5107(02)70431-8]
16. **He QB**, Xu T, Wang J, Li YH, Wang L, Zou XP. Risk factors for post-ERCP pancreatitis and hyperamylasemia: A retrospective single-center study. *J Dig Dis* 2015; **16**: 471-478 [PMID: 25955444 DOI: 10.1111/1751-2980.12258]
17. **Masci E**, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. *Endoscopy* 2003; **35**: 830-834 [PMID: 14551860 DOI: 10.1055/s-2003-42614]
18. **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]
19. **Wang P**, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol* 2009; **104**: 31-40 [PMID: 19098846 DOI: 10.1038/ajg.2008.5]
20. **Sharma A**, Dahiya P, Khullar R, Soni V, Bajjal M, Chowbey PK. Management of common bile duct stones in the laparoscopic era. *Indian J Surg* 2012; **74**: 264-269 [PMID: 23730054 DOI: 10.1007/s12262-012-0593-6]
21. **El Nakeeb A**, El Geidie A, El Hanafy E, Atef E, Askar W, Sultan AM, Hamdy E, El Shobary M, Hamed H, Abdelrafee A, Zeid MA. Management and Outcome of Borderline Common Bile Duct with Stones: A Prospective Randomized Study. *J Laparoendosc Adv Surg Tech A* 2016; **26**: 161-167 [PMID: 26828596 DOI: 10.1089/lap.2015.0493]
22. **Shojaieard A**, Esmaeilzadeh M, Ghafouri A, Mehrabi A. Various techniques for the surgical treatment of common bile duct stones: a meta review. *Gastroenterol Res Pract* 2009; **2009**: 840208 [PMID: 19672460 DOI: 10.1155/2009/840208]
23. **Lee HM**, Min SK, Lee HK. Long-term results of laparoscopic common bile duct exploration by choledochotomy for choledocholithiasis: 15-year experience from a single center. *Ann Surg Treat Res* 2014; **86**: 1-6 [PMID: 24761400 DOI: 10.4174/ast.2014.86.1.1]
24. **Sherman S**, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy. A prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. *Gastroenterology* 1991; **101**: 1068-1075 [PMID: 1889699]
25. **Kahaleh M**, Freeman M. Prevention and management of post-endoscopic retrograde cholangiopancreatography complications. *Clin Endosc* 2012; **45**: 305-312 [PMID: 22977824 DOI: 10.5946/ce.2012.45.3.305]
26. **Chen YK**, Foliente RL, Santoro MJ, Walter MH, Collen MJ. Endoscopic sphincterotomy-induced pancreatitis: increased risk associated with nondilated bile ducts and sphincter of Oddi dysfunction. *Am J Gastroenterol* 1994; **89**: 327-333 [PMID: 8122639]
27. **Freeman ML**, Guda NM. ERCP cannulation: a review of reported techniques. *Gastrointest Endosc* 2005; **61**: 112-125 [PMID: 15672074 DOI: 10.1016/S0016-5107(04)02463-0]
28. **Zhang QS**, Han B, Xu JH, Gao P, Shen YC. Needle-knife

- papillotomy and fistulotomy improved the treatment outcome of patients with difficult biliary cannulation. *Surg Endosc* 2016; Epub ahead of print [PMID: 27129550 DOI: 10.1007/s00464-016-4914-x]
- 29 **Ayoubi M**, Sansoè G, Leone N, Castellino F. Comparison between needle-knife fistulotomy and standard cannulation in ERCP. *World J Gastrointest Endosc* 2012; **4**: 398-404 [PMID: 23125897 DOI: 10.4253/wjge.v4.i9.398]
 - 30 **Swan MP**, Alexander S, Moss A, Williams SJ, Rupp D, Hope R, Bourke MJ. Needle knife sphincterotomy does not increase the risk of pancreatitis in patients with difficult biliary cannulation. *Clin Gastroenterol Hepatol* 2013; **11**: 430-436.e1 [PMID: 23313840 DOI: 10.1016/j.cgh.2012.12.017]
 - 31 **Jin YJ**, Jeong S, Lee DH. Utility of needle-knife fistulotomy as an initial method of biliary cannulation to prevent post-ERCP pancreatitis in a highly selected at-risk group: a single-arm prospective feasibility study. *Gastrointest Endosc* 2016; **84**: 808-813 [PMID: 27102829 DOI: 10.1016/j.gie.2016.04.011]
 - 32 **Mariani A**, Di Leo M, Giardullo N, Giussani A, Marini M, Buffoli F, Cipolletta L, Radaelli F, Ravelli P, Lombardi G, D'Onofrio V, Macchiarelli R, Iiritano E, Le Grazie M, Pantaleo G, Testoni PA. Early precut sphincterotomy for difficult biliary access to reduce post-ERCP pancreatitis: a randomized trial. *Endoscopy* 2016; **48**: 530-535 [PMID: 26990509 DOI: 10.1055/s-0042-102250]
 - 33 **Kim SJ**, Kang DH, Kim HW, Choi CW, Park SB, Song BJ, Hong YM. Needle-knife fistulotomy vs double-guidewire technique in patients with repetitive unintentional pancreatic cannulations. *World J Gastroenterol* 2015; **21**: 5918-5925 [PMID: 26019456]
 - 34 **Luo H**, Zhao L, Leung J, Zhang R, Liu Z, Wang X, Wang B, Nie Z, Lei T, Li X, Zhou W, Zhang L, Wang Q, Li M, Zhou Y, Liu Q, Sun H, Wang Z, Liang S, Guo X, Tao Q, Wu K, Pan Y, Guo X, Fan D. Routine pre-procedural rectal indometacin versus selective post-procedural rectal indometacin to prevent pancreatitis in patients undergoing endoscopic retrograde cholangiopancreatography: a multicentre, single-blinded, randomised controlled trial. *Lancet* 2016; **387**: 2293-301 [PMID: 27133971 DOI: 10.1016/S0140-6736(16)30310-5]
 - 35 **Elmunzer BJ**, Serrano J, Chak A, Edmundowicz SA, Papachristou GI, Scheiman JM, Singh VK, Varadurajulu S, Vargo JJ, Willingham FF, Baron TH, Coté GA, Romagnuolo J, Wood-Williams A, Depue EK, Spitzer RL, Spino C, Foster LD, Durkalski V. Rectal indomethacin alone versus indomethacin and prophylactic pancreatic stent placement for preventing pancreatitis after ERCP: study protocol for a randomized controlled trial. *Trials* 2016; **17**: 120 [PMID: 26941086 DOI: 10.1186/s13063-016-1251-2]
 - 36 **Yin HK**, Wu HE, Li QX, Wang W, Ou WL, Xia HH. Pancreatic Stenting Reduces Post-ERCP Pancreatitis and Biliary Sepsis in High-Risk Patients: A Randomized, Controlled Study. *Gastroenterol Res Pract* 2016; **2016**: 9687052 [PMID: 27057161 DOI: 10.1155/2016/9687052]
 - 37 **Qin X**, Lei WS, Xing ZX, Shi F. Prophylactic effect of somatostatin in preventing Post-ERCP pancreatitis: an updated meta-analysis. *Saudi J Gastroenterol* 2015; **21**: 372-378 [PMID: 26655132 DOI: 10.4103/1319-3767.167187]

P- Reviewer: Hauser G, Gonzalez-Ojeda A, Ikeuchi N, Malak M, Sferri TJ, Shi H **S- Editor:** Qi Y **L- Editor:** Wang TQ **E- Editor:** Li D



Randomized Controlled Trial

Vonoprazan 20 mg vs lansoprazole 30 mg for endoscopic submucosal dissection-induced gastric ulcers

Kazuya Takahashi, Yuichi Sato, Junji Kohisa, Jun Watanabe, Hiroki Sato, Kenichi Mizuno, Satoru Hashimoto, Shuji Terai

Kazuya Takahashi, Yuichi Sato, Department of Endoscopy, Niigata University Medical and Dental Hospital, Niigata 951-8510, Japan

Kazuya Takahashi, Junji Kohisa, Division of Gastroenterology and Hepatology, Sado General Hospital, Niigata 952-1209, Japan

Kazuya Takahashi, Hiroki Sato, Kenichi Mizuno, Satoru Hashimoto, Shuji Terai, Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata 951-8510, Japan

Jun Watanabe, Division of Gastroenterology and Hepatology, Nagaoka Red Cross Hospital, Niigata 940-0095, Japan

Author contributions: Takahashi K designed this study, collected and analyzed the data and drafted the manuscript; Terai S gave final approval of the version to be published; Sato Y revised the manuscript; Kohisa J, Watanabe J, Sato H, Mizuno K and Hashimoto S took part in this study as endoscopic operators or assistants.

Institutional review board statement: The study protocol was approved by the Sado General Hospital Institutional Ethics Committee.

Clinical trial registration statement: This study is registered at UMIN clinical Trial Registry. The registration identification number is UMIN000022006.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None declared.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Kazuya Takahashi, MD, PhD, Division of Gastroenterology and Hepatology, Niigata University Medical and Dental Hospital, 757-1, Asahimachidori, Chuo-ku, Niigata-city, Niigata 951-8510, Japan. kazuya911@med.niigata-u.ac.jp
Telephone: +81-25-2232207
Fax: +81-25-2230776

Received: May 29, 2016

Peer-review started: May 30, 2016

First decision: July 20, 2016

Revised: August 1, 2016

Accepted: September 13, 2016

Article in press: September 18, 2016

Published online: November 16, 2016

Abstract**AIM**

To compare the healing effects of vonoprazan and lansoprazole on gastric ulcers induced by endoscopic submucosal dissection (ESD).

METHODS

Data were obtained from a total of 26 patients. Fourteen patients were randomized to the vonoprazan group and 12 were randomized to the lansoprazole group. Patients were administered either 20 mg vonoprazan or 30 mg lansoprazole per day after ESD. Endoscopic images just after ESD, on day 8, and on day 28 were used for the evaluation of the shrinking rate of ESD ulcers. The shrinking rates and the incidence of delayed bleeding were compared between the 2 groups.

RESULTS

The shrinking rates of ESD ulcers on day 8 [vonoprazan

group: 61.8% (range: 24.0%-91.1%), lansoprazole group: 71.3% (range: 25.2%-88.6%)] and on day 28 [vonoprazan group: 95.3% (range: 76.2%-100%), lansoprazole group: 97.2% (range: 81.1%-99.8%)] were not statistically different between the 2 groups. On day 28, most of the ulcers in both groups healed to more than 90%, whereas 3 of 14 (21.4%) in the vonoprazan group and 1 of 12 (8.3%) in the lansoprazole group had delayed ulcer healing, which was not statistically different ($P = 0.356$). The frequency of delayed bleeding was 0 in the both groups. Taken together, there were no significant differences between the two drug groups.

CONCLUSION

Our study indicates that vonoprazan is potent for the management of ESD ulcers although lansoprazole is also sufficient and cost-effective.

Key words: Lansoprazole; Gastric cancer; Endoscopic submucosal dissection; Potassium-competitive acid blocker; Proton pump inhibitor; Vonoprazan

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Our study highlights the comparison of two drugs (vonoprazan and lansoprazole) for the treatment of gastric ulcers induced by endoscopic submucosal dissection (ESD). There were no significant differences between the two drugs with regard to ulcer shrinkage and delayed bleeding. Our study indicated vonoprazan was potent for the management of ESD ulcers although lansoprazole was also sufficient and cost-effective.

Takahashi K, Sato Y, Kohisa J, Watanabe J, Sato H, Mizuno K, Hashimoto S, Terai S. Vonoprazan 20 mg vs lansoprazole 30 mg for endoscopic submucosal dissection-induced gastric ulcers. *World J Gastrointest Endosc* 2016; 8(19): 716-722 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/716.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.716>

INTRODUCTION

Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is a significantly less invasive procedure compared with gastrectomy and is a common procedure. The main advantage of ESD is enabling en-bloc resection of the lesion. Consequently, ESD results in precise histopathological assessment and a low local recurrence rate^[1,2]. Since en-bloc resection of large lesions is possible with ESD, the iatrogenic ulcers tend to be large and the complications of ESD, including bleeding and perforation, are more frequent than those of endoscopic mucosal resection (EMR)^[1]. Therefore, the management of ESD-induced ulcers is important to prevent adverse events such as delayed bleeding or perforation.

Acid inhibitors such as proton pump inhibitors (PPIs)

and H₂-blockers have been used for the treatment of acid related diseases, including ESD-induced ulcers. PPIs are mainly used for the treatment of ESD-induced ulcers owing to their superiority to H₂ blockers^[3,4]. Although PPIs have been useful for the management of ESD-induced ulcers, they have several limitations including short plasma half-life, slow onset of effectiveness, and the problem of cytochrome P450 (CYP) 2C19 polymorphism^[4-8].

The potassium-competitive acid blocker (P-CAB) is a new class of gastric acid suppressant that inhibits gastric H⁺, K⁺-ATPase in a K⁺-competitive and reversible manner^[9,10]. Vonoprazan was the first orally bioavailable P-CAB and it was approved in Japan in 2014 for the treatment and prevention of acid-related diseases^[11]. Vonoprazan exhibits rapid, profound, and sustained suppression of gastric acid secretions and is not affected by CYP2C19 polymorphism^[10,12]. It has been reported that the acid-inhibitory effect of vonoprazan is more potent than that of PPIs^[6], resulting in greater effectiveness for acid-related diseases such as gastroesophageal reflux disease (GERD) or *Helicobacter pylori* (*H. pylori*) eradication. Therefore, vonoprazan could be more effective for the management of ESD-induced ulcers compared to PPIs, which are now the gold standard for the management of ESD-induced ulcers. To the best of our knowledge, there have been no reports comparing the healing effect of vonoprazan and PPIs on ESD-induced ulcers. We conducted a prospective randomized controlled study to compare the healing effect of P-CAB (vonoprazan) and PPI (lansoprazole) on ESD-induced ulcers. The primary aim was to evaluate the shrinking rate of ESD-induced ulcers and the secondary aim was to evaluate the preventive effect of vonoprazan on delayed bleeding.

MATERIALS AND METHODS

Patients

Thirty consecutive patients, who underwent ESD for EGC between August 2015 and March 2016 at Sado General Hospital, were enrolled in this study. Their medical records were checked to verify whether they were administered antiplatelet agents, anticoagulants, and steroids. *H. pylori* infection status was confirmed by urease test, histopathology, serum antibody, stool antigen, or urinary antibody. The existence of atrophic gastritis was investigated with the endoscopic images at ESD and classified as closed or open type according to the Kimura-Takemoto classification^[13]. Before ESD, a chest and abdominal computed tomography scan was performed on all patients. If metastasis or advanced cancer in other organs was detected, the patient was not included in this study. Furthermore, patients who had undergone gastric surgery before ESD were not included in this study. Those who needed any additional anticancer therapy (surgery and/or chemotherapy) after ESD were excluded. Written informed consent was obtained from the patients before enrollment. The study protocol was

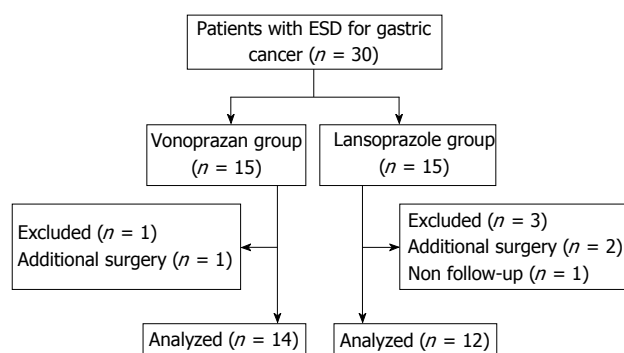


Figure 1 Flow chart of the participants in the study. Thirty patients were enrolled and four of them were excluded because they needed additional surgery or violated the protocol. Finally, 14 patients in the vonoprazan group and 12 patients in the lansoprazole group were included in the analysis. ESD: Endoscopic submucosal dissection.

approved by the Sado General Hospital Institutional Ethics Committee and carried out in accordance with the Declaration of Helsinki. This study was enlisted in UMIN clinical Trials Registry (UMIN000022006).

Study protocol

Patients were prospectively and randomly assigned into either the vonoprazan or the lansoprazole group using permuted block randomization (Figure 1). The treatment protocol is shown in Figure 2. Patients were admitted a day before ESD. From the day of ESD, intravenous infusion of PPI (lansoprazole 30 mg) was administered to all patients for 2 d. Two days after ESD, oral intake was initiated and patients in the vonoprazan group were administered vonoprazan (20 mg/d) and patients in the lansoprazole group were administered lansoprazole (30 mg/d) until 28 d after ESD. If the patients were already being administered antiplatelet agents or anticoagulants, these medicines were stopped before ESD and resumed 2 d after ESD. Eight days after the ESD, all patients underwent esophagogastroduodenoscopy (EGD) to evaluate the shrinking rate of ESD ulcers. After EGD on day 8, patients were discharged. Twenty-eight days after ESD, patients underwent follow-up EGD and the shrinking rate of the ulcers on day 28 was evaluated.

ESD procedure

ESD procedures were performed using a single channel upper gastrointestinal endoscope (GIF Q260J; Olympus, Tokyo, Japan) with a HookKnife (Olympus, Tokyo, Japan) and a DualKnife (Olympus, Tokyo, Japan). An electrosurgical current was applied using a standard electrosurgical generator (ICC 200; ERBE, Tübingen, Germany). The margin of the lesion was circumferentially dotted using a DualKnife in the forced coagulation mode (30 W). After the application of a 10% glycerin solution containing 0.005 mg/mL of epinephrine into the submucosal layer, a mucosal incision was made using a DualKnife in the endo-cut mode (60 W). Then, the submucosal layer was dissected with a HookKnife in the forced coagulation mode (60 W). Hemostatic forceps (Coagrasper; Olympus, Tokyo, Japan) were used to stop

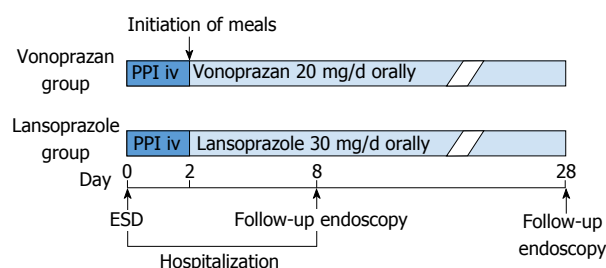


Figure 2 From the day of endoscopic submucosal dissection, intravenous infusion of proton pump inhibitor (lansoprazole 30 mg) was administered to all patients for 2 d. Then, oral intake was initiated and patients in the vonoprazan group were administered vonoprazan (20 mg daily) and patients in the lansoprazole group were administered lansoprazole (30 mg daily) until 28 d after ESD. Patients underwent follow-up EGD on day 8 and day 28. ESD: Endoscopic submucosal dissection; PPI: Proton pump inhibitor; iv: Intravenous injection.

or prevent bleeding in the soft coagulation mode (80 W).

Evaluation of ESD results

En bloc resection rate, location of the tumors, procedure time, submucosal fibrosis, and histopathology of the tumor were investigated and compared between the two groups. Furthermore, we evaluated the area of ESD ulcer as follows: Endoscopic images were taken just after ESD, on day 8, and on day 28, and image processing software (ImageJ) was used to calculate the area of ESD ulcers (Figure 3). Since this software calculated the area as pixels, measuring forceps were put on the ulcer base and used for the scale, and the area of ESD-induced ulcers was expressed in cubic millimeter. The shrinking rate on day 8 was defined as $[1 - (\text{the area of ESD-induced ulcer on day 8}) / (\text{the area of ESD-induced ulcer just after ESD})] \times 100 (\%)$ and the shrinking rate on day 28 was defined as $[1 - (\text{the area of ESD-induced ulcer on day 28}) / (\text{the area of ESD-induced ulcer just after ESD})] \times 100 (\%)$. Delayed ulcer healing was declared when the shrinking rate on day 28 was less than 90%. The shrinking rates on days 8 and 28 and the frequency of delayed ulcer healing were compared between the 2 groups. The frequency of delayed bleeding was also investigated and compared between the two groups.

Statistical analysis

Parametric data are expressed as mean \pm SD and non-parametric data are expressed as median (range). The χ^2 test was used for the categorical data and the Student's *t*-test and the Mann-Whitney *U* test were used for the numerical data. SPSS statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, United States) was used for the statistical analyses. *P* values of less than 0.05 were considered statistically significant in the χ^2 test and the Student's *t*-test. Since the critical value of *U* at *P* < 0.05 in this study was 45, *U* values of less than 45 were considered statistically significant in the Mann-Whitney *U* test.

RESULTS

Thirty patients were enrolled and four of them were

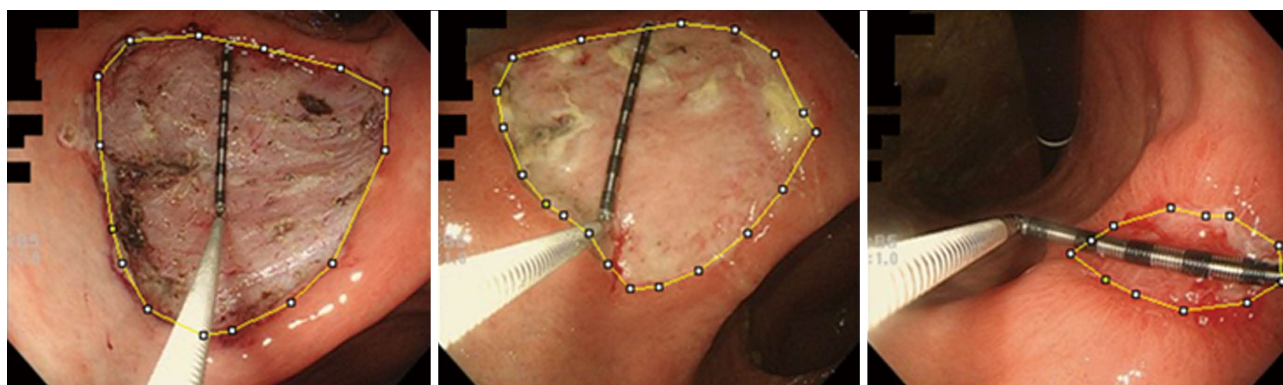


Figure 3 A representative case in the lansoprazole group. The area inside the yellow line was calculated using ImageJ. We placed measuring forceps on the ulcer base to use as a scale. The ulcer base gradually shrank and there were no adverse events. The shrinking rates on days 8 and 28 were 27.1% and 96.3%, respectively.

Table 1 Backgrounds of the patients and endoscopic submucosal dissection results *n* (%)

	Vonoprazan (<i>n</i> = 14)	Lansoprazole (<i>n</i> = 12)	<i>P</i> value
Backgrounds			
Age (yr)	71.9 ± 7.9	74.8 ± 8.3	0.371
Sex (M/F)	12/2	10/2	0.867
Anticoagulants	1 (7.1)	1 (8.3)	0.910
Antiplatelet agents	3 (21.4)	3 (21.4)	0.829
Steroids	1 (7.1)	0 (0)	0.345
<i>Helicobacter pylori</i> infection	4 (28.6)	5 (41.7)	0.484
Atrophic gastritis			
Closed type	3 (21.4)	0 (0)	0.088
Open type	11 (78.6)	12 (100.0)	
Location			
Upper	1	0	0.618
Middle	5	4	
Lower	8	8	
ESD results			
<i>En bloc</i> resection	14 (100.0)	12 (100.0)	
Procedure time (min)	88 (36-246)	51.5 (12-202)	0.123
Submucosal fibrosis	3 (25.0)	1 (8.3)	0.356
Histopathology			
Tub1	12	10	0.504
Tub1 + tub2	1	2	
Tub1 + tub2 + por2	1	0	

Data were expressed as number (%), mean ± SD, or median (range). A *P* value less than 0.05 was considered significant. M: Male; F: Female; ESD: Endoscopic submucosal dissection.

excluded because they needed additional surgery or violated the protocol (Figure 1). Data were obtained from a total of 26 patients. Fourteen patients were randomized to the vonoprazan group and the remaining 12 patients were randomized to the lansoprazole group. There were no statistically significant differences between the two groups with regard to backgrounds, including age and sex; use of anticoagulants, antiplatelet agents, and steroids; *H. pylori* infection state; the degree of endoscopic gastric atrophy; and the location of the tumors (Table 1). Regarding ESD results, *en bloc* resection rate, procedure time, histopathology of lesions, and the frequency of submucosal fibrosis were not statistically different between the two groups (Table 1).

The results of the evaluation of ESD-induced ulcers and delayed bleeding are shown in Table 2. The median areas of ESD-induced ulcers just after ESD in the vonoprazan group and the lansoprazole group were 1446.9 (range: 605-3977.4) mm² and 1262.6 (range: 597.8-7322.3) mm², respectively, and were not statistically different. The median shrinking rates of ESD-induced ulcers on day 8 were 61.8% (range: 24.0%-91.1%) in the vonoprazan group and 71.3% (range: 25.2%-88.6%) in the lansoprazole group and those on day 28 were 95.3% (range: 76.2%-100%) in the vonoprazan group and 97.2% (range: 81.1%-99.8%) in the lansoprazole group. The median shrinking rates of ESD-induced ulcers on both days 8 and 28 were not statistically different. On day 28, most of the ulcers in both groups healed to more than 90%, whereas 3 of 14 (21.4%) in the vonoprazan group and 1 of 12 (8.3%) in the lansoprazole group had delayed ulcer healing, which was not statistically different (*P* = 0.356). The frequency of delayed bleeding was 0 in the both groups. Taken together, there were no significant differences between the two drug groups.

DISCUSSION

In this study, the shrinking rates of ESD ulcers on days 8 and 28 were not statistically different between the two groups, and all of the patients in both groups were discharged without any severe complications. This suggests that lansoprazole was sufficient for the management of ESD ulcers although vonoprazan is theoretically more potent with regard to acid suppression.

PPIs have been widely used for the treatment of acid-related diseases, including ESD ulcers, and the therapeutic effect of PPIs has been satisfactory. However, there are some inadequacies that should be addressed. First, PPIs have a relatively short plasma half-life (60-90 min)^[5,6]. Therefore, taking PPIs twice a day could be insufficient for inhibiting gastric acid at night. Second, PPIs are prodrugs and are activated under acid-secretion conditions. Hence, the effect of PPIs could be affected by food intake^[4,6]. Third, since the onset of PPI effect is slow and it takes time to achieve maximum efficacy, rapid effects cannot be achieved^[4,6,7]. These limitations

Table 2 The evaluation of the endoscopic submucosal dissection induced ulcers and delayed bleeding

	Vonoprazan	Lansoprazole	<i>P</i> value ¹	<i>U</i> value ²
Area of the ulcer just after ESD (mm ³)	1446.9 (605-3977.4)	1262.6 (597.8-7322.3)		89
Results of the follow-up endoscopy				
Area of the ulcer on day 8 (mm ³)	533.5 (93.6-1735.9)	459.8 (90.5-5479.5)		93
Shrinking rate on day 8 (%)	61.8 (24.0-91.1)	71.3 (25.2-88.6)		70.5
Area of the ulcer on day 28 (mm ³)	61.6 (0-289.1)	28.7 (1.1-639.4)		93
Shrinking rate on day 28 (%)	95.3 (76.2-100)	97.2 (81.1-99.8)		68
Delayed ulcer healing <i>n</i> (%)	3/14 (21.4)	1/12 (8.3)	0.356	
Delayed bleeding <i>n</i> (%)	0/14 (0)	0/12 (0)	1	

¹ χ^2 ; ²Mann-Whitney *U* test. Data were expressed as number (%), mean \pm SD, or median (range). *U* value less than 45 and *P* value less than 0.05 were considered statistically significant. ESD: Endoscopic submucosal dissection.

could affect the clinical course after ESD. Furthermore, the problem of CYP 2C19 polymorphism could also inhibit the effectiveness of PPIs. With regard to CYP2C19 polymorphism, there are inter-ethnic differences regarding the frequency of extensive and poor metabolizers. In the Japanese population, the frequency of poor metabolizers is reported to be 18.0%-22.5%^[8]. Although the frequency of poor metabolizers is relatively high in Japan compared to that in Western countries, the majority of the population still consists of extensive metabolizers. It has been reported that plasma PPI concentrations and intragastric pH are lower in extensive metabolizers compared with those in poor metabolizers, resulting in poor results of acid-suppression therapies in patients with GERD or *H. pylori* eradication^[4,8]. Therefore, PPIs could be insufficient for the management of ESD ulcers, especially in extensive metabolizers.

On the other hand, vonoprazan, which is a novel acid inhibitor and classified as a P-CAB, has a long-lasting and rapid effect on gastric acid inhibition, and it is not affected by the acid secretory state, mealtime, or CYP2C19 polymorphism^[5,6,11,12,14]. It has been reported that vonoprazan is more potent regarding acid inhibition and more efficient for acid-related diseases^[6,11,14]. Vonoprazan could theoretically be more potent for the management of ESD ulcers. However, in our study, vonoprazan did not show superiority to lansoprazole with regard to ulcer healing after ESD. It has been reported that EMR ulcers heal faster than peptic ulcers because of high blood flow at the margin of EMR ulcers^[15-17]. The mechanism of ESD ulcers is similar to that of EMR ulcers and even large ESD ulcers heal within 8 wk after treatment with normal doses of PPIs^[18]. In this study, the area of the ESD ulcers reduced to less than 10% on day 28 in most of the cases in both groups, faster than peptic ulcer healing. Therefore, we concluded that vonoprazan was potent and lansoprazole was also effective for healing ESD ulcers. With regard to medical expenses, vonoprazan (20 mg daily) and lansoprazole (30 mg daily) cost 240 JPY (almost \$2.4) and 140 JPY (almost \$1.4), respectively. In our hospital, we usually use acid suppression medicines for at least 2 mo on the basis of a previous study^[18], and the difference in the medical expenses between treatment with vonoprazan and lansoprazole for each patient is up to 5600 JPY (almost \$56). Therefore, lansoprazole is

more cost-effective although both of them are valid for the management of ESD ulcers.

Our secondary aim was the evaluation of the preventive effect of vonoprazan on delayed bleeding compared to lansoprazole. Clinically, the prevention of delayed bleeding is important after ESD, and the frequency of delayed bleeding has been reported to be approximately 5%^[19-24]. Intragastric pH is an important factor for the coagulation system and platelet aggregation, and the activity of fibrinolysis is impaired at pH values above 6^[25,26]. The most delayed bleeding occurs within the first 24 to 48 h^[19]. Therefore, vonoprazan is theoretically superior for the prevention of delayed bleeding owing to its sustained, rapid, and more potent effect on acid suppression^[6,11,12]. In our study, the delayed bleeding rate was 0% in both groups although our sample size was too small for the precise evaluation of the preventive effect on delayed bleeding. There are several reasons for this result. First, the acid suppression of both vonoprazan and lansoprazole was potent enough to prevent delayed bleeding; second, we carefully coagulated thick blood vessels that might bleed afterward. It has been reported that patients with large lesions or those being administered antithrombotic drugs have a high risk for delayed bleeding or perforation^[19,21-24]. PPIs are occasionally not adequate to prevent complications in such patients. Vonoprazan is expected to reduce the incident rates of delayed bleeding because of its potent acid suppression.

To the best of our knowledge, this is the first report comparing the healing effects of vonoprazan and lansoprazole on ESD ulcers. However, there are some limitations of this study. First, the sample size was not large enough to obtain conclusive results. However, both vonoprazan and lansoprazole seemed potent enough for the management of ESD ulcers; second, our protocol might not be appropriate because we used intravenous lansoprazole for both groups in the first 2 day after ESD, resulting in underestimation of the healing and preventive effect of vonoprazan; third, we did not investigate the polymorphism of CYP2C19 in this study. This is important for making definitive conclusions. In extensive metabolizers, vonoprazan might prove to be superior to PPIs; fourth, anticoagulant, antiplatelet agent, and steroid users should have been removed from the

study to prevent their associated complications from affecting the comparison. However, they were included in the present study.

In summary, our study indicated vonoprazan was potent for the management of ESD ulcers although lansoprazole was also sufficient and cost-effective. Since vonoprazan theoretically has more potent acid-suppression and is not affected by CYP2C19 polymorphism, it could be more effective in the high risk groups or extensive metabolizers. A further prospective study with these patients is needed to make a definitive conclusion.

ACKNOWLEDGMENTS

We would like to thank Editage (<http://www.editage.jp>) for English language editing.

COMMENTS

Background

Proton pump inhibitors (PPIs) have been used for the management of ulcers induced by endoscopic submucosal dissection (ESD). Vonoprazan, an orally bioavailable potassium-competitive acid blocker, is a new class of gastric acid suppressant that inhibits gastric H⁺, K⁺-ATPase in a K⁺-competitive and reversible manner. It was approved in Japan in 2014 for the treatment and prevention of acid-related diseases including ESD-induced ulcers. The aim of this study was to compare the healing effects of vonoprazan and lansoprazole on ESD-induced ulcers.

Research frontiers

Vonoprazan exhibits rapid, profound, and sustained suppression of gastric acid secretions and is not affected by CYP2C19 polymorphism. It has been reported that the acid-inhibitory effect of vonoprazan is more potent than that of PPIs, resulting in greater effectiveness for acid-related diseases such as gastroesophageal reflux disease or *Helicobacter pylori* eradication. Therefore, vonoprazan could be more effective for the management of ESD-induced ulcers compared to PPIs. So far there have been no reports comparing the healing effect of vonoprazan and PPIs on ESD-induced ulcers.

Innovations and breakthroughs

The authors compared shrinking rates of ESD-induced ulcers on days 8 and 28 between the vonoprazan group and the lansoprazole group, and showed that the shrinking rates of ESD ulcers on days 8 and 28 were not statistically different between the two groups.

Applications

The result of this study suggested that vonoprazan was potent for the management of ESD ulcers although lansoprazole was also sufficient and cost-effective.

Terminology

Vonoprazan is a potent option for the management of ESD-induced ulcers.

Peer-review

This article is relatively novel. There is no report on the drug used to treat the post-ESD ulcers. These results are thought to be very useful article from the terms of cost effective.

REFERENCES

- 1 Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]
- 2 Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]
- 3 Yang Z, Wu Q, Liu Z, Wu K, Fan D. Proton pump inhibitors versus histamine-2-receptor antagonists for the management of iatrogenic gastric ulcer after endoscopic mucosal resection or endoscopic submucosal dissection: a meta-analysis of randomized trials. *Digestion* 2011; **84**: 315-320 [PMID: 22075541 DOI: 10.1159/000331138]
- 4 Sachs G, Shin JM, Munson K, Vagin O, Lambrecht N, Scott DR, Weeks DL, Melchers K. Review article: the control of gastric acid and *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2000; **14**: 1383-1401 [PMID: 11069309]
- 5 Shin JM, Inatomi N, Munson K, Strugatsky D, Tokhtaeva E, Vagin O, Sachs G. Characterization of a novel potassium-competitive acid blocker of the gastric H,K-ATPase, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438). *J Pharmacol Exp Ther* 2011; **339**: 412-420 [PMID: 21828261 DOI: 10.1124/jpet.111.185314]
- 6 Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T, Shiramoto M. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects--a randomised open-label cross-over study. *Aliment Pharmacol Ther* 2015; **42**: 719-730 [PMID: 26193978 DOI: 10.1111/apt.13325]
- 7 Mejia A, Kraft WK. Acid peptic diseases: pharmacological approach to treatment. *Expert Rev Clin Pharmacol* 2009; **2**: 295-314 [PMID: 21822447 DOI: 10.1586/ecp.09.8]
- 8 Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005; **20**: 153-167 [PMID: 15988117 DOI: 10.2133/dmpk.20.153]
- 9 Arikawa Y, Nishida H, Kurasawa O, Hasuoka A, Hirase K, Inatomi N, Hori Y, Matsukawa J, Imanishi A, Kondo M, Tarui N, Hamada T, Takagi T, Takeuchi T, Kajino M. Discovery of a novel pyrrole derivative 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine fumarate (TAK-438) as a potassium-competitive acid blocker (P-CAB). *J Med Chem* 2012; **55**: 4446-4456 [PMID: 22512618 DOI: 10.1021/jm300318t]
- 10 Hori Y, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. *J Pharmacol Exp Ther* 2011; **337**: 797-804 [PMID: 21411494 DOI: 10.1124/jpet.111.179556]
- 11 Garnock-Jones KP. Vonoprazan: first global approval. *Drugs* 2015; **75**: 439-443 [PMID: 25744862 DOI: 10.1007/s40265-015-0368-z]
- 12 Jenkins H, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, Yoneyama T, Ashida K, Ogama Y, Warrington S. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 2015; **41**: 636-648 [PMID: 25707624 DOI: 10.1111/apt.13121]
- 13 Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1969; **1**: 87-97 [DOI: 10.1055/s-0028-1098086]
- 14 Ashida K, Sakurai Y, Nishimura A, Kudou K, Hiramatsu N, Umegaki E, Iwakiri K, Chiba T. Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. *Aliment Pharmacol Ther* 2015; **42**: 685-695 [PMID: 26201312 DOI: 10.1111/apt.13331]
- 15 Kobayashi M, Takeuchi M, Hashimoto S, Mizuno K, Sato Y, Narisawa R, Aoyagi Y. Contributing factors to gastric ulcer healing after endoscopic submucosal dissection including the promoting effect of rebamipide. *Dig Dis Sci* 2012; **57**: 119-126 [PMID: 21842241 DOI: 10.1007/s10620-011-1850-4]
- 16 Lee SY, Kim JJ, Lee JH, Kim YH, Rhee PL, Paik SW, Rhee JC.

- Healing rate of EMR-induced ulcer in relation to the duration of treatment with omeprazole. *Gastrointest Endosc* 2004; **60**: 213-217 [PMID: 15278047 DOI: 10.1016/S0016-5107(04)01683-9]
- 17 **Hashimoto T**, Adachi K. Changes in gastric mucosal blood flow during healing of EMR-induced ulcer -Comparison with peptic ulcer. *Dig Endosc* 1997; **9**: 127-131 [DOI: 10.1111/j.1443-1661.1997.tb00472.x]
- 18 **Kakushima N**, Yahagi N, Fujishiro M, Iguchi M, Oka M, Kobayashi K, Hashimoto T, Omata M. The healing process of gastric artificial ulcers after endoscopic submucosal dissection. *Dig Endosc* 2004; **16**: 327-331 [DOI: 10.1111/j.1443-1661.2004.00413.x]
- 19 **Kim SJ**, Choi CW, Kang DH, Kim HW, Park SB. Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2016; **8**: 173-179 [PMID: 26862367 DOI: 10.4253/wjge.v8.i3.173]
- 20 **Toyonaga T**, Man-i M, East JE, Nishino E, Ono W, Hirooka T, Ueda C, Iwata Y, Sugiyama T, Dozaiku T, Hirooka T, Fujita T, Inokuchi H, Azuma T. 1,635 Endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. *Surg Endosc* 2013; **27**: 1000-1008 [PMID: 23052530 DOI: 10.1007/s00464-012-2555-2]
- 21 **Koh R**, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]
- 22 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]
- 23 **Okada K**, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]
- 24 **Choi CW**, Kim HW, Kang DH, Hong YM, Kim SJ, Park SB, Cho M, Kim DJ, Hong JB. Clinical outcomes of second-look endoscopy after gastric endoscopic submucosal dissection: predictive factors with high risks of bleeding. *Surg Endosc* 2014; **28**: 2213-2220 [PMID: 24570014 DOI: 10.1007/s00464-014-3457-2]
- 25 **Oh JH**, Choi MG, Dong MS, Park JM, Paik CN, Cho YK, Jeong JJ, Lee IS, Kim SW, Han SW, Choi KY, Chung IS. Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. *J Gastroenterol Hepatol* 2007; **22**: 1429-1434 [PMID: 17645482 DOI: 10.1111/j.1440-1746.2007.05059.x]
- 26 **Green FW**, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology* 1978; **74**: 38-43 [PMID: 21830]

P- Reviewer: Matsumoto K, Song WC, Tsuji Y **S- Editor:** Gong ZM
L- Editor: A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 December 16; 8(20): 723-794





Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

EDITORS-IN-CHIEF

Atsushi Imagawa, *Kan-onji*
Juan Manuel Herrerias Gutierrez, *Sevilla*

ASSOCIATE EDITORS

Chisato Hamashima, *Tokyo*

GUEST EDITORIAL BOARD MEMBERS

Chung-Yi Chen, *Kaohsiung*
Ming-Jen Chen, *Taipei*
Wai-Keung Chow, *Taichung*
Kevin Cheng-Wen Hsiao, *Taipei*
Chia-Long Lee, *Hsinchu*
Kuang-Wen Liao, *Hsin-Chu*
Yi-Hsin Lin, *Hsinchu*
Pei-Jung Lu, *Tainan*
Yan-Sheng Shan, *Tainan*
Ming-Yao Su, *Tao-Yuan*
Chi-Ming Tai, *Kaohsiung*
Yao-Chou Tsai, *New Taipei*
Yih-Huei Uen, *Tainan*
Hsiu-Po Wang, *Taipei*
Yuan-Huang Wang, *Taipei*
Shu Chen Wei, *Taipei*
Sheng-Lei Yan, *Changhua*
Hsu-Heng Yen, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Australia

John F Beltrame, *Adelaide*
Guy D Eslick, *Sydney*
Vincent Lam, *Sydney*



Austria

Alexander Klaus, *Vienna*

Karl A Miller, *Hallein*
Markus Raderer, *Vienna*



Brazil

Vitor Arantes, *Belo Horizonte*
Djalma E Coelho, *Rio de Janeiro*
Daniel C Damin, *Porto Alegre*
William Kondo, *Curitiba*
Fauze Maluf-Filho, *Sao Paulo*
José Luiz S Souza, *Sao Paulo*



Canada

Sonny S Dhalla, *Brandon*
Choong-Chin Liew, *Richmond Hill*
Ping-Chang Yang, *Hamilton*



China

Kin Wai Edwin Chan, *Hong Kong*
Jun-Qiang Chen, *Nanning*
Kent-Man Chu, *Hong Kong*
Shi-Gang Ding, *Beijing*
Song-Ze Ding, *Zhengzhou*
Xiang-Wu Ding, *Xiangyang*
Ya-Dong Feng, *Nanjing*
Xin Geng, *Tianjin*
Chuan-Yong Guo, *Shanghai*
Song-Bing He, *Suzhou*
Hai Hu, *Shanghai*
San-Yuan Hu, *Jinan*
Zhao-Hui Huang, *Wuxi*
Bo Jiang, *Guangzhou*
Brian H Lang, *Hong Kong*
Xue-Liang Li, *Nanjing*
Zhi-Qing Liang, *Chongqing*
Zhi-Qiang Ling, *Hangzhou*

Chibo Liu, *Taizhou*
Xiao-Wen Liu, *Shanghai*
Xing'e Liu, *Hangzhou*
Samuel Chun-Lap Lo, *Hong Kong*
Shen Lu, *Dalian*
He-Sheng Luo, *Wuhan*
Simon SM Ng, *Hong Kong*
Hong-Zhi Pan, *Harbin*
Bing Peng, *Chengdu*
Guo-Ming Shen, *Hefei*
Xue-Ying Shi, *Beijing*
Xiao-Dong Sun, *Hangzhou*
Na-Ping Tang, *Shanghai*
Anthony YB Teoh, *Hong Kong*
Qiang Tong, *Wuhan*
Dao-Rong Wang, *Yangzhou*
Xian Wang, *Hangzhou*
Xiao-Lei Wang, *Shanghai*
Qiang Xiao, *Nanning*
Zhu-Ping Xiao, *Jishou*
Li-Shou Xiong, *Guangzhou*
Ying-Min Yao, *Xi'an*
Bo Yu, *Beijing*
Qing-Yun Zhang, *Beijing*
Ping-Hong Zhou, *Shanghai*
Yong-Liang Zhu, *Hangzhou*



Croatia

Mario Tadic, *Zagreb*



Czech Republic

Marcela Kopacova, *Hradec Králové*



Denmark

Jakob Lykke, *Slagelse*

**Ecuador**

Carlos Robles-Medranda, *Guayaquil*

**Egypt**

Asmaa G Abdou, *Shebein Elkom*
Ahmed AR ElGeidie, *Mansoura*
Mohamed Abdel-Sabour Mekky, *Assiut*

**France**

Jean Michel Fabre, *Montpellier*

**Germany**

Jorg G Albert, *Frankfurt*
Hüseyin Kemal Cakmak, *Karlsruhe*
Robert Grützmänn, *Dresden*
Thilo Hackert, *Heidelberg*
Arthur Hoffman, *Frankfurt*
Thomas E Langwieler, *Nordhausen*
Andreas Sieg, *Heidelberg*
Jorg Rüdiger Siewert, *Freiburg*

**Greece**

Sotirios C Botaitis, *Alexandroupolis*
George A Giannopoulos, *Piraeus*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanios, *Thessaloniki*
John A Karagiannis, *Athens*
Gregory Kouraklis, *Athens*
Spiros D Ladas, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
Dimitrios Vynios, *Patras*
Elias Xirouchakis, *Athens*

**Hungary**

László Czakó, *Szeged*
Laszlo Herszenyi, *Budapest*

**India**

Pradeep S Anand, *Bhopal*
Deepraj S Bhandarkar, *Mumbai*
Hemanga Kumar Bhattacharjee, *New Delhi*
Radha K Dhiman, *Chandigarh*
Mahesh K Goenka, *Kolkata*
Asish K Mukhopadhyay, *Kolkata*
Manickam Ramalingam, *Coimbatore*
Aga Syed Sameer, *Srinagar*
Omar J Shah, *Srinagar*
Shyam S Sharma, *Jaipur*
Jayashree Sood, *New Delhi*

**Indonesia**

Ari F Syam, *Jakarta*

**Iran**

Alireza Aminsharifi, *Shiraz*

Homa Davoodi, *Gorgan*
Ahad Eshraghian, *Shiraz*
Ali Reza Maleki, *Gorgan*
Yousef Rasmi, *Urmia*
Farhad Pourfarzi, *Ardabil*

**Iraq**

Ahmed S Abdulamir, *Baghdad*

**Ireland**

Ronan A Cahill, *Dublin*
Kevin C Conlon, *Dublin*

**Israel**

Haggi Mazeh, *Jerusalem*

**Italy**

Ferdinando Agresta, *Adria (RO)*
Alberto Arezzo, *Torino*
Corrado R Asteria, *Mantua*
Massimiliano Berretta, *Aviano (PN)*
Vittorio Bresadola, *Udine*
Lorenzo Camellini, *Reggio Emilia*
Salvatore Maria Antonio Campo, *Rome*
Gabriele Capurso, *Rome*
Luigi Cavanna, *Piacenza*
Francesco Di Costanzo, *Firenze*
Salvatore Cucchiara, *Rome*
Paolo Declich, *Rho*
Massimiliano Fabozzi, *Aosta*
Enrico Fiori, *Rome*
Luciano Fogli, *Bologna*
Francesco Franceschi, *Rome*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Carlo M Girelli, *Busto Arsizio*
Gaetano La Greca, *Catania*
Fabrizio Guarneri, *Messina*
Giovanni Lezoche, *Ancona*
Paolo Limongelli, *Naples*
Marco M Lirici, *Rome*
Valerio Mais, *Cagliari*
Andrea Mingoli, *Rome*
Igor Monsellato, *Milan*
Marco Moschetta, *Bari*
Lucia Pacifico, *Rome*
Giovanni D De Palma, *Naples*
Paolo Del Rio, *Parma*
Pierpaolo Sileri, *Rome*
Cristiano Spada, *Rome*
Stefano Trastulli, *Terni*
Nereo Vettoretto, *Chiari (BS)*
Mario Alessandro Vitale, *Rome*
Nicola Zampieri, *Verona*

**Japan**

Hiroki Akamatsu, *Osaka*
Shotaro Enomoto, *Wakayama*
Masakatsu Fukuzawa, *Tokyo*
Takahisa Furuta, *Hamamatsu*
Naoki Hotta, *Nagoya*

Hiroshi Kashida, *Osaka-saayama*
Motohiko Kato, *Suita*
Yoshiro Kawahara, *Okayama*
Hiroto Kita, *Tokyo*
Nozomu Kobayashi, *Utsunomiya*
Shigeo Koido, *Chiba*
Koga Komatsu, *Yurionhoj*
Kazuo Konishi, *Tokyo*
Keiichiro Kume, *Kitakyushu*
Katsuhiko Mabe, *Sapporo*
Iruru Maetani, *Tokyo*
Nobuyuki Matsuhashi, *Tokyo*
Kenshi Matsumoto, *Tokyo*
Satohiro Matsumoto, *Saitama*
Hiroto Miwa, *Nishinomiya*
Naoki Muguruma, *Tokushima*
Yuji Naito, *Kyoto*
Noriko Nakajima, *Tokyo*
Katsuhiko Nosho, *Sapporo*
Satoshi Ogiso, *Kyoto*
Keiji Ogura, *Tokyo*
Shiro Oka, *Hiroshima*
Hiroyuki Okada, *Okayama*
Yasushi Sano, *Kobe*
Atsushi Sofuni, *Tokyo*
Hiromichi Sonoda, *Otsu*
Haruhisa Suzuki, *Tokyo*
Gen Tohda, *Fukui*
Yosuke Tsuji, *Tokyo*
Toshio Uraoka, *Tokyo*
Hiroyuki Yamamoto, *Kawasaki*
Shuji Yamamoto, *Shiga*
Kenjiro Yasuda, *Kyoto*
Naohisa Yoshida, *Kyoto*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashiwara*

**Lebanon**

Eddie K Abdalla, *Beirut*

**Lithuania**

Laimas Jonaitis, *Kaunas*

**Malaysia**

Sreenivasan Sasidharan, *Minden*

**Mexico**

Quintín H Gonzalez-Contreras, *Mexico*
Carmen Maldonado-Bernal, *Mexico*
Jose M Remes-Troche, *Veracruz*
Mario A Riquelme, *Monterrey*

**Netherlands**

Marco J Bruno, *Rotterdam*

**Norway**

Airazat M Kazaryan, *Skien*
Thomas de Lange, *Rud*



Poland

Thomas Brzozowski, *Cracow*
 Piotr Pierzchalski, *Krakow*
 Stanislaw Sulkowski, *Bialystok*
 Andrzej Szkaradkiewicz, *Poznań*



Portugal

Andreia Albuquerque, *Porto*
 Pedro N Figueiredo, *Coimbra*
 Ana Isabel Lopes, *Lisbon*
 Rui A Silva, *Porto*
 Filipa F Vale, *Lisbon*



Romania

Lucian Negreanu, *Bucharest*



Singapore

Surendra Mantoo, *Singapore*
 Francis Seow-Choen, *Singapore*
 Kok-Yang Tan, *Singapore*



Slovenia

Pavel Skok, *Maribor*
 Bojan Tepes, *Rogaska Slatina*



South Korea

Seung Hyuk Baik, *Seoul*
 Joo Young Cho, *Seoul*
 Young-Seok Cho, *UiJeongbu*
 Ho-Seong Han, *Seoul*
 Hye S Han, *Seoul*
 Seong Woo Jeon, *Daegu*
 Won Joong Jeon, *Jeju*
 Min Kyu Jung, *Daegu*
 Gwang Ha Kim, *Busan*
 Song Cheol Kim, *Seoul*
 Tae Il Kim, *Seoul*
 Young Ho Kim, *Daegu*
 Hyung-Sik Lee, *Busan*
 Kil Yeon Lee, *Seoul*
 SangKil Lee, *Seoul*

Jong-Baeck Lim, *Seoul*
 Do Youn Park, *Busan*
 Dong Kyun Park, *Incheon*
 Jaekyu Sung, *Daejeon*



Spain

Sergi Castellvi-Bel, *Barcelona*
 Angel Cuadrado-Garcia, *Sanse*
 Alfredo J Lucendo, *Tomelloso*
 José F Noguera, *Valencia*
 Enrique Quintero, *Tenerife*
 Luis Rabago, *Madrid*
 Eduardo Redondo-Cerezo, *Granada*
 Juan J Vila, *Pamplona*



Thailand

Somchai Amornnotin, *Bangkok*
 Pradermchai Kongkam, *Pathumwan*



Turkey

Ziya Anadol, *Ankara*
 Cemil Bilir, *Rize*
 Ertan Bulbuloglu, *Kahramanmaras*
 Vedat Goral, *Izmir*
 Alp Gurkan, *Istanbul*
 Serkan Kahyaoglu, *Ankara*
 Erdinc Kamer, *Izmir*
 Cuneyt Kayaalp, *Malatya*
 Erdal Kurtoglu, *Turkey*
 Oner Mentis, *Ankara*
 Orhan V Ozkan, *Sakarya*



United Arab Emirates

Maher A Abbas, *Abu Dhabi*



United Kingdom

Nadeem A Afzal, *Southampton*
 Emad H Aly, *Aberdeen*
 Gianpiero Gravante, *Leicester*
 Karim Mukhtar, *Liverpool*
 Samir Pathak, *East Yorkshire*
 Jayesh Sagar, *Frimley*
 Muhammad S Sajid, *Worthing, West Sussex*

Sanchoy Sarkar, *Liverpool*
 Audun S Sigurdsson, *Telford*
 Tony CK Tham, *Belfast*
 Kym Thorne, *Swansea*
 Her Hsin Tsai, *Hull*
 Edward Tudor, *Taunton*
 Weiguang Wang, *Wolverhampton*



United States

Emmanuel Atta Agaba, *Bronx*
 Mohammad Alsolaiman, *Lehi*
 Erman Aytac, *Cleveland*
 Jodie A Barkin, *Miami*
 Corey E Basch, *Wayne*
 Charles Bellows, *Albuquerque*
 Jianyuan Chai, *Long Beach*
 Edward J Ciaccio, *New York*
 Konstantinos Economopoulos, *Boston*
 Viktor E Eysselein, *Torrance*
 Michael R Hamblin, *Boston*
 Shantel Hebert-Magee, *Orlando*
 Cheryl L Holt, *College Park*
 Timothy D Kane, *Washington*
 Matthew Kroh, *Cleveland*
 I Michael Leitman, *New York*
 Wanguo Liu, *New Orleans*
 Charles Maltz, *New York*
 Robert CG Martin, *Louisville*
 Hiroshi Mashimo, *West Roxbury*
 Abraham Mathew, *Hershey*
 Amosy E M'Koma, *Nashville*
 Klaus Monkemuller, *Birmingham*
 James M Mullin, *Wynnewood*
 Farr Reza Nezhat, *New York*
 Gelu Osian, *Baltimore*
 Eric M Pauli, *Hershey*
 Srinivas R Puli, *Peoria*
 Isaac Raijman, *Houston*
 Robert J Richards, *Stony Brook*
 William S Richardson, *New Orleans*
 Bryan K Richmond, *Charleston*
 Praveen K Roy, *Marshfield*
 Rodrigo Ruano, *Houston*
 Danny Sherwinter, *Brooklyn*
 Bronislaw L Slomiany, *Newark*
 Aijaz Sofi, *Toledo*
 Stanislaw P Stawicki, *Columbus*
 Nicholas Stylopoulos, *Boston*
 XiangLin Tan, *New Brunswick*
 Wahid Wassef, *Worcester*
 Nathaniel S Winstead, *Houma*

REVIEW

- 723 Endoscopic evaluation in diagnosis and management of inflammatory bowel disease
Moran CP, Neary B, Doherty GA
- 733 Colorectal cancer screening: Opportunities to improve uptake, outcomes, and disparities
Shahidi N, Cheung WY
- 741 Evidence based review of the impact of image enhanced endoscopy in the diagnosis of gastric disorders
Hussain I, Ang TL

MINIREVIEWS

- 756 Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms
Yoshio T, Nishida T, Hayashi Y, Iijima H, Tsujii M, Fujisaki J, Takehara T

ORIGINAL ARTICLE

Retrospective Study

- 763 Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection
Ballard DD, Choksi N, Lin J, Choi EY, Elmunzer BJ, Appelman H, Rex DK, Fatima H, Kessler W, DeWitt JM
- 770 Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience
Shingina A, Ou G, Takach O, Svarta S, Kwok R, Tong J, Donaldson K, Lam E, Enns R
- 777 Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis
Hayashi S, Nishida T, Shimakoshi H, Shimoda A, Amano T, Sugimoto A, Takahashi K, Mukai K, Matsubara T, Yamamoto M, Nakajima S, Fukui K, Inada M

Observational Study

- 785 Current state of practice for colonic diverticular bleeding in 37 hospitals in Japan: A multicenter questionnaire study
Niikura R, Nagata N, Doyama H, Ota R, Ishii N, Mabe K, Nishida T, Hikichi T, Sumiyama K, Nishikawa J, Uraoka T, Kiyotoki S, Fujishiro M, Koike K

Contents

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 20 December 16, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Hiroyuki Okada, MD, PhD, Professor, Department of Endoscopy, Okayama University Hospital, Okayama 7008558, Japan

AIM AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGE covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

We encourage authors to submit their manuscripts to *WJGE*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Endoscopy is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Juan Manuel Herrerias Gutierrez, PhD, Academic Fellow, Chief Doctor, Professor, Unidad de Gestión Clínica de Aparato Digestivo, Hospital Universitario Virgen Macarena, Sevilla 41009, Sevilla, Spain

Atsushi Imagawa, PhD, Director, Doctor, Department of Gastroenterology, Mitoyo General Hospital, Kan-onji, Kagawa 769-1695, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com>

www.wjgnet.com/1948-5190/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
Fang-Fang Ji, Vice Director
World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE
December 16, 2016

COPYRIGHT
© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

Endoscopic evaluation in diagnosis and management of inflammatory bowel disease

Carthage P Moran, Barra Neary, Glen A Doherty

Carthage P Moran, Barra Neary, Glen A Doherty, Centre for Colorectal Disease, St. Vincent's University Hospital and School of Medicine, University College Dublin, D04 T6F4 Dublin, Ireland

Author contributions: Moran CP and Neary B performed literature review and wrote the paper; Doherty GA contributed critical revision of the manuscript for important intellectual content.

Conflict-of-interest statement: No conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Carthage P Moran, MB, Centre for Colorectal Disease, St. Vincent's University Hospital and School of Medicine, University College Dublin, Elm Park, Dublin 4, D04 T6F4 Dublin, Ireland. cmoran@ucc.ie
Telephone: +353-1-2214134

Received: March 30, 2016

Peer-review started: April 5, 2016

First decision: June 12, 2016

Revised: August 16, 2016

Accepted: September 21, 2016

Article in press: September 22, 2016

Published online: December 16, 2016

Abstract

Endoscopy is a keystone in the management of patients with inflammatory bowel disease (IBD). It is the fundamental diagnostic tool for IBD, and can help discern between ulcerative colitis and Crohn's disease.

Endoscopic assessment provides an objective end point in clinical trials, and identifies patients in clinical practice who may benefit from treatment escalation and may assist risk stratification in patients seeking to discontinue therapy. Recent advances in endoscopic assessment of patients with IBD include video capsule endoscopy, and chromoendoscopy. Technological advances enable improved visualization and focused biopsy sampling. Endoscopic resection and close surveillance of dysplastic lesions where feasible is recommended instead of prophylactic colectomy.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Endoscopy; Capsule endoscopy; Cancer surveillance; Colonoscopy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Ileo-colonoscopy remains the most important test in the diagnosis and monitoring of inflammatory bowel disease (IBD). Video capsule endoscopy shows very high sensitivity for small bowel mucosal lesions not accessible to conventional flexible endoscopes. Both techniques facilitate monitoring of response to treatment. Endoscopic activity indices are important for monitoring treatment response and can help identify patients who may benefit from treatment escalation. Colorectal cancer surveillance in patients with IBD is shifting from high frequency random biopsies, to that of high quality visual inspection and targeted biopsies of suspected dysplasia, enabled by technological advances including chromoendoscopy and high-definition endoscopes.

Moran CP, Neary B, Doherty GA. Endoscopic evaluation in diagnosis and management of inflammatory bowel disease. *World J Gastrointest Endosc* 2016; 8(20): 723-732 Available from: <http://www.wjgnet.com/1948-5190/full/v8/i20/723.htm>
DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.723>

INTRODUCTION

Endoscopy plays an integral role in the diagnosis and management of patients with inflammatory bowel disease (IBD). In patients with lower gastro-intestinal symptoms suggestive of IBD, colonoscopy with intubation, evaluation and biopsies of the terminal ileum enables assessment of disease activity and extent, severity and histological evaluation (Figure 1). Detailed real-time endoscopic examination can help in delineating between ulcerative colitis (UC) and Crohn's disease (CD), and assessing disease behavior in patients with CD. Upper gastrointestinal (GI) endoscopy enables assessment and diagnosis of upper GI CD. The diagnosis of CD can be difficult, small bowel and upper gastrointestinal investigations are recommended after ileo-colonoscopy^[1]. Video capsule endoscopy (VCE) is useful in the diagnosis and evaluation of patients with IBD, especially non-stricturing small bowel disease.

Endoscopy enables objective measurement of disease response to medical and surgical therapies. Colorectal cancer (CRC) surveillance is imperative in patients with longstanding colonic IBD, except in patients with proctitis or colonic CD limited to only involving one segment of the colorectum^[2]. Although essential in the management of patients with IBD, endoscopy is invasive and expensive, placing a burden on patients^[3] and healthcare systems. Newer, less invasive tests have not replaced the use of endoscopy in our patients, but rather are used in tandem. Endoscopic ultrasound, and therapeutic endoscopic techniques such as stent placement and balloon dilation are covered elsewhere^[4]. This review will focus on paramount roles that endoscopy plays in the management of adults with IBD.

ENDOSCOPIC ASSESSMENT OF DISEASE

Ileo-colonoscopy is the gold standard investigation for the diagnosis of UC and ileo-colonic CD. Real time endoscopic assessment can help delineate between CD and UC, although no endoscopic feature is specific for either. The key features that suggest a diagnosis of CD include perianal disease (careful examination of the perianal region at the time of endoscopy, prior to scope insertion, can reveal fistula tract openings, fissures, strictures and tags), skip lesions, cobblestoning, fistula and strictures, as well as isolated ileal disease. A diagnosis of UC is favoured by continuous colonic inflammation in affected bowel, with obvious demarcation between inflamed and non-inflamed bowel^[2]. Patients with UC can be mistaken to have CD secondary to backwash ileitis and "skip lesions"; attributed to a caecal patch^[5], characterised by localized peri-appendiceal inflammation, and from treatment effect giving the impression of a spared distal colon^[6]. To avoid this pitfall, it is recommended to document endoscopic features in each colonic segment and terminal ileum at index ileo-colonoscopy, in addition to taking serial segmental biopsies (from affected

mucosa and any raised lesions, and normal appearing mucosa)^[2,4]. The presence of fistulae and strictures increase the index of suspicion for CD rather than UC, however these need to be fully investigated (to outrule mimics and to ensure that a CRC associated with UC is not dismissed).

In patients with acute severe colitis, a flexible sigmoidoscopy without purgatives is recommended as initial endoscopic investigation^[2], to confirm the presence, extent and severity of inflammation, to outrule pseudomembranes (although this may be absent in IBD patients with co-morbid *Clostridium difficile* infection) and obtain tissue for histological analysis (which is useful to outrule cytomegalovirus infection in immune suppressed patients). Early endoscopic assessment can help identify patients at risk of needing rescue medical therapy^[7].

One must be aware of conditions that can masquerade as flares of IBD (Table 1)^[8-24]. Endoscopic assessment can be useful; however many conditions such as infective colitis, the findings can be non-specific and overlap with features of IBD. The founding tenets of medical practice: History taking (including a careful drug and travel history) and clinical examination are to be used in tandem with other laboratory, endoscopic and histologic assessment.

ENDOSCOPIC SCORING SYSTEMS

Endoscopic evaluation is the gold standard to assess objective signs of mucosal inflammation and healing, frequently used in clinical trials. However, inter-observer variability in the assessment of endoscopic findings in patients with IBD has led to the development of several endoscopic scoring systems for both CD and UC, few of which have been validated. Scoring systems aim to interpret endoscopic disease appearance and translate these findings into a quantified score. Baron *et al.*^[25] introduced the first scoring system for UC in 1964, they recognised the importance of discontinuous variables in describing endoscopic findings to reduce inter-observer variability^[25]. With time numerous other scoring systems^[26,27] have been introduced, mainly for use as outcome measures in clinical trials, Table 2 lists some of the commonly used endoscopic indices. Ensuring objective endoscopic evidence of baseline disease activity in clinical trials is associated with reduced placebo remission rates^[28,29].

Endoscopic scoring systems can be used in clinical practice to identify patients who may benefit from escalation of medical therapy. In acute severe colitis (ASC), the UCEIS helps predict patient outcomes. Nearly 80% of patients admitted to a single institution with ASC, recording a UCEIS score ≥ 7 required rescue medical therapy with infliximab or ciclosporine^[7]. When UCEIS was ≥ 5 , 33% of patients required colectomy during follow-up, compared with 9% of patients with UCEIS ≤ 4 ^[7].

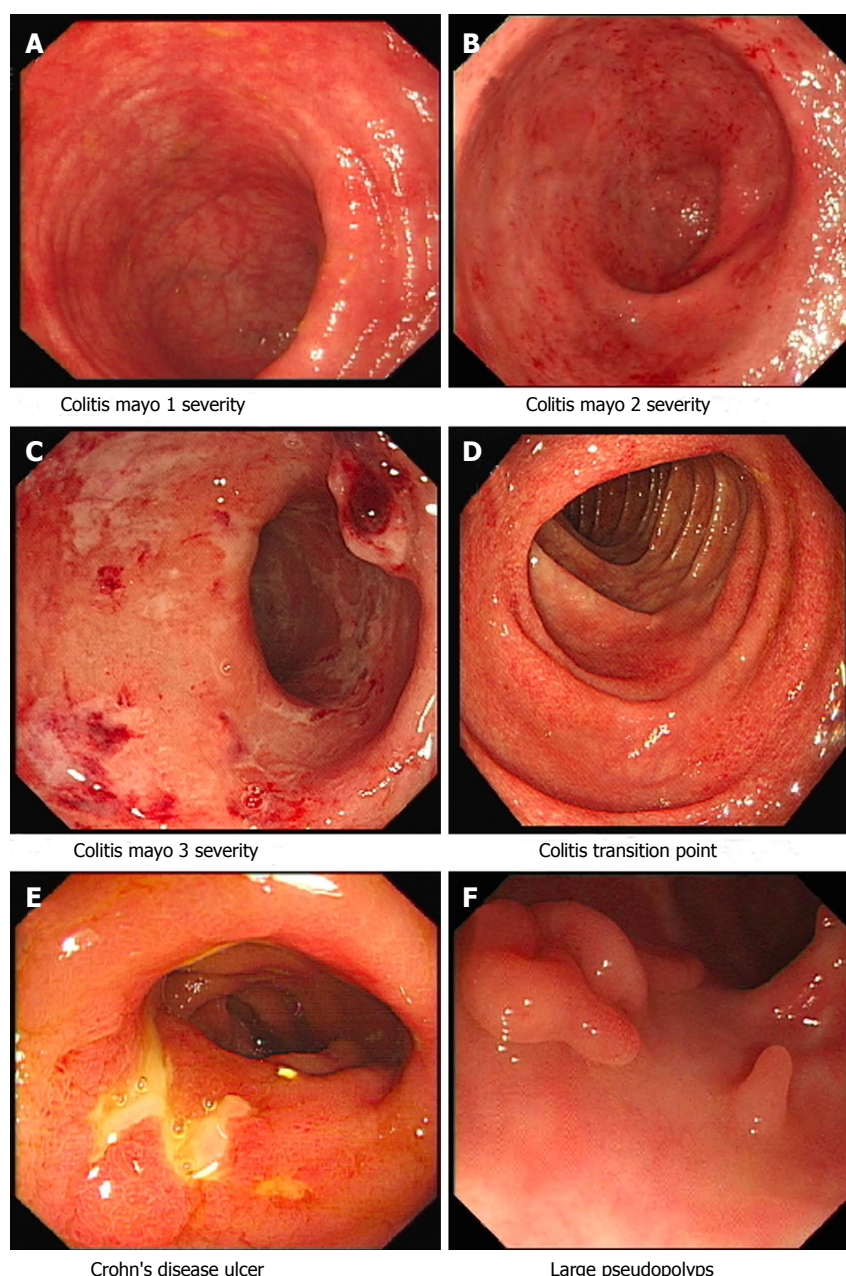


Figure 1 Common endoscopic findings in patients with inflammatory bowel disease.

Early post-operative endoscopic assessment, using the Rutgeert's score, in patients with CD who undergo intestinal resection is useful in predicting the risk of clinical relapse and need for future surgery^[30]. Recent data suggest the Rutgeerts score, which quantifies the degree of recurrent mucosal lesions in the pre-anastomotic ileum, can improve selection of patient's who require escalation of treatment to reduce risk of post-operative disease recurrence^[31]. A recent study escalated treatment of patients with a Rutgeert's score of i2 or greater, this was associated with significant improvements in mucosal healing and endoscopic recurrence, compared to standard treatment^[31]. Prophylactic postoperative Azathioprine use was not superior to endoscopic driven therapy in a study of patients with

CD deemed to be high risk for recurrence, in which the primary endpoint was endoscopic remission (i0-i1) at week 102 post-op^[32].

Endoscopic response can also help predict patient outcomes. The International Organization for the study of IBD recommends defining endoscopic response as a decrease from baseline in CDEIS or SES-CD score of at least 50%^[33]. Mucosal healing and endoscopic response at 26 wk, was predictive of corticosteroid free remission at week 50 in a subgroup analysis of 172 patients from the SONIC trial^[34].

CAPSULE ENDOSCOPY

When CD is diagnosed at ileo-colonoscopy, it is recom-

Table 1 Mimics of active inflammatory bowel disease

Condition	Comment	Ref.
ITB	Skip lesions, cobblestoning of mucosa, aphthous and linear ulcers are found more frequently in patients with CD compared to ITB	[8,9]
Segmental colitis associated with diverticulosis	Patulous ileocaecal valve, transverse ulcers more common in ITB	[9,10]
CMV colitis superimposed in IBD	Inflammatory changes limited to the segment of bowel containing the diverticula with rectal sparing	[11]
	Mucosal bleeding on light contact, wide mucosal defects and punched out ulcers more common in UC complicated by CMV	[12]
	The presence of ulcers helps predict CMV in patients with UC but not CD	[13]
	Other studies could not identify striking differences on endoscopy	[14]
<i>Clostridium difficile</i> associated disease	Biopsies of inflamed mucosa needed assess for inclusion bodies characteristic for CMV colitis	[15]
Campylobacter colitis	Pseudomembranes seldom occur in patients with IBD and <i>Clostridium difficile</i> infection	[16,17]
	Can produce similar appearances to that of UC, detailed endoscopic assessment can help discern from IBD, in addition to stool cultures and biopsies	
Ischaemic colitis	Typically a segmental disease, with normal mucosa proximal and distal to affected region of colon	[18]
	Rectum usually spared	[19]
Medication effects	Endoscopic assessment of Ipilimumab induced colitis reveals absent vascular pattern, and erythema in most patients. Variety of endoscopic features described in recent retrospective study	[20]
	NSAID induced colopathy can affect the whole colon, but has a right sided predominance.	[21]
	Colonic findings include ulceration, strictures and diaphragm like strictures	
Solitary rectal ulcer syndrome	Ulcerative lesions (either single or multiple) most common finding, however can present with erythema or polypoid lesions	[22]
Behçet disease	Predilection for ulcers in the ileo-caecal region. Ulcers are typically larger than 1 cm, deep and have discrete margins	[23]
Amebic colitis	Endoscopic findings can vary from procto-sigmoiditis to right colonic involvement, biopsy and microscopic identification of Entamoeba species useful in evaluation of suspected amebiasis	[24]

IBD: Inflammatory bowel disease; ITB: Intestinal tuberculosis; CMV: Cytomegalovirus; CD: Crohn's disease; NSAID: Non-steroidal anti-inflammatory drug.

Table 2 Endoscopic activity indices

Endoscopic score	Comment	Variables	Ref.
Ulcerative colitis endoscopic index of severity	Easy to use. Scoring based on area of bowel most severely affected. Correlates well with patient reported symptoms	Vascular pattern, bleeding, ulcers/erosions	[83-85]
Mayo endoscopic score	Commonly used in clinical practice, four point scale (0-3) (Figure 1)	Vascular pattern, erythema, bleeding, friability, erythema, erosions and ulcers	[86]
Modified mayo endoscopic score	Total endoscopic mucosal activity accounted. Easy to use. Correlates well with clinical and histological activity	Combines disease extent with MES severity	[87]
Ulcerative colitis colonoscopic index of severity	Total score based on parameters throughout the colon. Validated	Vascular pattern, ulceration, granularity, friability/bleeding	[88]
CDEIS	Complex scoring system, time consuming. Validated. Utilised to monitor endoscopic response to treatment	Deep and superficial ulceration, surface of ulcerations, surface of lesions	[33,89]
SES-CD	Correlates well with CDEIS and clinical parameters	Ulcer size, stenosis, ulcerated and affected surfaces	[34,90]
Rutgeerts' score	Utilised to monitor endoscopic response to treatment		
	To assess degree of postoperative recurrence at ileo-colonic anastomosis in Crohn's disease. Easy to use in clinical practice	Aphthous ulceration, large ulcers, stenosis, nodularity and ileitis	[30]

SES-CD: Simple endoscopic score for Crohn's disease; CDEIS: Crohn's disease endoscopic index of severity.

mended to assess the extent of small bowel disease. VCE can be useful in the management of patients with known^[35,36] or suspected IBD^[37], by visualising mucosa not readily accessible by standard endoscopy. VCE is generally safe in patients with CD^[35], the main complication of VCE is that of capsule retention. This can be reduced by excluding patients with known or suspected obstruction, and testing with patency capsule

(although recent retrospective study of patients with CD capsule retention was not reduced by use of patency capsule in all patients, compared to selective use of patency capsule^[38]). Imaging studies or patency capsule is recommended prior to capsule endoscopy in patients with known small bowel CD^[4].

A prospective, multi-centered, blinded cohort study of patients with suspected CD found that VCE is equivalent

to ileo-colonoscopy in detecting ileo-caecal inflammation, and is superior to small bowel follow through studies^[37]. In patients with suspected inflammatory phenotype CD, VCE is safe and can confirm diagnosis of CD in the presence of a normal ileo-colonoscopy^[37]. VCE was superior to MRE and CTE in detecting mucosal lesions proximal to the terminal ileum, in a blinded prospective study of patients with suspected or newly diagnosed CD^[39]. However, some authors have suggested that there is a trade-off between sensitivity and specificity with VCE. In particular, while VCE has greater sensitivity for small bowel mucosal lesions in individuals with suspected CD, there is a risk that presence of minor mucosal erosions can give rise to "false positive" diagnosis^[40]. This underlines the importance of use of a scoring system (the Lewis index^[41], is validated^[42] and is comprised of three parameters: stenosis, ulceration and mucosal oedema).

A recent retrospective study of CD patients with isolated small bowel disease, undergoing VCE at diagnosis, found that moderate to severe disease as defined by the Lewis Score^[41], was associated with need for hospitalisation and corticosteroid use after 12 mo follow-up^[43]. Conversely a retrospective study of patients with suspected CD, a low Lewis score (defined as < 135) is associated with a low probability CD diagnosis being confirmed on follow-up^[44]. VCE also enables assessment of mucosal healing after initiating immunomodulator or biological therapy^[45].

VCE may be contraindicated in patients with stricturing CD. MRE and CTE are utilized in patients with complicated phenotype CD requiring small bowel evaluation, although their use can be limited by patient factors and local availability. Recently the magnetic resonance index of activity has been shown to correlate well with the SES-CD in the assessment of ileal lesions^[46].

CRC SURVEILLANCE

Following index endoscopy, endoscopic re-evaluation to guide treatment is typically repeated every few years. Endoscopic surveillance is recommended to commence after 8^[2,4,47] to 10^[48] years from initial symptoms in patients with colonic disease, as some patients are at increased risk of developing CRC^[49]. Patients with extensive colonic disease, concomitant PSC^[50], young age at diagnosis, history of sporadic CRC in first degree relative, advanced age^[51], severe inflammation^[52] and longer duration of disease are at increased risk of developing CRC^[53,54]. The optimal surveillance interval is uncertain, the major gastrointestinal societies have differing recommendations^[2,4,47,48] but most now increasingly recognize that surveillance efforts are best focused on those at highest risk.

The goal of surveillance is to reduce CRC related mortality and morbidity, by detecting asymptomatic CRC and premalignant lesions. The risk of CRC in

patients with IBD is less than previously reported (meta-analysis of population based studies described a pooled standardized incidence ratio of 1.7^[53]), and is not increased in all patients. The incidence of CRC in patients with UC has decreased in the last few decades^[55]. A nationwide Danish cohort found that patients diagnosed with UC in the 1980s were at increased risk of CRC, however that excessive risk of CRC has declined and no longer exceeds that of the general population^[54]. CRC pathogenesis in patients with IBD is thought to occur mainly from dysplasia rather than adenoma to CRC sequence. Patients with colonic CD (3.9%) and UC (6.3%) were found to have reduced risk of developing sporadic adenomatous polyps compared to control population (25.9%)^[56]. Interestingly patients with small bowel CD had similar rate of adenomas as control population^[56].

The development of flat dysplasia in patients with colonic IBD makes endoscopic surveillance challenging. Traditionally surveillance consisted of numerous random biopsies (4 quadrant biopsies every 10 cm, minimum of 32 biopsies^[47]), in addition to any suspicious lesions. The aim of random biopsy sampling is to detect dysplasia, often without visible mucosal abnormalities, before to progresses to CRC. However the principle that dysplasia in patients with IBD occurs usually occurs without visible mucosal abnormalities, has been challenged^[57,58].

In patients with UC diagnosed with LGD, risk factors for progression to HGD or CRC include lesions greater than 1 cm, and lesions invisible on endoscopy^[59]. Patients with UC were found to have a low risk of progression to CRC after resection of polypoid dysplasia, in a meta-analysis not including any studies using chromoendoscopy^[60]. This finding supports current practice of resection and surveillance of raised lesions with dysplasia^[49] (although non-adenoma like raised lesions with dysplasia are usually difficult to resect by polypectomy). In a prospective study of patients with undergoing surveillance colonoscopy, CE was superior to random biopsy or WLE in detecting dysplasia^[61]. These findings contrast with a large retrospective study, which found no difference between CE and WLE with random and targeted biopsies, in detection rates for dysplasia^[62]. Narrow band imaging has not been shown to be superior to white light endoscopy for detecting dysplasia in patients with IBD^[63,64]. CE with targeted biopsies are more cost effective than traditional WLE endoscopy with random biopsies^[65], and are recommended as preferred method of surveillance in recent guidelines^[2,4,48].

The incidence of CRC amongst patients with IBD enrolled in regular surveillance appears to be lower than previously reported^[52,66], likely reflecting improvements in medical care and quality of endoscopies performed; with both of this factors benefiting from technological advances. In patients with IBD who develop CRC, those involved in surveillance programmes have better survival rates than those not enrolled in regular surveillance^[67].

MUCOSAL HEALING

Clinical remission and endoscopic remission correlate poorly^[68], especially in CD. VCE reveals that in patients with small bowel CD in clinical remission, mucosal healing (defined as a Lewis score < 135) is rare^[69]. Mucosal healing has become an important treatment target in managing patients with IBD, and is associated with improved outcomes^[70,71]. A recent meta-analysis found that mucosal healing was associated with long-term clinical remission, corticosteroid free remission and avoidance of colectomy^[71]. Mucosal healing at 26 wk was predictive of corticosteroid free remission at week 50 in a subgroup analysis of 172 patients from the SONIC trial^[34]. Considerations influencing the choice of modality to assess mucosal healing are discussed in a recent review^[72], colonoscopy is the gold standard in ileo-colonic disease. Faecal calprotectin has been proposed as a surrogate non-invasive marker for mucosal healing, which may rationalize the use of endoscopy in assessing mucosal healing^[73]. Faecal markers may not, however, have adequate negative predictive value in all patients, especially those with limited, small bowel disease.

There is a discrepancy between the endoscopic and histological assessment in UC^[74], especially mild disease^[75]. Endoscopic mucosal healing or inactivity, does not always equate to quiescent microscopic disease^[76]. Histological remission is not yet a routinely sought objective in the management of IBD^[77], however histological remission better predicts need for hospitalisation and corticosteroid use in patients with UC compared to endoscopic remission^[78]. A recent prospective study of 179 patients with UC in clinical remission, revealed an association between baseline histology grade and risk of clinical relapse^[79]. Patients with an elevated histological grade (Geboes^[80] grade ≥ 3.1) at baseline had a relative risk of clinical relapse, over 12 mo follow-up, of 3.5 (95%CI: 1.9-6.4, $P < 0.0001$)^[79]. To aid assessment of histological disease activity in patients with IBD, there needs to be close co-operation between endoscopists and histopathologists^[81].

Confocal laser endomicroscopy has the potential to provide real-time microscopic assessment ("endopathology"), which can help predict disease relapse in patients with endoscopic and clinical remission^[82].

CONCLUSION

Endoscopy remains integral in the diagnosis and management of IBD, endoscopic disease assessment is essential for objective monitoring of treatment response. Endoscopic severity scores facilitate monitoring of endoscopic response to treatment, and help identify patients who may benefit from escalation of therapy.

The paradigm of CRC surveillance in patients with IBD is shifting from high frequency random biopsies, to that of high quality visual inspection and targeted

biopsies of suspected dysplasia, enabled by technological advances including CE and high-definition endoscopes. Current practice in the management of dysplasia entails resection of dysplastic lesions where possible, rather than colectomy.

REFERENCES

- 1 **Van Assche G**, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, Ochsenschlohn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010; **4**: 7-27 [PMID: 21122488 DOI: 10.1016/j.crohns.2009.12.003]
- 2 **Annese V**, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kiefflich R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: 982-1018 [PMID: 24184171 DOI: 10.1016/j.crohns.2013.09.016]
- 3 **Denters MJ**, Schreuder M, Depla AC, Mallant-Hent RC, van Kouwen MC, Deutekom M, Bossuyt PM, Fockens P, Dekker E. Patients' perception of colonoscopy: patients with inflammatory bowel disease and irritable bowel syndrome experience the largest burden. *Eur J Gastroenterol Hepatol* 2013; **25**: 964-972 [PMID: 23660935 DOI: 10.1097/MEG.0b013e328361ded3]
- 4 **Shergill AK**, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Foley K, Hwang JH, Jue TL, Khashab MA, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD, DeWitt JM. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc* 2015; **81**: 1101-21.e1-13 [PMID: 25800660 DOI: 10.1016/j.gie.2014.10.030]
- 5 **Rubin DT**, Rothe JA. The peri-appendiceal red patch in ulcerative colitis: review of the University of Chicago experience. *Dig Dis Sci* 2010; **55**: 3495-3501 [PMID: 20936357 DOI: 10.1007/s10620-010-1424-x]
- 6 **Bernstein CN**, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. *Gastrointest Endosc* 1995; **42**: 232-237 [PMID: 7498688 DOI: 10.1016/S0016-5107(95)70097-8]
- 7 **Corte C**, Fernandezpulle N, Catuneanu AM, Burger D, Cesarini M, White L, Keshav S, Travis S. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. *J Crohns Colitis* 2015; **9**: 376-381 [PMID: 25770163 DOI: 10.1093/ecco-jcc/jjv047]
- 8 **Makharia GK**, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, Deo V, Aggarwal A, Tiwari RP, Sreenivas V, Gupta SD. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am J Gastroenterol* 2010; **105**: 642-651 [PMID: 20087333 DOI: 10.1038/ajg.2009.585]
- 9 **Lee YJ**, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI, Chang SJ, Yu CS. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. *Endoscopy* 2006; **38**: 592-597 [PMID: 16673312 DOI: 10.1055/s-2006-924996]
- 10 **Zhang T**, Fan R, Wang Z, Hu S, Zhang M, Lin Y, Tang Y, Zhong J. Differential diagnosis between Crohn's disease and intestinal tuberculosis using integrated parameters including clinical manifestations, T-SPOT, endoscopy and CT enterography. *Int J Clin Exp Med* 2015; **8**: 17578-17589 [PMID: 26770348]
- 11 **Lamps LW**, Knapple WL. Diverticular disease-associated segmental colitis. *Clin Gastroenterol Hepatol* 2007; **5**: 27-31 [PMID: 17234553 DOI: 10.1016/j.cgh.2006.10.024]
- 12 **Suzuki H**, Kato J, Kuriyama M, Hiraoka S, Kuwaki K, Yamamoto K. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection. *World J Gastroenterol* 2010; **16**: 1245-1251 [PMID: 20222169 DOI: 10.3748/wjg.v16.i10.1245]

- 13 **McCurdy JD**, Jones A, Enders FT, Killian JM, Loftus EV, Smyrk TC, Bruining DH. A model for identifying cytomegalovirus in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2015; **13**: 131-137; quiz e7 [PMID: 24993369 DOI: 10.1016/j.cgh.2014.05.026]
- 14 **Iida T**, Ikeya K, Watanabe F, Abe J, Maruyama Y, Ohata A, Teruyuki S, Sugimoto K, Hanai H. Looking for endoscopic features of cytomegalovirus colitis: a study of 187 patients with active ulcerative colitis, positive and negative for cytomegalovirus. *Inflamm Bowel Dis* 2013; **19**: 1156-1163 [PMID: 23619714 DOI: 10.1097/MIB.0b013e31828075ce]
- 15 **Ben-Horin S**, Margalit M, Bossuyt P, Maul J, Shapira Y, Bojic D, Chermesh I, Al-Rifai A, Schoepfer A, Bosani M, Allez M, Lakatos PL, Bossa F, Eser A, Stefanelli T, Carbonnel F, Katsanos K, Checchin D, de Miera IS, Reinisch W, Chowers Y, Moran GW. Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection. *J Crohns Colitis* 2010; **4**: 194-198 [PMID: 21122505 DOI: 10.1016/j.crohns.2009.11.001]
- 16 **Mee AS**, Shield M, Burke M. *Campylobacter* colitis: differentiation from acute inflammatory bowel disease. *J R Soc Med* 1985; **78**: 217-223 [PMID: 3973886]
- 17 **Loss RW**, Mangla JC, Pereira M. *Campylobacter* colitis presentin as inflammatory bowel disease with segmental colonic ulcerations. *Gastroenterology* 1980; **79**: 138-140 [PMID: 7380209]
- 18 **Brandt LJ**, Feuerstadt P, Blaszcza MC. Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. *Am J Gastroenterol* 2010; **105**: 2245-2252; quiz 2253 [PMID: 20531399 DOI: 10.1038/ajg.2010.217]
- 19 **Sherid M**, Sifuentes H, Samo S, Sulaiman S, Husein H, Tupper R, Sethuraman SN, Spurr C, Vainder JA, Sridhar S. Ischemic colitis: A forgotten entity. Results of a retrospective study in 118 patients. *J Dig Dis* 2014; **15**: 606-613 [PMID: 25139520 DOI: 10.1111/1751-2980.12182]
- 20 **Verschuren EC**, van den Eertwegh AJ, Wonders J, Slangen RM, van Delft F, van Bodegraven A, Neeffjes-Borst A, de Boer NK. Clinical, Endoscopic, and Histologic Characteristics of Ipilimumab-Associated Colitis. *Clin Gastroenterol Hepatol* 2016; **14**: 836-842 [PMID: 26748223 DOI: 10.1016/j.cgh.2015.12.028]
- 21 **Aftab AR**, Donnellan F, Zeb F, Kevans D, Cullen G, Courtney G. NSAID-induced colopathy. A case series. *J Gastrointest Liver Dis* 2010; **19**: 89-91 [PMID: 20361083]
- 22 **Abid S**, Khawaja A, Bhimani SA, Ahmad Z, Hamid S, Jafri W. The clinical, endoscopic and histological spectrum of the solitary rectal ulcer syndrome: a single-center experience of 116 cases. *BMC Gastroenterol* 2012; **12**: 72 [PMID: 22697798 DOI: 10.1186/1471-230X-12-72]
- 23 **Lee CR**, Kim WH, Cho YS, Kim MH, Kim JH, Park IS, Bang D. Colonoscopic findings in intestinal Behçet's disease. *Inflamm Bowel Dis* 2001; **7**: 243-249 [PMID: 11515851 DOI: 10.1097/00054725-200108000-00010]
- 24 **Lee KC**, Lu CC, Hu WH, Lin SE, Chen HH. Colonoscopic diagnosis of amebiasis: a case series and systematic review. *Int J Colorectal Dis* 2015; **30**: 31-41 [PMID: 25346004 DOI: 10.1007/s00384-014-2040-6]
- 25 **Baron JH**, Connell AM, Lennard-jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964; **1**: 89-92 [PMID: 14075156 DOI: 10.1136/bmj.1.5375.89]
- 26 **Khanna R**, Bouguen G, Feagan BG, D'Haens G, Sandborn WJ, Dubcenco E, Baker KA, Levesque BG. A systematic review of measurement of endoscopic disease activity and mucosal healing in Crohn's disease: recommendations for clinical trial design. *Inflamm Bowel Dis* 2014; **20**: 1850-1861 [PMID: 25029615 DOI: 10.1097/MIB.0000000000000131]
- 27 **Samaan MA**, Mosli MH, Sandborn WJ, Feagan BG, D'Haens GR, Dubcenco E, Baker KA, Levesque BG. A systematic review of the measurement of endoscopic healing in ulcerative colitis clinical trials: recommendations and implications for future research. *Inflamm Bowel Dis* 2014; **20**: 1465-1471 [PMID: 24831558 DOI: 10.1097/MIB.0000000000000046]
- 28 **Jairath V**, Zou G, Parker CE, Macdonald JK, Mosli MH, Khanna R, Shackelton LM, Vandervoort MK, AlAmeel T, Al Beshir M, AlMadi M, Al-Taweel T, Atkinson NS, Biswas S, Chapman TP, Dulai PS, Glaire MA, Hoekman D, Koutsoumpas A, Minas E, Samaan MA, Travis S, D'Haens G, Levesque BG, Sandborn WJ, Feagan BG. Systematic Review and Meta-analysis: Placebo Rates in Induction and Maintenance Trials of Ulcerative Colitis. *J Crohns Colitis* 2016; **10**: 607-618 [PMID: 26746169 DOI: 10.1093/ecco-jcc/jjw004]
- 29 **Feagan BG**, Sandborn WJ, D'Haens G, Pola S, McDonald JW, Rutgeerts P, Munkholm P, Mittmann U, King D, Wong CJ, Zou G, Donner A, Shackelton LM, Gilgen D, Nelson S, Vandervoort MK, Fahmy M, Loftus EV, Panaccione R, Travis SP, Van Assche GA, Vermeire S, Levesque BG. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. *Gastroenterology* 2013; **145**: 149-157.e2 [PMID: 23528626 DOI: 10.1053/j.gastro.2013.03.025]
- 30 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963 [PMID: 2394349 DOI: 10.1016/0016-5085(90)90613-6]
- 31 **De Cruz P**, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, Liew D, Prideaux L, Lawrance IC, Andrews JM, Bampton PA, Gibson PR, Sparrow M, Leong RW, Florin TH, Geary RB, Radford-Smith G, Macrae FA, Debinski H, Selby W, Kronborg I, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Desmond PV. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; **385**: 1406-1417 [PMID: 25542620 DOI: 10.1016/S0140-6736(14)61908-5]
- 32 **Ferrante M**, Papamichael K, Duricova D, D'Haens G, Vermeire S, Archavlis E, Rutgeerts P, Bortlik M, Mantzaris G, Van Assche G. Systematic versus Endoscopy-driven Treatment with Azathioprine to Prevent Postoperative Ileal Crohn's Disease Recurrence. *J Crohns Colitis* 2015; **9**: 617-624 [PMID: 25926532 DOI: 10.1093/ecco-jcc/jjv076]
- 33 **Vuitton L**, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, Danese S, D'Haens G, Lowenberg M, Khanna R, Fiorino G, Travis S, Mary JY, Peyrin-Biroulet L. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut* 2016; **65**: 1447-1455 [PMID: 26353983 DOI: 10.1136/gutjnl-2015-309903]
- 34 **Ferrante M**, Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens GR, van der Woude CJ, Danese S, Diamond RH, Oortwijn AF, Tang KL, Miller M, Cornillie F, Rutgeerts PJ. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. *Gastroenterology* 2013; **145**: 978-986.e5 [PMID: 23954314 DOI: 10.1053/j.gastro.2013.08.010]
- 35 **Kopylov U**, Nemeth A, Koulaouzidis A, Makins R, Wild G, Afif W, Bitton A, Johansson GW, Bessissow T, Eliakim R, Toth E, Seidman EG. Small bowel capsule endoscopy in the management of established Crohn's disease: clinical impact, safety, and correlation with inflammatory biomarkers. *Inflamm Bowel Dis* 2015; **21**: 93-100 [PMID: 25517597 DOI: 10.1097/MIB.0000000000000255]
- 36 **Long MD**, Barnes E, Isaacs K, Morgan D, Herfarth HH. Impact of capsule endoscopy on management of inflammatory bowel disease: a single tertiary care center experience. *Inflamm Bowel Dis* 2011; **17**: 1855-1862 [PMID: 21830264 DOI: 10.1002/ibd.21571]
- 37 **Leighton JA**, Gralnek IM, Cohen SA, Toth E, Cave DR, Wolf DC, Mullin GE, Ketover SR, Legnani PE, Seidman EG, Crowell MD, Bergwerk AJ, Peled R, Eliakim R. Capsule endoscopy is superior to small-bowel follow-through and equivalent to ileocolonoscopy in suspected Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 609-615 [PMID: 24075891 DOI: 10.1016/j.cgh.2013.09.028]
- 38 **Koulaouzidis A**, Sipponen T, Nemeth A, Makins R, Kopylov U, Nadler M, Giannakou A, Yung DE, Johansson GW, Bartzis L, Thorlacius H, Seidman EG, Eliakim R, Plevris JN, Toth E.

- Association Between Fecal Calprotectin Levels and Small-bowel Inflammation Score in Capsule Endoscopy: A Multicenter Retrospective Study. *Dig Dis Sci* 2016; **61**: 2033-2040 [PMID: 27007135 DOI: 10.1007/s10620-016-4104-7]
- 39 **Jensen MD**, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. *Clin Gastroenterol Hepatol* 2011; **9**: 124-129 [PMID: 21056692 DOI: 10.1016/j.cgh.2010.10.019]
- 40 **Doherty GA**, Moss AC, Cheifetz AS. Capsule endoscopy for small-bowel evaluation in Crohn's disease. *Gastrointest Endosc* 2011; **74**: 167-175 [PMID: 21497806 DOI: 10.1016/j.gie.2011.01.067]
- 41 **Gralnek IM**, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008; **27**: 146-154 [PMID: 17956598 DOI: 10.1111/j.1365-2036.2007.03556.x]
- 42 **Cotter J**, Dias de Castro F, Magalhães J, Moreira MJ, Rosa B. Validation of the Lewis score for the evaluation of small-bowel Crohn's disease activity. *Endoscopy* 2015; **47**: 330-335 [PMID: 25412092 DOI: 10.1055/s-0034-1390894]
- 43 **Dias de Castro F**, Boal Carvalho P, Monteiro S, Rosa B, Firmino-Machado J, Moreira MJ, Cotter J. Lewis Score--Prognostic Value in Patients with Isolated Small Bowel Crohn's Disease. *J Crohns Colitis* 2015; **9**: 1146-1151 [PMID: 26377028 DOI: 10.1093/ecco-jcc/jjv166]
- 44 **Monteiro S**, Boal Carvalho P, Dias de Castro F, Magalhães J, Machado F, Moreira MJ, Rosa B, Cotter J. Capsule Endoscopy: Diagnostic Accuracy of Lewis Score in Patients with Suspected Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 2241-2246 [PMID: 26197449 DOI: 10.1097/MIB.0000000000000517]
- 45 **Hall B**, Holleran G, Chin JL, Smith S, Ryan B, Mahmud N, McNamara D. A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. *J Crohns Colitis* 2014; **8**: 1601-1609 [PMID: 25257546 DOI: 10.1016/j.crohns.2014.09.005]
- 46 **Takenaka K**, Ohtsuka K, Kitazume Y, Nagahori M, Fujii T, Saito E, Fujioka T, Matsuoka K, Naganuma M, Watanabe M. Correlation of the Endoscopic and Magnetic Resonance Scoring Systems in the Deep Small Intestine in Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 1832-1838 [PMID: 26020602 DOI: 10.1097/MIB.0000000000000449]
- 47 **Farraye FA**, Odze RD, Eaden J, Itzkowitz SH, McCabe RP, Dassopoulos T, Lewis JD, Ullman TA, James T, McLeod R, Burgart LJ, Allen J, Brill JV. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010; **138**: 738-745 [PMID: 20141808 DOI: 10.1053/j.gastro.2009.12.037]
- 48 **Cairns SR**, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010; **59**: 666-689 [PMID: 20427401 DOI: 10.1136/gut.2009.179804]
- 49 **Laine L**, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015; **148**: 639-651.e28 [PMID: 25702852 DOI: 10.1053/j.gastro.2015.01.031]
- 50 **Zheng HH**, Jiang XL. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies. *Eur J Gastroenterol Hepatol* 2016; **28**: 383-390 [PMID: 26938805 DOI: 10.1097/MEG.0000000000000576]
- 51 **Wang YR**, Cangemi JR, Loftus EV, Picco MF. Rate of early/missed colorectal cancers after colonoscopy in older patients with or without inflammatory bowel disease in the United States. *Am J Gastroenterol* 2013; **108**: 444-449 [PMID: 23295277 DOI: 10.1038/ajg.2012.429]
- 52 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006; **130**: 1030-1038 [PMID: 16618396 DOI: 10.1053/j.gastro.2005.12.035]
- 53 **Lutgens MW**, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013; **19**: 789-799 [PMID: 23448792 DOI: 10.1097/MIB.0b013e31828029c0]
- 54 **Jess T**, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012; **143**: 375-381.e1; quiz e13- e 14 [PMID: 22522090 DOI: 10.1053/j.gastro.2012.04.016]
- 55 **Castañó-Milla C**, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. *Aliment Pharmacol Ther* 2014; **39**: 645-659 [PMID: 24612141 DOI: 10.1111/apt.12651]
- 56 **Ben-Horin S**, Izhaki Z, Haj-Natur O, Segev S, Eliakim R, Avidan B. Rarity of adenomatous polyps in ulcerative colitis and its implications for colonic carcinogenesis. *Endoscopy* 2016; **48**: 215-222 [PMID: 26427000 DOI: 10.1055/s-0034-1393119]
- 57 **van den Broek FJ**, Stokkers PC, Reitsma JB, Boltjes RP, Ponsioen CY, Fockens P, Dekker E. Random biopsies taken during colonoscopic surveillance of patients with longstanding ulcerative colitis: low yield and absence of clinical consequences. *Am J Gastroenterol* 2014; **109**: 715-722 [PMID: 21427710 DOI: 10.1038/ajg.2011.93]
- 58 **Rubin DT**, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? *Gastrointest Endosc* 2007; **65**: 998-1004 [PMID: 17451704 DOI: 10.1016/j.gie.2006.09.025]
- 59 **Choi CH**, Ignjatovic-Wilson A, Askari A, Lee GH, Warusavitarne J, Moorghen M, Thomas-Gibson S, Saunders BP, Rutter MD, Graham TA, Hart AL. Low-grade dysplasia in ulcerative colitis: risk factors for developing high-grade dysplasia or colorectal cancer. *Am J Gastroenterol* 2015; **110**: 1461-1471; quiz 1472 [PMID: 26416190 DOI: 10.1038/ajg.2015.248]
- 60 **Wanders LK**, Dekker E, Pullens B, Bassett P, Travis SP, East JE. Cancer risk after resection of polypoid dysplasia in patients with longstanding ulcerative colitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 756-764 [PMID: 23920032 DOI: 10.1016/j.cgh.2013.07.024]
- 61 **Marion JF**, Waye JD, Israel Y, Present DH, Suprun M, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Abreu MT, Ullman TA, McBride RB, Aisenberg J, Mayer L. Chromoendoscopy Is More Effective Than Standard Colonoscopy in Detecting Dysplasia During Long-term Surveillance of Patients With Colitis. *Clin Gastroenterol Hepatol* 2016; **14**: 713-719 [PMID: 26656297 DOI: 10.1016/j.cgh.2015.11.011]
- 62 **Mooiweer E**, van der Meulen-de Jong AE, Ponsioen CY, Fidder HH, Siersema PD, Dekker E, Oldenburg B. Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study. *Am J Gastroenterol* 2015; **110**: 1014-1021 [PMID: 25823770 DOI: 10.1038/ajg.2015.63]
- 63 **Ignjatovic A**, East JE, Subramanian V, Suzuki N, Guenther T, Palmer N, Bassett P, Ragunath K, Saunders BP. Narrow band imaging for detection of dysplasia in colitis: a randomized controlled trial. *Am J Gastroenterol* 2012; **107**: 885-890 [PMID: 22613903 DOI: 10.1038/ajg.2012.67]
- 64 **Leifeld L**, Rogler G, Stallmach A, Schmidt C, Zuber-Jerger I, Hartmann F, Plauth M, Drabik A, Hofstädter F, Dienes HP, Kruis W. White-Light or Narrow-Band Imaging Colonoscopy in Surveillance of Ulcerative Colitis: A Prospective Multicenter Study. *Clin Gastroenterol Hepatol* 2015; **13**: 1776-1781.e1 [PMID: 25952309 DOI: 10.1016/j.cgh.2015.04.172]
- 65 **Konijeti GG**, Shrive MG, Ananthakrishnan AN, Chan AT. Cost-

- effectiveness analysis of chromoendoscopy for colorectal cancer surveillance in patients with ulcerative colitis. *Gastrointest Endosc* 2014; **79**: 455-465 [PMID: 24262637 DOI: 10.1016/j.gie.2013.10.026]
- 66 **Mooiweer E**, van der Meulen-de Jong AE, Ponsioen CY, van der Woude CJ, van Bodegraven AA, Jansen JM, Mahmmoud N, Kremer W, Siersema PD, Oldenburg B. Incidence of Interval Colorectal Cancer Among Inflammatory Bowel Disease Patients Undergoing Regular Colonoscopic Surveillance. *Clin Gastroenterol Hepatol* 2015; **13**: 1656-1661 [PMID: 25956835 DOI: 10.1016/j.cgh.2015.04.183]
 - 67 **Lutgens MW**, Oldenburg B, Siersema PD, van Bodegraven AA, Dijkstra G, Hommes DW, de Jong DJ, Stokkers PC, van der Woude CJ, Vleggaar FP. Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. *Br J Cancer* 2009; **101**: 1671-1675 [PMID: 19826420 DOI: 10.1038/sj.bjc.6605359]
 - 68 **Peyrin-Biroulet L**, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, Rutgeerts P, Tang LK, Cornillie FJ, Sandborn WJ. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014; **63**: 88-95 [PMID: 23974954 DOI: 10.1136/gutjnl-2013-304984]
 - 69 **Kopylov U**, Yablecovitch D, Lahat A, Neuman S, Levhar N, Greener T, Klang E, Rozendorn N, Amitai MM, Ben-Horin S, Eliakim R. Detection of Small Bowel Mucosal Healing and Deep Remission in Patients With Known Small Bowel Crohn's Disease Using Biomarkers, Capsule Endoscopy, and Imaging. *Am J Gastroenterol* 2015; **110**: 1316-1323 [PMID: 26215531 DOI: 10.1038/ajg.2015.221]
 - 70 **Shah SC**, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 317-333 [PMID: 26607562 DOI: 10.1111/apt.13475]
 - 71 **Shah SC**, Colombel JF, Sands BE, Narula N. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 1245-1255.e8 [PMID: 26829025 DOI: 10.1016/j.cgh.2016.01.015]
 - 72 **Dulai PS**, Levesque BG, Feagan BG, D'Haens G, Sandborn WJ. Assessment of mucosal healing in inflammatory bowel disease: review. *Gastrointest Endosc* 2015; **82**: 246-255 [PMID: 26005012 DOI: 10.1016/j.gie.2015.03.1974]
 - 73 **Theede K**, Holck S, Ibsen P, Ladelund S, Nordgaard-Lassen I, Nielsen AM. Level of Fecal Calprotectin Correlates With Endoscopic and Histologic Inflammation and Identifies Patients With Mucosal Healing in Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2015; **13**: 1929-36.e1 [PMID: 26051392 DOI: 10.1016/j.cgh.2015.05.038]
 - 74 **Guardiola J**, Lobatón T, Rodríguez-Alonso L, Ruiz-Cerulla A, Arjol C, Loayza C, Sanjuan X, Sánchez E, Rodríguez-Moranta F. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. *Clin Gastroenterol Hepatol* 2014; **12**: 1865-1870 [PMID: 24993368 DOI: 10.1016/j.cgh.2014.06.020]
 - 75 **Lemmens B**, Arijis I, Van Assche G, Sagaert X, Geboes K, Ferrante M, Rutgeerts P, Vermeire S, De Hertogh G. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 1194-1201 [PMID: 23518809 DOI: 10.1097/MIB.0b013e318280e75f]
 - 76 **Rosenberg L**, Nanda KS, Zenlea T, Gifford A, Lawlor GO, Falchuk KR, Wolf JL, Cheifetz AS, Goldsmith JD, Moss AC. Histologic markers of inflammation in patients with ulcerative colitis in clinical remission. *Clin Gastroenterol Hepatol* 2013; **11**: 991-996 [PMID: 23591275 DOI: 10.1016/j.cgh.2013.02.030]
 - 77 **Bryant RV**, Winer S, Travis SP, Riddell RH. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. *J Crohns Colitis* 2014; **8**: 1582-1597 [PMID: 25267173 DOI: 10.1016/j.crohns.2014.08.011]
 - 78 **Bryant RV**, Burger DC, Delo J, Walsh AJ, Thomas S, von Herbay A, Buchel OC, White L, Brain O, Keshav S, Warren BF, Travis SP. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut* 2016; **65**: 408-414 [PMID: 25986946 DOI: 10.1136/gutjnl-2015-309598]
 - 79 **Zenlea T**, Yee EU, Rosenberg L, Boyle M, Nanda KS, Wolf JL, Falchuk KR, Cheifetz AS, Goldsmith JD, Moss AC. Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study. *Am J Gastroenterol* 2016; **111**: 685-690 [PMID: 26977756 DOI: 10.1038/ajg.2016.50]
 - 80 **Geboes K**, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000; **47**: 404-409 [PMID: 10940279 DOI: 10.1136/gut.47.3.404]
 - 81 **Marchal Bressenot A**, Riddell RH, Boulagnon-Rombi C, Reinisch W, Danese S, Schreiber S, Peyrin-Biroulet L. Review article: the histological assessment of disease activity in ulcerative colitis. *Aliment Pharmacol Ther* 2015; **42**: 957-967 [PMID: 26304292 DOI: 10.1111/apt.13375]
 - 82 **Buda A**, Hatem G, Neumann H, D'Inca R, Mescoli C, Piselli P, Jackson J, Bruno M, Sturmiolo GC. Confocal laser endomicroscopy for prediction of disease relapse in ulcerative colitis: a pilot study. *J Crohns Colitis* 2014; **8**: 304-311 [PMID: 24094597 DOI: 10.1016/j.crohns.2013.09.005]
 - 83 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lémann M, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyszyn BR, Bernhardt CA, Mary JY, Sandborn WJ. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012; **61**: 535-542 [PMID: 21997563 DOI: 10.1136/gutjnl-2011-300486]
 - 84 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyszyn BR, Schnell P, Bernhardt CA, Mary JY, Sandborn WJ. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013; **145**: 987-995 [PMID: 23891974 DOI: 10.1053/j.gastro.2013.07.024]
 - 85 **Travis SP**, Schnell D, Feagan BG, Abreu MT, Altman DG, Hanauer SB, Krzeski P, Lichtenstein GR, Marteau PR, Mary JY, Reinisch W, Sands BE, Schnell P, Yacyszyn BR, Colombel JF, Bernhardt CA, Sandborn WJ. The Impact of Clinical Information on the Assessment of Endoscopic Activity: Characteristics of the Ulcerative Colitis Endoscopic Index Of Severity [UCEIS]. *J Crohns Colitis* 2015; **9**: 607-616 [PMID: 25956538 DOI: 10.1093/ecco-jcc/jjv077]
 - 86 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-amino-salicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/NEJM198712243172603]
 - 87 **Lobatón T**, Bessissow T, De Hertogh G, Lemmens B, Maedler C, Van Assche G, Vermeire S, Bisschops R, Rutgeerts P, Bitton A, Afif W, Marcus V, Ferrante M. The Modified Mayo Endoscopic Score (MMES): A New Index for the Assessment of Extension and Severity of Endoscopic Activity in Ulcerative Colitis Patients. *J Crohns Colitis* 2015; **9**: 846-852 [PMID: 26116558 DOI: 10.1093/ecco-jcc/jjv111]
 - 88 **Samuel S**, Bruining DH, Loftus EV, Thia KT, Schroeder KW, Tremaine WJ, Faubion WA, Kane SV, Pardi DS, de Groen PC, Harmsen WS, Zinsmeister AR, Sandborn WJ. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013; **11**: 49-54.e1 [PMID: 22902762 DOI: 10.1016/j.cgh.2012.08.003]
 - 89 **Mary JY**, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989; **30**: 983-989 [PMID: 2668130 DOI: 10.1136/gut.30.7.983]

- 90 **Daperno M**, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new,

simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60**: 505-512 [PMID: 15472670 DOI: 10.1016/S0016-5107(04)01878-4]

P- Reviewer: Actis GC, Wenzl HH, Yildiz K **S- Editor:** Qiu S
L- Editor: A **E- Editor:** Wu HL



Colorectal cancer screening: Opportunities to improve uptake, outcomes, and disparities

Neal Shahidi, Winson Y Cheung

Neal Shahidi, Division of Gastroenterology, Department of Medicine, University of British Columbia, Vancouver, BC V6Z 2K5, Canada

Winson Y Cheung, Division of Medical Oncology, Department of Medicine, University of British Columbia, Vancouver, BC V5Z 4E6, Canada

Winson Y Cheung, British Columbia Cancer Agency, Vancouver, BC V5Z 4E6, Canada

Author contributions: Shahidi N and Cheung WY made substantial contributions to conception and design of the study, acquisition of data or analysis and interpretation of data; Shahidi N and Cheung WY contributed to drafting of the article or making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Winson Y Cheung, MD, MPH, FRCPC, Associate Professor, Division of Medical Oncology, Department of Medicine, University of British Columbia, 600 W 10th Avenue, Vancouver, BC V5Z 4E6, Canada. wcheung@bccancer.bc.ca
Telephone: +1-604-8776000
Fax: +1-604-8770585

Received: June 28, 2016

Peer-review started: June 29, 2016

First decision: August 10, 2016

Revised: September 5, 2016

Accepted: September 13, 2016

Article in press: September 18, 2016

Published online: December 16, 2016

Abstract

Colorectal cancer screening has become a standard of care in industrialized nations for those 50 to 75 years of age, along with selected high-risk populations. While colorectal cancer screening has been shown to reduce both the incidence and mortality of colorectal cancer, it is a complex multi-disciplinary process with a number of important steps that require optimization before tangible improvements in outcomes are possible. For both opportunistic and programmatic colorectal cancer screening, poor participant uptake remains an ongoing concern. Furthermore, current screening modalities (such as the guaiac based fecal occult blood test, fecal immunochemical test and colonoscopy) may be used or performed suboptimally, which can lead to missed neoplastic lesions and unnecessary endoscopic evaluations. The latter poses the risk of adverse events, such as perforation and post-polypectomy bleeding, as well as financial impacts to the healthcare system. Moreover, ongoing disparities in colorectal cancer screening persist among marginalized populations, including specific ethnic minorities (African Americans, Hispanics, Asians, Indigenous groups), immigrants, and those who are economically disenfranchised. Given this context, we aimed to review the current literature on these important areas pertaining to colorectal cancer screening, particularly focusing on the guaiac based fecal occult blood test, the fecal immunochemical test and colonoscopy.

Key words: Fecal occult blood test; Fecal immunochemical test; Colonoscopy; Neoplasia; Polyp

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Colorectal cancer (CRC) screening has become a standard of care in industrialized nations for those aged 50 to 75 years. While CRC screening has been shown to reduce the incidence and mortality of CRC, it is a complex multi-disciplinary process that frequently presents challenges to implementation. This is a focused review on 3 pivotal areas of CRC screening that require improvement: (1) suboptimal uptake of CRC screening; (2) poor outcomes manifesting as missed lesions and adverse events during the screening process; and (3) ongoing disparities among marginalized populations.

Shahidi N, Cheung WY. Colorectal cancer screening: Opportunities to improve uptake, outcomes, and disparities. *World J Gastrointest Endosc* 2016; 8(20): 733-740 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/733.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.733>

INTRODUCTION

Colorectal cancer (CRC) is a critical health concern. It is the second most commonly diagnosed cancer in women and the third most commonly diagnosed cancer in men^[1,2], with North America, Europe and Australia having the highest incidence rates worldwide^[2,3]. In part due to the increasingly widespread adoption of Western dietary and lifestyle behaviors, the incidence of CRC is also rising in developing nations^[3,4]. Therefore, CRC represents a significant economic burden globally, with Medicare treatment costs within the United State estimated at over \$7 billion dollars^[5]. This highlights the importance of effective CRC screening with the intent to minimize the CRC disease burden through the removal of adenomatous neoplasia and the detection of CRC at an earlier stage at which point treatment is more successful. CRC screening has been shown to be effective at reducing the incidence and mortality of CRC^[6-13]. In addition, economic analyses^[14-18] evaluating CRC screening have highlighted it as a cost-effective, and possibly cost-saving, intervention^[18]. Consequently, many North American organizations including the Canadian Association of Gastroenterology (CAG)^[19], the American College of Gastroenterology (ACG)^[20], the Canadian Task Force on Preventative Health Care (CTFPHC)^[21], the United States Preventative Services Task Force (USPSTF)^[22] and the United States Multi-Society Task Force^[23] have endorsed multiple different screening methods including: Fecal occult blood tests (FOBTs) such as the guaiac-based (gFOBT) as well as fecal immunochemical (FIT) tests, fecal DNA tests, flexible sigmoidoscopy (FSIG), colonoscopy (CSPY), and computed tomographic colonography (Table 1).

Although the concept of screening is intuitively simplistic, the implementation of population-based CRC screening is a complex interdisciplinary process. Most notably, participation in initial and subsequent CRC screening have still not reached well-recognized

benchmarks^[24,25]. Moreover, screening test performance is an ongoing area of concern, given the potential for missed neoplasia as well as procedure-related adverse events. These issues are further exacerbated by persistent disparities in CRC screening among marginalized populations^[26]. Considering these issues, we sought to review these important areas and propose opportunities for optimization. For the purposes of this article, we will focus on the two predominant methods for CRC screening used in Canada and the United States, namely FOBTs (including gFOBT and FIT) and CSPY.

UPTAKE AND RETENTION

For CRC screening to be effective, high levels of participation in initial and subsequent CRC screening are required. Likewise, when gFOBT or FIT are used, abnormal results must be promptly followed by an evaluation with CSPY^[27]. Failure at any of these steps carries with it the potential to impair the effectiveness of CRC screening.

Initial CRC screening

In the United States, CRC screening uptake appears to be increasing^[28]. Unfortunately, estimates still remain below national targets^[28]. Based on findings derived from the 2010 National Health Interview Survey, a United States-based survey assessing a representative sample of the United States civilian population, only 59% of those aged 50 to 75 years were up-to-date with CRC screening as per the 2008 USPSTF recommendations (high-sensitivity FOBT every year; or FSIG every 5 years and high-sensitivity FOBT every 3 years; or CSPY every 10 years)^[24]. In comparison, estimates gathered from the 2012 Behavioral Risk Factor Surveillance System survey, another United States-based survey assessing a representative sample of the United States civilian population, close to 65% of those aged 50 to 75 years were up-to-date with CRC screening as per the same USPSTF recommendations^[28]. Of note, a concerning finding was that 28% stated they had never been screened for CRC.

In Canada, CRC screening rates also appear to be increasing, but they are similarly below current national benchmarks^[27]. Estimates from the 2012 Canadian Community Health Survey, a Canadian-based survey assessing a representative sample of the Canadian population, only 55% of those aged 50 to 74 years were up-to-date with CRC screening (FOBT every 2 years; or FSIG or CSPY every 10 years)^[25]. In recent years, Canada has made a concerted effort to transition to nationwide programmatic screening. Emerging data from 5 Canadian provinces between 2009 and 2011 collated by the Canadian Partnership Against Cancer (CPAC) revealed that participation in programmatic CRC screening (either gFOBT or FIT) ranged from 5% to 37% only^[27]. These estimates captured programmatic CRC screening alone whereas CRC utilization considers both programmatic and non-programmatic CRC

Table 1 Colorectal cancer screening recommendations for guaiac-based fecal occult blood test, fecal immunochemical test and colonoscopy among asymptomatic average-risk adults

	USPSTF ^[22]	CTFPHC ^[21]	CAG ^[19]	USMSTF ^[23]	ACG ^[20]
Publication year	2016	2016	2010	2008	2008
Country	United States	Canada	Canada	United States	United States
Age cut-off	50 to 75 ²	50 to 74	50 to 75 ²	Start at 50	Start at 50
gFOBT	Every year	Every 2 yr	Every 1 or 2 yr ³	Every year	Every year
FIT	Every year	Every 2 yr	Every 1 or 2 yr ³	Every year	Every year
CSPY	Every 10 yr	Not recommended	Not recommended ⁴	Every 10 yr	Every 10 yr
Preferred test ¹	No preference	No preference	FIT ⁵	CSPY	CSPY

¹Preferred test considering gFOBT, FIT and CSPY as potential CRC screening tests; ²CRC screening can be considered between ages 76 to 85 years on an individual basis; ³Frequency of testing dependent on jurisdictional resources; ⁴Recommendation against CSPY for population-based CRC screening. CSPY was a recommended option for opportunistic screening; ⁵Preference in the setting of programmatic CRC screening. ACG: American College of Gastroenterology; CAG: Canadian Association of Gastroenterology; CRC: Colorectal cancer; CSPY: Colonoscopy; CTFPHC: Canadian Task Force on Preventative Health Care; FIT: Fecal immunochemical test; gFOBT: Guaiac-based fecal occult blood test; USMSTF: United States Multi-Society Task Force; USPSTF: United States Preventative Services Task Force.

screening. FIT or gFOBT utilization ranged from 6% to 44% in 2009, and increased to 12% to 58% in 2011^[27].

Confirmatory testing with CSPY

Follow-up CSPY after an abnormal gFOBT or FIT result has also been highlighted as an area requiring further optimization. In 2001, a prospective study of 2410 participants aged ≥ 70 years were assessed, of which 212 has a positive gFOBT result^[29]. After 6 mo and 1 year, only 22% and 42%, respectively, had undergone endoscopic evaluation. In Canada between 2009 and 2011, 45% of subjects participating in programmatic screening underwent CSPY within 60 d and 81% underwent CSPY within 180 d after an abnormal gFOBT or FIT^[27]. There were significant variations between provinces whereby estimates ranged from 68% to 90%.

Serial screening at subsequent intervals

To benefit from CRC screening, retention during subsequent screening cycles is required. In a United States-based cohort of 11110 participants who had undergone gFOBT for CRC screening, only 44% completed repeat testing in the next 2-year follow-up period^[30]. In another large United States-based retrospective cohort of over 1 million participants across 136 Veteran Affairs medical centers, only 41% of men and 44% of women received adequate screening over a 5-year period (FOBT in 4 of the 5 years or ≥ 1 FOBT as well as CSPY, FSIG or double-contrast barium enema)^[31]. When stratifying outcomes based on the 384527 men and 10469 women who only used FOBT, only 14% (both groups) completed FOBT testing in 4 of the 5 years.

While findings from programmatic screening are more optimistic, they are still not ideal. Two studies from the Netherlands that assessed gFOBT and/or FIT showed that participation in the second round of testing ranged between 63% to 86%^[32,33]. In the evaluation of an Italian FIT-based CRC screening program over 4 rounds in a 7-year period, participation ranged between 56% to 63%^[34].

POOR OUTCOMES

Test performance is a major determinant of health outcomes, especially considering the potential clinical and economic implications of false positive and false negative results. In the setting of CRC screening, false negative findings equate to missed neoplastic lesions. This delay in diagnosis can have a profound impact on outcomes whereby potentially curable disease is rendered palliative. Likewise, false positive results can lead to additional healthcare resource use in the form of unnecessary CSPYs. Although CSPY is a generally safe procedure, it is not without adverse events, specifically post-polypectomy bleeding and perforation.

Fecal occult blood test performance

In comparing FIT and gFOBT, FIT has clearly emerged as the superior option for CRC screening^[35,36], which is now reflected in both national^[19] and international^[37] guidelines. However, FIT still has some inherent limitations. In a recent meta-analysis of 19 unique evaluations, FIT sensitivity was 79%^[38]. However, with adjustment of the FIT cut-off, sensitivity ranged from 67% to 86%. Interestingly, single sample FIT had similar sensitivity as several sample FIT. Aside from modifying the quantitative threshold to define test positivity, other factors have been identified that affect FIT sensitivity. For example, the version of FIT being used has been implicated in test performance variability. In the Taiwanese nation-wide screening program, 956005 participants underwent CRC screening using either OC-Sensor (Eiken Chemical Co, Tokyo, Japan) or HM-Jack (Kyowa Medex Co Ltd, Tokyo, Japan). Even though identical positive test cut-offs (20 μ g hemoglobin/g feces) were used^[39], significant differences between the two quantitative FITs were found when examining the positive predictive value for cancer and rates of interval cancer. Additional factors that affect FIT performance include processing time and temperature. As FIT is based on the detection of the protein globin, it is susceptible to false-negative results secondary to protein degradation. In a 2009 study, van Rossum

et al.^[40] compared FIT performance based on time between sampling and laboratory delivery (< 5 d vs ≥ 5 d). There was a significant reduction in adenoma detection rate (ADR) when samples were returned after ≥ 5 d. Moreover, it was found that mean fecal hemoglobin values decreased by 29 ng hemoglobin/mL buffer solution per day. In regards to the effect of temperature on FIT result, an Italian FIT CRC screening program found that an increase in temperature of one degree Celsius reduced the likelihood of FIT positivity by 0.7%^[41]. Similarly, there was a 13% reduction in detecting CRC or advanced adenomas in the summer compared to the winter.

Missed lesions on CSPY

It is well documented that CSPY may not reliably prevent CRC^[42-47] because of the potential of missed lesions^[47,48] or incomplete polypectomy^[49,50] at initial procedure. This is further compounded by variations in CRC tumorigenesis^[51]. In a recent meta-analysis that characterized the miss rates of polyps which were corroborated by tandem CSPY, the pooled miss rate for polyps of any size was 22%^[48]. For adenomas, the pooled miss rates were 2.1% for adenomas ≥ 10 mm, 13% for adenomas 5 to 10 mm and 26% for adenomas 1 to 5 mm. Moreover, there is marked variability in ADR between endoscopists^[52-55] in which estimates have ranged from 7% to 44%^[52-55]. In a 2010 study that evaluated 186 endoscopists alongside 45026 patients (188788 person-years), ADR was significantly associated with the risk of interval cancer^[56]. In comparing ADR $< 20\%$ vs ADR $\geq 20\%$, the hazard ratios were > 10 for interval CRC. In a 2014 study of 136 endoscopists, it was determined that a 1% increase in ADR was associated with a 3% decrease in risk of CRC^[57]. The aforementioned evidence underscores the importance of ADR and reinforces its value as an important CSPY quality indicator. This has been endorsed by multiple societies^[58,59], with the American Society for Gastrointestinal Endoscopy (ASGE) recommending an ADR of $\geq 25\%$ ($\geq 30\%$ in men, $\geq 20\%$ in women) among asymptomatic average-risk individuals^[59].

Another limitation of CSPY pertains to proximal CRC (lesions proximal to the splenic flexure)^[42,45,60]. Proximal lesions are different from those that are distal in many ways. For instance, proximal masses can be missed secondary to inadequate bowel preparation^[59], complicated by incomplete CSPY^[61], and prone to suboptimally removed lesions. Further, CRC tumorigenesis between proximal and distal lesions can be different^[51,62]. In a 2009 study of 10292 patients who died of CRC and 51460 matched-controls, it was shown that receipt of a complete CSPY was significantly associated with less death secondary to left-sided CRC; however, a similar relationship was not found for right-sided CRC^[42]. In a subsequent 2010 study, amongst 54803 patients who underwent index CSPY, a 29% reduction in overall CRC mortality was identified^[45]. However, there was no reduction in CRC

mortality for proximal CRC. In another 2010 study that investigated 3287 individuals undergoing screening CSPY, a preceding CSPY within 10 years decreased the prevalence of advanced colorectal neoplasms, but this had little, if any, effect on reducing the prevalence of proximal advanced colorectal neoplasms^[60].

CSPY - adverse events

Serious adverse events secondary to CSPY are well-recognized. Although they are relatively infrequent, they remain a concern, particularly in settings where CSPYs are performed outside current recommendations for screening and surveillance^[63]. It is estimated that the risk of serious adverse events, specifically perforation and post-polypectomy bleeding, is approximately 1 per 1000 CSPYs^[64,65].

Perforation is the most serious adverse event associated with CSPY. In a 2008 study^[64], using administrative-level data among 97091 individuals who underwent outpatient CSPY, the rate of perforation was 0.85/1000 and the rate of death was 0.074/1000. Factors associated with increased risk of perforation were older age, male sex, polypectomy, and having the CSPY performed by a low-volume endoscopist. These findings were supported by a 2009 study^[65] of 53220 CSPYs performed in a Medicare population, highlighting a perforation rate of 0.6/1000. In terms of post-polypectomy bleeding, two studies described rates to be 1.64/1000^[64] and 6.4/1000^[65] respectively. Similar risk factors were observed to increase the likelihood of post-polypectomy bleeding, including older age, male sex, polypectomy and having the CSPY performed by a low-volume endoscopist^[64]. In addition, large polyp size, proximal location, and use of anti-coagulation^[66] worsened the risk.

In the recent ASGE quality indicators for colonoscopy guidelines, performance targets for perforation have been set at $< 1:500$ (all examinations), $< 1:1000$ (screening examinations) and $< 1\%$ for post-polypectomy bleeding. As per the ASGE, it was recommended that rates exceeding these recommendations should prompt a review of CSPY technique of the endoscopist in question.

ONGOING DISPARITIES

Disparities in CRC screening are an unfortunate reality. With an estimated 49190 deaths due to CRC within the United States in 2016, a disproportionate burden will occur within marginalized populations^[1]. People of specific ethnic minorities, immigrants, and those in lower socioeconomic backgrounds are less likely to receive screening^[24,67]. For United States and Canada to successfully achieve their respective screening targets, these disparities need to be addressed and minimized.

Ethnic and immigrant minorities

Ethnic minorities have been found to have lower CRC screening uptake. This is apparent across multiple ethnicities including African Americans^[68], Hispanics^[1],

Asians^[69], and Indigenous populations (American Indians and Alaska Natives within the United States; First Nations and Metis within Canada)^[70]. Multiple factors have been implicated as drivers of this disparity. A lack of knowledge concerning CRC and poor awareness of the concept and importance of CRC screening are key drivers, but fear of discomfort, anxiety of waiting for results, and general mistrust of healthcare professionals have been cited in the literature as reasons why selected patient subgroups fail to seek screening^[71-73]. The latter is especially concerning since it can lead to decreased physician engagement and poor continuity of care. Similar to other factors associated with treatment disparities, ethnic populations may also be more vulnerable to the effects of lower socioeconomic status^[74], a lack of health insurance^[75] and barriers in communication^[75]. Lastly, differences in CRC tumorigenesis^[76] may play a further role whereby a CRC diagnosis affects patients at younger ages when screening is generally not recommended. Likewise, immigrants^[75,77] represent another subgroup of patients who are less likely to undergo CRC screening. In a 2013 study^[75] that compared United States-born citizens to non-citizens who participated in the California Health Interview Survey, 67% vs 46% underwent CRC screening. Potential factors contributing to this disparity were living in rural areas, a lack of health insurance, and not being proficient in the English language.

Socioeconomic status

There is notable interplay between drivers of disparity and socioeconomic status. Individuals with low socioeconomic status have poorer uptake of CRC screening^[78,79]. In a 2009 study assessing Medicare enrollees ages 65 to 80 years, individuals less educated or belonging to low-income groups were less likely to undergo CRC screening^[80]. Unfortunately, even when the cost of CRC screening is alleviated, disparity still persists^[81]. In England, the Bowel Cancer Screening Program does not pose any financial costs to participants because it is operated by the National Health Service since 2006. Despite this fact, there were marked variations in CRC screening uptake among the first 2.1 million participants. In the least socially and economically deprived areas, uptake was highest at 61% whereas uptake was lowest at 35% in the most deficient areas^[81,82]. To a large extent, the ongoing drivers of these differences remain unclear within this subgroup; however, it is postulated that stress, low social supports, competing life demands, and literacy are strongly implicated^[72,83] and thus challenging to mitigate systematically.

CONCLUSION

In conclusion, while CRC screening has clearly proven its ability to reduce the incidence and mortality of CRC, there are critical areas requiring further improvements.

For the benefits of CRC screening to materialize, increased uptake and retention during subsequent screening cycles is paramount. Additionally, refinement of current screening test performance measures along with optimization of CSPPY quality to prevent procedure-related adverse events are essential as an increasing number of jurisdictions continue to introduce and implement programmatic CRC screening. Lastly, effective interventions that target and consider the unique needs of the marginalized subsets of our population is crucial if our goal is to enhance outcomes for all. With universal adoption of programmatic CRC screening and continued advances in screening modalities, it is our hope that CRC screening can provide meaningful morbidity and mortality benefits to patients in an equitable and cost-effective manner.

REFERENCES

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]
- 2 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 3 Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1893-1907 [PMID: 20647400 DOI: 10.1158/1055-9965.EPI-10-0437]
- 4 Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009; **59**: 366-378 [PMID: 19897840 DOI: 10.3322/caac.20038]
- 5 Goede SL, Kuntz KM, van Ballegooijen M, Knudsen AB, Lansdorp-Vogelaar I, Tangka FK, Howard DH, Chin J, Zaubler AG, Seeff LC. Cost-Savings to Medicare From Pre-Medicare Colorectal Cancer Screening. *Med Care* 2015; **53**: 630-638 [PMID: 26067885 DOI: 10.1097/MLR.0000000000000380]
- 6 Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; **348**: 1467-1471 [PMID: 8942774 DOI: 10.1016/S0140-6736(96)03430-7]
- 7 Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; **348**: 1472-1477 [PMID: 8942775 DOI: 10.1016/S0140-6736(96)03386-7]
- 8 Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, Snover DC, Schuman LM. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000; **343**: 1603-1607 [PMID: 11096167 DOI: 10.1056/NEJM200011303432203]
- 9 Jørgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut* 2002; **50**: 29-32 [PMID: 11772963 DOI: 10.1136/gut.50.1.29]
- 10 Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D, Dassonville F, Bonithon-Kopp C. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 2004; **126**: 1674-1680 [PMID: 15188160 DOI: 10.1053/j.gastro.2004.02.018]
- 11 Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; **375**: 1624-1633 [PMID: 20430429 DOI: 10.1016/S0140-6736(10)60551-X]
- 12 Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T,

- Laiyemo AO, Bresalier R, Andriole GL, Buys SS, Crawford ED, Fouad MN, Isaacs C, Johnson CC, Reding DJ, O'Brien B, Carrick DM, Wright P, Riley TL, Purdue MP, Izmirlian G, Kramer BS, Miller AB, Gohagan JK, Prorok PC, Berg CD. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med* 2012; **366**: 2345-2357 [PMID: 22612596 DOI: 10.1056/NEJMoa1114635]
- 13 **Shaukat A**, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, Church TR. Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013; **369**: 1106-1114 [PMID: 24047060 DOI: 10.1056/NEJMoa1300720]
- 14 **Telford JJ**, Levy AR, Sambrook JC, Zou D, Enns RA. The cost-effectiveness of screening for colorectal cancer. *CMAJ* 2010; **182**: 1307-1313 [PMID: 20624866 DOI: 10.1503/cmaj.090845]
- 15 **Heitman SJ**, Hilsden RJ, Au F, Dowden S, Manns BJ. Colorectal cancer screening for average-risk North Americans: an economic evaluation. *PLoS Med* 2010; **7**: e1000370 [PMID: 21124887 DOI: 10.1371/journal.pmed.1000370]
- 16 **Coldman AJ**, Phillips N, Brisson J, Flanagan W, Wolfson M, Nadeau C, Fitzgerald N, Miller AB. Using the Cancer Risk Management Model to evaluate colorectal cancer screening options for Canada. *Curr Oncol* 2015; **22**: e41-e50 [PMID: 25908920 DOI: 10.3747/co.22.2013]
- 17 **Wilschut JA**, Hol L, Dekker E, Jansen JB, Van Leerdam ME, Lansdorp-Vogelaar I, Kuipers EJ, Habbema JD, Van Ballegooijen M. Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. *Gastroenterology* 2011; **141**: 1648-55.e1 [PMID: 21784045 DOI: 10.1053/j.gastro.2011.07.020]
- 18 **Lansdorp-Vogelaar I**, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. *J Natl Cancer Inst* 2009; **101**: 1412-1422 [PMID: 19779203 DOI: 10.1093/jnci/djp319]
- 19 **Leddin DJ**, Enns R, Hilsden R, Plourde V, Rabeneck L, Sadowski DC, Signh H. Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010. *Can J Gastroenterol* 2010; **24**: 705-714 [PMID: 21165377 DOI: 10.1155/2010/683171]
- 20 **Rex DK**, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009; **104**: 739-750 [PMID: 19240699 DOI: 10.1038/ajg.2009.104]
- 21 **Bacchus CM**, Dunfield L, Gorber SC, Holmes NM, Birtwhistle R, Dickinson JA, Lewin G, Singh H, Klarenbach S, Mai V, Tonelli M. Recommendations on screening for colorectal cancer in primary care. *CMAJ* 2016; **188**: 340-348 [PMID: 26903355 DOI: 10.1503/cmaj.151125]
- 22 **Bibbins-Domingo K**, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FA, Gillman MW, Harper DM, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Owens DK, Phillips WR, Phipps MG, Pignone MP, Siu AL. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; **315**: 2564-2575 [PMID: 27304597 DOI: 10.1001/jama.2016.5989]
- 23 **Levin B**, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; **134**: 1570-1595 [PMID: 18384785 DOI: 10.1053/j.gastro.2008.02.002]
- 24 **Centers for Disease Control and Prevention (CDC)**. Cancer screening - United States, 2010. *MMWR Morb Mortal Wkly Rep* 2012; **61**: 41-45 [PMID: 22278157]
- 25 **Singh H**, Bernstein CN, Samadder JN, Ahmed R. Screening rates for colorectal cancer in Canada: a cross-sectional study. *CMAJ Open* 2015; **3**: E149-E157 [PMID: 26389092 DOI: 10.9778/cmajo.20140073]
- 26 **Doubeni CA**, Corley DA, Zauber AG. Colorectal Cancer Health Disparities and the Role of US Law and Health Policy. *Gastroenterology* 2016; **150**: 1052-1055 [PMID: 27016715 DOI: 10.1053/j.gastro.2016.03.012]
- 27 **Canadian Partnership Against Cancer**. Colorectal Cancer Screening in Canada: Program Performance Results Report, January 2009 - December 2011. Toronto: Canadian Partnership Against Cancer, 2013
- 28 **Centers for Disease Control and Prevention (CDC)**. Vital signs: colorectal cancer screening test use--United States, 2012. *MMWR Morb Mortal Wkly Rep* 2013; **62**: 881-888 [PMID: 24196665]
- 29 **Carlson CM**, Kirby KA, Casadei MA, Partin MR, Kistler CE, Walter LC. Lack of follow-up after fecal occult blood testing in older adults: inappropriate screening or failure to follow up? *Arch Intern Med* 2011; **171**: 249-256 [PMID: 20937917 DOI: 10.1001/archinternmed.2010.372]
- 30 **Fenton JJ**, Elmore JG, Buist DS, Reid RJ, Tancredi DJ, Baldwin LM. Longitudinal adherence with fecal occult blood test screening in community practice. *Ann Fam Med* 2010; **8**: 397-401 [PMID: 20843880 DOI: 10.1370/afm.1133]
- 31 **Gellad ZF**, Stechuchak KM, Fisher DA, Olsen MK, McDuffie JR, Ostbye T, Yancy WS. Longitudinal adherence to fecal occult blood testing impacts colorectal cancer screening quality. *Am J Gastroenterol* 2011; **106**: 1125-1134 [PMID: 21304501 DOI: 10.1038/ajg.2011.11]
- 32 **Denters MJ**, Deutekom M, Bossuyt PM, Stroobants AK, Fockens P, Dekker E. Lower risk of advanced neoplasia among patients with a previous negative result from a fecal test for colorectal cancer. *Gastroenterology* 2012; **142**: 497-504 [PMID: 22108194 DOI: 10.1053/j.gastro.2011.11.024]
- 33 **van Roon AH**, Goede SL, van Ballegooijen M, van Vuuren AJ, Looman CW, Biermann K, Reijerink JC, Mannetje H, van der Togt AC, Habbema JD, van Leerdam ME, Kuipers EJ. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. *Gut* 2013; **62**: 409-415 [PMID: 22387523 DOI: 10.1136/gutjnl-2011-301583]
- 34 **Crotta S**, Segnan N, Paganin S, Dagnes B, Rosset R, Senore C. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. *Clin Gastroenterol Hepatol* 2012; **10**: 633-638 [PMID: 22426085 DOI: 10.1016/j.cgh.2012.02.030]
- 35 **van Rossum LG**, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, Verbeek AL, Jansen JB, Dekker E. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008; **135**: 82-90 [PMID: 18482589 DOI: 10.1053/j.gastro.2008.03.040]
- 36 **Park DI**, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, Han DS. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol* 2010; **105**: 2017-2025 [PMID: 20502450 DOI: 10.1038/ajg.2010.179]
- 37 **Halloran SP**, Launoy G, Zappa M. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Faecal occult blood testing. *Endoscopy* 2012; **44** Suppl 3: SE65-SE87 [PMID: 23012123]
- 38 **Lee JK**, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014; **160**: 171 [PMID: 24658694 DOI: 10.7326/M13-1484]
- 39 **Chiang TH**, Chuang SL, Chen SL, Chiu HM, Yen AM, Chiu SY, Fann JC, Chou CK, Lee YC, Wu MS, Chen HH. Difference in performance of fecal immunochemical tests with the same hemoglobin cutoff concentration in a nationwide colorectal cancer screening program. *Gastroenterology* 2014; **147**: 1317-1326 [PMID: 25200099 DOI: 10.1053/j.gastro.2014.08.043]
- 40 **van Rossum LG**, van Rijn AF, van Oijen MG, Fockens P, Laheij RJ, Verbeek AL, Jansen JB, Dekker E. False negative fecal occult blood tests due to delayed sample return in colorectal cancer screening. *Int J Cancer* 2009; **125**: 746-750 [PMID: 19408302 DOI: 10.1002/ijc.24458]

- 41 **Grazzini G**, Ventura L, Zappa M, Ciatto S, Confortini M, Rapi S, Rubeca T, Visioli CB, Halloran SP. Influence of seasonal variations in ambient temperatures on performance of immunochemical faecal occult blood test for colorectal cancer screening: observational study from the Florence district. *Gut* 2010; **59**: 1511-1515 [PMID: 20603498 DOI: 10.1136/gut.2009.200873]
- 42 **Baxter NN**, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; **150**: 1-8 [PMID: 19075198 DOI: 10.7326/0003-4819-150-1-200901060-00306]
- 43 **Lakoff J**, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. *Clin Gastroenterol Hepatol* 2008; **6**: 1117-1121; quiz 1064 [PMID: 18691942 DOI: 10.1016/j.cgh.2008.05.016]
- 44 **Singh H**, Nugent Z, Mahmud SM, Demers AA, Bernstein CN. Predictors of colorectal cancer after negative colonoscopy: a population-based study. *Am J Gastroenterol* 2010; **105**: 663-673; quiz 674 [PMID: 19904239 DOI: 10.1038/ajg.2009.650]
- 45 **Singh H**, Nugent Z, Demers AA, Kliever EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010; **139**: 1128-1137 [PMID: 20600026 DOI: 10.1053/j.gastro.2010.06.052]
- 46 **Brenner H**, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med* 2011; **154**: 22-30 [PMID: 21200035 DOI: 10.7326/0003-4819-154-1-201101040-00004]
- 47 **Pohl H**, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. *Clin Gastroenterol Hepatol* 2010; **8**: 858-864 [PMID: 20655393 DOI: 10.1016/j.cgh.2010.06.028]
- 48 **van Rijn JC**, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol* 2006; **101**: 343-350 [PMID: 16454841 DOI: 10.1111/j.1572-0241.2006.00390.x]
- 49 **Pabby A**, Schoen RE, Weissfeld JL, Burt R, Kikendall JW, Lance P, Shike M, Lanza E, Schatzkin A. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. *Gastrointest Endosc* 2005; **61**: 385-391 [PMID: 15758908 DOI: 10.1016/S0016-5107(04)02765-8]
- 50 **Farrar WD**, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. *Clin Gastroenterol Hepatol* 2006; **4**: 1259-1264 [PMID: 16996804 DOI: 10.1016/j.cgh.2006.07.012]
- 51 **Arain MA**, Sawhney M, Sheikh S, Anway R, Thyagarajan B, Bond JH, Shaikat A. CIMP status of interval colon cancers: another piece to the puzzle. *Am J Gastroenterol* 2010; **105**: 1189-1195 [PMID: 20010923 DOI: 10.1038/ajg.2009.699]
- 52 **Barclay RL**, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med* 2006; **355**: 2533-2541 [PMID: 17167136 DOI: 10.1056/NEJMoa055498]
- 53 **Chen SC**, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. *Am J Gastroenterol* 2007; **102**: 856-861 [PMID: 17222317 DOI: 10.1111/j.1572-0241.2006.01054.x]
- 54 **Shaikat A**, Oancea C, Bond JH, Church TR, Allen JI. Variation in detection of adenomas and polyps by colonoscopy and change over time with a performance improvement program. *Clin Gastroenterol Hepatol* 2009; **7**: 1335-1340 [PMID: 19665583 DOI: 10.1016/j.cgh.2009.07.027]
- 55 **Imperiale TF**, Glowinski EA, Juliar BE, Azzouz F, Ransohoff DF. Variation in polyp detection rates at screening colonoscopy. *Gastrointest Endosc* 2009; **69**: 1288-1295 [PMID: 19481649 DOI: 10.1016/j.gie.2007.11.043]
- 56 **Kaminski MF**, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010; **362**: 1795-1803 [PMID: 20463339 DOI: 10.1056/NEJMoa0907667]
- 57 **Corley DA**, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**: 1298-1306 [PMID: 24693890 DOI: 10.1056/NEJMoa1309086]
- 58 **Rex DK**, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006; **101**: 873-885 [PMID: 16635231 DOI: 10.1016/j.gie.2006.02.021]
- 59 **Rex DK**, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, Lieb JG, Park WG, Rizk MK, Sawhney MS, Shaheen NJ, Wani S, Weinberg DS. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; **81**: 31-53 [PMID: 25480100 DOI: 10.1016/j.gie.2014.07.058]
- 60 **Brenner H**, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst* 2010; **102**: 89-95 [PMID: 20042716 DOI: 10.1093/jnci/djp436]
- 61 **Baxter NN**, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. *Gastroenterology* 2011; **140**: 65-72 [PMID: 20854818 DOI: 10.1053/j.gastro.2010.09.006]
- 62 **Azzoni C**, Bottarelli L, Campanini N, Di Cola G, Bader G, Mazzeo A, Salvemini C, Morari S, Di Mauro D, Donadei E, Roncoroni L, Bordini C, Sarli L. Distinct molecular patterns based on proximal and distal sporadic colorectal cancer: arguments for different mechanisms in the tumorigenesis. *Int J Colorectal Dis* 2007; **22**: 115-126 [PMID: 17021745 DOI: 10.1007/s00384-006-0093-x]
- 63 **Goodwin JS**, Singh A, Reddy N, Riall TS, Kuo YF. Overuse of screening colonoscopy in the Medicare population. *Arch Intern Med* 2011; **171**: 1335-1343 [PMID: 21555653 DOI: 10.1001/archinternmed.2011.212]
- 64 **Rabeneck L**, Paszat LF, Hilsden RJ, Saskin R, Leddin D, Grunfeld E, Wai E, Goldwasser M, Sutradhar R, Stukel TA. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. *Gastroenterology* 2008; **135**: 1899-1906, 1906.e1 [PMID: 18938166 DOI: 10.1053/j.gastro.2008.08.058]
- 65 **Warren JL**, Klabunde CN, Mariotto AB, Meekins A, Topor M, Brown ML, Ransohoff DF. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med* 2009; **150**: 849-857, W152 [PMID: 19528563 DOI: 10.7326/0003-4819-150-12-200906160-00008]
- 66 **Singh M**, Mehta N, Murthy UK, Kaul V, Arif A, Newman N. Postpolypectomy bleeding in patients undergoing colonoscopy on uninterrupted clopidogrel therapy. *Gastrointest Endosc* 2010; **71**: 998-1005 [PMID: 20226452 DOI: 10.1016/j.gie.2009.11.022]
- 67 **Meissner HI**, Breen N, Klabunde CN, Vernon SW. Patterns of colorectal cancer screening uptake among men and women in the United States. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 389-394 [PMID: 16492934 DOI: 10.1158/1055-9965.EPI-05-0678]
- 68 **Lai Y**, Wang C, Civan JM, Palazzo JP, Ye Z, Hyslop T, Lin J, Myers RE, Li B, Jiang B, Sama A, Xing J, Yang H. Effects of Cancer Stage and Treatment Differences on Racial Disparities in Survival From Colon Cancer: A United States Population-Based Study. *Gastroenterology* 2016; **150**: 1135-1146 [PMID: 26836586 DOI: 10.1053/j.gastro.2016.01.030]
- 69 **Homayoon B**, Shahidi NC, Cheung WY. Impact of asian ethnicity on colorectal cancer screening: a population-based analysis. *Am J Clin Oncol* 2013; **36**: 167-173 [PMID: 22441340 DOI: 10.1097/COC.0b013e3182439068]
- 70 **Steele CB**, Cardinez CJ, Richardson LC, Tom-Orme L, Shaw KM. Surveillance for health behaviors of American Indians and Alaska Natives-findings from the behavioral risk factor surveillance system, 2000-2006. *Cancer* 2008; **113**: 1131-1141 [PMID: 18720374 DOI: 10.1002/cncr.23727]
- 71 **Robb K**, Wardle J, Stubbings S, Ramirez A, Austoker J, Macleod U, Hiom S, Waller J. Ethnic disparities in knowledge of cancer screening programmes in the UK. *J Med Screen* 2010; **17**: 125-131 [PMID: 20956722 DOI: 10.1258/jms.2010.009112]

- 72 **von Wagner C**, Good A, Whitaker KL, Wardle J. Psychosocial determinants of socioeconomic inequalities in cancer screening participation: a conceptual framework. *Epidemiol Rev* 2011; **33**: 135-147 [PMID: 21586673 DOI: 10.1093/epirev/mxq018]
- 73 **Born W**, Engelman K, Greiner KA, Bhattacharya SB, Hall S, Hou Q, Ahluwalia JS. Colorectal cancer screening, perceived discrimination, and low-income and trust in doctors: a survey of minority patients. *BMC Public Health* 2009; **9**: 363 [PMID: 19781085 DOI: 10.1186/1471-2458-9-363]
- 74 **Doubeni CA**, Jambaulikar GD, Fouayzi H, Robinson SB, Gunter MJ, Field TS, Roblin DW, Fletcher RH. Neighborhood socioeconomic status and use of colonoscopy in an insured population--a retrospective cohort study. *PLoS One* 2012; **7**: e36392 [PMID: 22567154 DOI: 10.1371/journal.pone.0036392]
- 75 **Shahidi NC**, Homayoon B, Cheung WY. Factors associated with suboptimal colorectal cancer screening in US immigrants. *Am J Clin Oncol* 2013; **36**: 381-387 [PMID: 22643567 DOI: 10.1097/COC.0b013e318248da66]
- 76 **Shavers VL**. Racial/ethnic variation in the anatomic subsite location of in situ and invasive cancers of the colon. *J Natl Med Assoc* 2007; **99**: 733-748 [PMID: 17668639]
- 77 **Lee HY**, Im H. Colorectal cancer screening among Korean American immigrants: unraveling the influence of culture. *J Health Care Poor Underserved* 2013; **24**: 579-598 [PMID: 23728030 DOI: 10.1353/hpu.2013.0087]
- 78 **Seeff LC**, Nadel MR, Klabunde CN, Thompson T, Shapiro JA, Vernon SW, Coates RJ. Patterns and predictors of colorectal cancer test use in the adult U.S. population. *Cancer* 2004; **100**: 2093-2103 [PMID: 15139050 DOI: 10.1002/cncr.20276]
- 79 **Ioannou GN**, Chapko MK, Dominitz JA. Predictors of colorectal cancer screening participation in the United States. *Am J Gastroenterol* 2003; **98**: 2082-2091 [PMID: 14499792 DOI: 10.1111/j.1572-0241.2003.07574.x]
- 80 **Doubeni CA**, Laiyemo AO, Reed G, Field TS, Fletcher RH. Socioeconomic and racial patterns of colorectal cancer screening among Medicare enrollees in 2000 to 2005. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2170-2175 [PMID: 19622721 DOI: 10.1158/1055-9965.EPI-09-0104]
- 81 **Wardle J**, von Wagner C, Kralj-Hans I, Halloran SP, Smith SG, McGregor LM, Vart G, Howe R, Snowball J, Handley G, Logan RF, Rainbow S, Smith S, Thomas MC, Counsell N, Morris S, Duffy SW, Hackshaw A, Moss S, Atkin W, Raine R. Effects of evidence-based strategies to reduce the socioeconomic gradient of uptake in the English NHS Bowel Cancer Screening Programme (ASCEND): four cluster-randomised controlled trials. *Lancet* 2016; **387**: 751-759 [PMID: 26680217 DOI: 10.1016/S0140-6736(15)01154-X]
- 82 **Logan RF**, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut* 2012; **61**: 1439-1446 [PMID: 22156981 DOI: 10.1136/gutjnl-2011-300843]
- 83 **Lo SH**, Waller J, Vrinten C, Kobayashi L, von Wagner C. Social Cognitive Mediators of Sociodemographic Differences in Colorectal Cancer Screening Uptake. *Biomed Res Int* 2015; **2015**: 165074 [PMID: 26504782 DOI: 10.1155/2015/165074]

P- Reviewer: Ferreiro-Iglesias R **S- Editor:** Qi Y
L- Editor: A **E- Editor:** Wu HL



Evidence based review of the impact of image enhanced endoscopy in the diagnosis of gastric disorders

Ikram Hussain, Tiing Leong Ang

Ikram Hussain, Tiing Leong Ang, Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore 529889, Singapore

Author contributions: Both authors contributed equally to the writing of this manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Tiing Leong Ang, MBBS, MRCP (UK), FRCP Edin, Associate Professor, Department of Gastroenterology and Hepatology, Changi General Hospital, 2 Simei Street 3, Singapore 529889, Singapore. tiing_leong_ang@cgh.com.sg
Telephone: +65-67888833
Fax: +65-67616202

Received: March 29, 2016
Peer-review started: April 1, 2016
First decision: June 12, 2016
Revised: July 28, 2016
Accepted: September 21, 2016
Article in press: September 22, 2016
Published online: December 16, 2016

Abstract

Gastric cancer is the third most common cause of cancer-related death. Advanced stages of gastric cancers

generally have grim prognosis. But, good prognosis can be achieved if such cancers are detected, diagnosed and resected at early stages. However, early gastric cancers and its precursors often produce only subtle mucosal changes and therefore quite commonly remain elusive at the conventional examination with white light endoscopy. Image-enhanced endoscopy makes mucosal lesions more conspicuous and can therefore potentially yield earlier and more accurate diagnoses. Recent years have seen growing work of research in support of various types of image enhanced endoscopy (IEE) techniques (*e.g.*, dye-chromoendoscopy; magnification endoscopy; narrow-band imaging; flexible spectral imaging color enhancement; and I-SCAN) for a variety of gastric pathologies. In this review, we will examine the evidence for the utilization of various IEE techniques in the diagnosis of gastric disorders.

Key words: Gastritis; Gastric cancer; Image enhanced endoscopy; Chromoendoscopy; Narrow band imaging

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Image-enhanced endoscopy is useful for an accurate real-time diagnosis of a variety of gastric diseases. But, good prognosis can be achieved if such cancers are detected, diagnosed and resected at early stages. However, early gastric cancers and its precursors often produce only subtle mucosal changes and therefore quite commonly remain elusive at the conventional examination with white light endoscopy. Image-enhanced endoscopy makes mucosal lesions more conspicuous and can therefore potentially yield earlier and more accurate diagnoses. Recent years have seen growing work of research in support of various types of image enhanced endoscopy (IEE) techniques (*e.g.*, dye-chromoendoscopy; magnification endoscopy; narrow-band imaging; flexible spectral imaging color enhancement; and I-SCAN) for a variety of gastric

pathologies. In this review, we will examine the evidence for the utilization of various IEE techniques in the diagnosis of gastric disorders.

Hussain I, Ang TL. Evidence based review of the impact of image enhanced endoscopy in the diagnosis of gastric disorders. *World J Gastrointest Endosc* 2016; 8(20): 741-755 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/741.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.741>

INTRODUCTION

In 1957, Hirschowitz *et al*^[1] pioneered the use of flexible endoscope to visualize the gastrointestinal (GI) tract. These early fibreoptic endoscopes were cumbersome to use and had dim views of the GI tract. Diagnosis of frank gastric pathologies (*e.g.*, ulcer or malignant tumor) was straightforward. However, subtle abnormalities in the mucosa often got missed or misdiagnosed. This is especially relevant in stomach where early and confident detection of subtle pre-malignant features has potential to save the organ and life of a patient^[2].

Recent years have witnessed tremendous progress in various novel endoscopic techniques. These techniques claim easy and confident detection, diagnosis and assistance in endoscopic resection of gastric subtle mucosal abnormalities. Simplistically, these techniques make a GI mucosal lesion appear more conspicuous. In a consensus methodological classification (in year 2008), such techniques were classified into five categories by Tajiri *et al*^[3]: (1) conventional white light endoscopy (WLE); (2) image-enhanced endoscopy (IEE); (3) magnification endoscopy (ME); (4) microscopic endoscopy; and (5) tomographic. As these technologies offer different advantages and disadvantages, some have become indispensable tools inside every endoscopy room while others remain research tools.

Like in any disease, the endoscopic assessment of a mucosal abnormality also follows the logical sequence comprising "identification (or screening)", "characterization", "confirmation" by a gold standard (*e.g.*, histology), and finally "treatment". Explicit identification or screening of significant lesions is important to achieve low false miss-rates during endoscopy. At the same time, an accurate characterization, before histological assessment, is equally crucial to enable endoscopic resection for a significant lesion while leaving behind benign findings. Various IEE techniques have been studied for "identification" and "characterization" of gastric pathologies. In this review, we will study various IEE techniques and review their respective evidences for utilization in stomach.

METHODOLOGY

Publications in English language, limited to humans,

were searched in the databases of "PUBMED/MEDLINE", "the Cochrane Library", and "Google Scholar". The studies were searched between January 1995 and January 2016. Only studies published in peer-reviewed journals were taken into consideration. Relevant studies from the references of selected articles were also screened. The search keywords were: "Endoscopy, digestive system", "Narrow band", "Narrow-band imaging (NBI)", "White light", "Image enhance", "Image enhanced", "Endoscopy/methods", "Gastroscopy/methods", "White light endoscopy", "Chromoendoscopy (CE)", "Blue laser", "Fujinon intelligent", "Flexible spectral imaging color enhancement (FICE)", "I-SCAN", "Methylene blue", "Indigo carmine", "Acetic acid", "Dye endoscopy", "Helicobacter", "Gastric atrophy", "atrophic gastritis (AG)", "Intestinal metaplasia", "Gastric tumor", "Gastric cancer", "Stomach cancer", and "Gastric neoplasm". The two sets of keywords were combined individually. The studies were searched as free texts and as Medical Subject Headings terms.

WHITE-LIGHT ENDOSCOPY

The last decades of 20th century saw the advent of video-endoscopes equipped with charge-coupled devices (CCDs). These CCD chips produced image signal of 100000 to 400000 pixels, allowing clear images of GI mucosa^[4]. Each pixel represents a unit of sample image, and therefore higher pixel-density meant greater spatial resolution and sharper images. Although good in detecting significant lesions in the GI tract, these standard definition (SD) video-endoscopes still had high miss-rates for subtle mucosal abnormalities.

The currently available high-definition (HD) endoscopes produce images with resolution of up to a million pixels and can magnify the mucosal image by 30- to 35 fold. These images can be further magnified optically by having an in-built motor-driven optical lens at the tip of endoscope. The lens can be focused upon an area-of-interest to provide a genuinely close-up image without sacrificing any pixel or image resolution. Contrary to the electronic magnification, the optical zoom produces a truly magnified (up to 150-times) and sharp image. Since the lens needs to be focused 2-3 mm away from the lesion, it is almost essential to have short hood or cap at the tip of magnifying-endoscope to maintain the focal length. These advances in endoscopic resolution have accompanied the considerable improvements in endoscope processors, which can convert tremendous amount of photonic data into a high-definition image without many artefacts. To get such HD images, it is imperative to have a compatible set of HD endoscopes, processor, monitors and transmission cables. Figure 1 illustrates cases of EGC detected by HD-WLE. They appear as a mildly depressed lesion with discoloration compared to adjacent normal mucosa.

Very few studies have directly compared HD-endoscopy with SD-endoscopy. For example in colon, these HD endoscopes showed marginal benefit in a meta-analysis

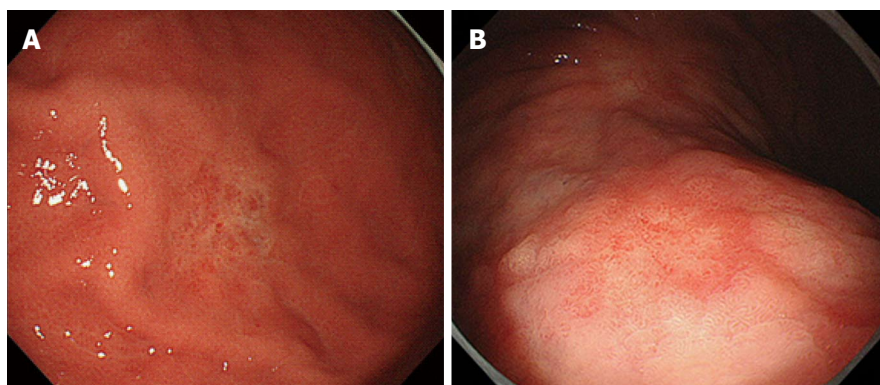


Figure 1 High definition white light endoscopy view. A: A depressed lesion with mucosal discoloration due to early gastric cancer; B: High definition white light endoscopy view of early gastric cancer.

with a number needed to treat of 25 to identify one additional polyp or adenoma^[5]. Such objective data are not available for the upper GI tract but the expectation is similar.

WLE WITH MAGNIFICATION

WLE with magnification has potential to provide detailed mucosal views. In 1978, Sakaki *et al.*^[6] described classification of the stomach mucosa according to the “minute gastric mucosal patterns”. Since 1999, true magnifying endoscopes (for example, GIF-Q240Z by Olympus Corporation or EG-450ZH by Fujinon) were introduced which could optically zoom the image by up to 80 times. Such spatially resolved and magnified images revealed surface and microvascular patterns of stomach mucosa in great details. These studies are summarized in Table 1.

Appearance of normal gastric mucosa with “only ME”

Magnified views of normal gastric mucosa have been classified and named differently by various authors. In a preliminary study in 2001, Yao *et al.*^[7] described the magnifying views of antrum as coil-shaped network with rare collecting venules, and of corpus as honey-comb pattern with interspersed collecting venules. Absence of sub-epithelial capillary network (SECN) along with proliferation of irregular microvessels was observed in differentiated early gastric cancer (EGC). Similarly, Yagi *et al.*^[8] studied the mucosal patterns in normal stomach without *Helicobacter pylori* (*H. pylori*) infection. The study concluded that the presence of regular arrangement of collecting venules (RAC) could predict the absence of *H. pylori* gastritis with 95.5% accuracy. Moreover, the presence of well-defined ridge pattern (wDRP) in antrum had 100% specificity for the absence of *H. pylori* gastritis, although its sensitivity was relatively low at 54.5%. In another study, the ME views of corpus were grouped into four types (Z-0 to Z-3) and almost all patients without *H. pylori* gastritis had Z-0 pattern^[9].

H. pylori assessment with “only ME”

Six prospective studies have reported the use of “only ME” in predicting the gastritis (especially *H. pylori* gastritis)^[8-13]. However, a variety of different mucosal classifications were used and proposed to correlate with *H. pylori* status. As mentioned in the earlier section, Yagi *et al.*^[8,9] correlated *H. pylori* status with RAC in corpus, wDRP in antrum and Z0-Z4 classification in corpus with good success. Based on the same Z0-Z4 classification, a group from Turkey showed superior results with *H. pylori* detection when compared with standard endoscopy^[10]. In another study, Anagnostopoulos *et al.*^[11] grouped ME views of corpus (GIF Q240-Z, 115 × magnifications) into four types with high inter-observer agreement. Their classification identified *H. pylori* gastritis with sensitivity and specificity of 100% and 92.7% respectively. Similarly, other authors have reported excellent results with other classifications.

Worldwide, *H. pylori* gastric infection is considered the primary carcinogen for development of gastric adenocarcinoma^[14]. Real-time diagnosis of *H. pylori* and other types of gastritis with ME may be beneficial in a sense that detection of such types of abnormal mucosal patterns may make an endoscopist more vigilant to the possibility of dysplastic gastric lesions. However it should be emphasized that there are inherent difficulties in interpretation of these subjective classifications and all studies have been done by experts. Moreover, given the widespread availability of relatively cheap, objective and sensitive tests to detect *H. pylori* gastritis (e.g., rapid urease test), routine utilization of ME alone for diagnosis of *H. pylori* should be undertaken with caution and biopsy based tests remain the standard for diagnosis.

Characterization of EGC with “only ME”

As the area of mucosal view is small with ME, its role for screening or identification of pre or early malignant lesions in stomach is limited. However, ME has a role in characterization of subtle gastric lesions which are detected by screening WLE. A variety of patterns have been described to differentiate EGC from benign

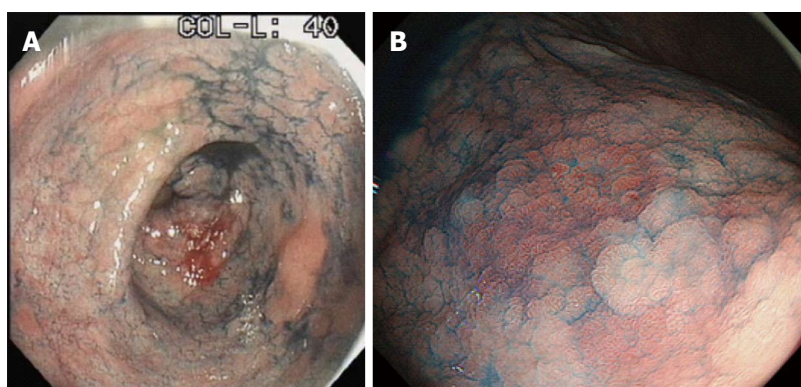


Figure 2 Mucosal irregularities and boundaries of a lesion. A: Gastric adenoma accentuated by indigo carmine; B: Early gastric cancer accentuated by indigo carmine.

Table 1 Summary of studies using magnification with white light

Use in stomach	Type of evidence	Description	Remarks
Identification of normal gastric mucosa	Descriptive study ^[7] ; Cross-sectional study with comparison to histology ^[8]	Normal corpus: Regular honeycomb pattern Normal antrum: Coil-shaped network with rare collecting venules	Different descriptive classifications have been used, but all emphasize on regular and uninterrupted mucosal and vascular patterns
Diagnosis of <i>H. pylori</i> gastritis	Six prospective studies with histology as the comparator ^[8-13]	High sensitivities and specificities for diagnosis of <i>H. pylori</i>	Multiple and varied pattern classifications with different endoscopes. Inherent subjectivity in classifications is an issue
Characterization of EGC	Six prospective studies with histology as the comparator ^[15-20]	Better results as compared to the traditional white light endoscopy	Multiple classifications bring inherent subjectivity; the most prevalent classification is the “VS” classification ^[17] which describes: Differentiated EGC: Irregular microvessels with a demarcation line Undifferentiated EGC: Absent demarcation line and absent sub-epithelial capillary networks

H. pylori: *Helicobacter pylori*; EGC: Early gastric cancer.

gastric mucosa. A variety of patterns have also been described for characterization of differentiated EGC from undifferentiated EGC. There have been six prospective studies using ME-alone for characterization of EGC^[15-20]. In 2001, Tobita^[15] from Japan first described ME findings in 103 depressed gastric lesions (including 63 malignant lesions) using Fujinon, EG-410CR at $\times 60$ magnification. It was concluded that the findings of “irregular protrusion” and “minute vessels in amorphia” were specific for malignancy. However, the classification had inherent subjectivity as it was assessed by one expert and was not been validated externally. In another prospective study in 2002, Tajiri *et al.*^[16] compared WLE-examination with ME (Olympus, GIF-Q240Z) in 211 consecutive gastric lesions. The authors found 89 EGC (58 depressed-type, 31 elevated-type). Using their classification, the accuracy of ME-examination was significantly superior to WLE-examination for any type of small (≤ 1 cm) EGC. In the same year, Yao *et al.*^[17] proposed a classification of magnified views of gastric mucosa which subsequently became the most widely utilized classification in studies of ME with IEE techniques. The mucosa was classified based on “microvascular” and “microsurface” patterns,

later known as the “VS classification”. Non-cancerous mucosa were found to have regular appearances of SECN, all differentiated EGC had a demarcation line and irregular microvessels, while all undifferentiated EGC had absent demarcation line with absent or reduced SECN. In 2007, Yao *et al.*^[18] validated their classification on a larger sample. For characterization of EGC with ME, other authors have used varied classification with good results^[19,20].

Overall, the efficacy of ME-alone in the stomach has been studied by a few authors, mainly from Japan. The various uses of ME-alone in stomach are summarized in Table 1. However as will be discussed later, the majority of studies of ME in stomach have been performed in combination with other IEE techniques.

CONVENTIONAL CHROMOENDOSCOPY

Introduced in the 1990s, CE refers to spraying of harmless dyes to stain the mucosal surface. This is usually done after a preliminary inspection with WLE. The staining of surface makes subtle mucosal patterns more obvious. A variety of stains have been used in the GI tract and these are classified into three types



Figure 3 Gastric intestinal metaplasia highlighted by methylene blue.

based on their actions: Absorptive (or vital) stains, contrast stains, and reactive stains. Absorptive stains (e.g., Lugol's iodine, methylene blue) have property of differential absorption into different cell types, thus highlighting one type of tissue over other. For example, methylene blue is absorbed by cells of small intestine and colon, and therefore a stained focus in the stomach theoretically indicates IM. On the contrary, the contrast stains (e.g., indigo carmine) do not react with the cells, but accumulate in the pits and crevices of a mucosal lesion thus accentuating the surface pattern (or the topography), mucosal irregularities and boundaries of a lesion (Figure 2). The last category, the reactive stains (e.g., acetic acid, phenol red) change color by coming in contact with a particular protein on the surface. For example, Phenol red and Congo red are reactive stains which turn red in an alkaline gastric environment signalling infection with *H. pylori*.

CE can be performed in two ways: (1) pan-CE, which involves spraying the dye blindly and voluminously to screen for any abnormal areas; or (2) targeted staining, where a dye is sprayed over a lesion of interest to further characterize it. Several studies have attempted a variety of stains in the stomach, either alone or in combination, to identify, characterize and outline focal lesions (e.g., IM or EGC). CE is technically easy to perform and has shown significant advantages in detecting flat colorectal neoplasia and colitis-associated neoplasia^[21].

Use of acetic acid in stomach

Acetic acid causes a reversible and transient alteration in the tertiary structure of the cellular proteins which leads to temporary opacification of mucosal surface. This produces a vivid mucosal image with crypts turning brown while the intervening epithelial surface appearing white. While the non-cancerous mucosa changes into white, the dysplastic and cancerous cells remain unstained, producing a good contrast. After spray of acetic acid, the mucosal details are visualized with magnification. This combination of acetic acid instillation and ME is often termed as "Enhanced-magnification endoscopy (EME)", which allows visualization of villi and crypts. In 2005, Yagi *et al.*^[22] studied the value of EME in stomach in 45 patients. The mean duration

of whitening differed with each histologic type: Low-grade adenoma, 94 s; high-grade adenoma, 24.3 s; non-invasive carcinoma, 20.1 s; invasive intramucosal carcinoma, 3.5 s; and submucosal carcinoma or beyond, 2.5 s. Therefore, the acetic-acid with ME was useful in differentiating between neoplasia and non-neoplasia based on duration of whitening.

One year later in 2006, Tanaka *et al.*^[23] proposed a classification of EME findings in stomach based on forty seven consecutive patients, into five categories: Type I, small round pits; type II, slit-like pits; type III, gyrus and villous patterns; type IV, irregular arrangements and sizes; type V, destructive patterns. Elevated gastric carcinomas showed type III or IV patterns; while depressed carcinomas showed type IV or V patterns. Later the same group, in a separate observational study, found that the surface patterns were evident in 100% of lesions by EME as compared to only 66.4% with conventional or magnification endoscopies^[24]. The type IV-V lesions were strongly associated with gastric cancer with a sensitivity of 100% and specificity of 89.7%.

Use of congo-red and phenol-red in stomach

Utilizing its tendency to turn red in an alkaline environment, this Congo-red has been used for detection of AG, *H. pylori* infection and IM. Data are limited. Phenol-red has been used in old studies to map the gastric mucosa for *H. pylori* infection. With phenol red spraying endoscopy, Kohli *et al.*^[25] identified *H. pylori* infection with sensitivity and specificity of 100% and 84.6% respectively.

Use of methylene-blue in stomach

Methylene blue is absorbed by intestinal cells and thus highlights gastric IM (Figure 3). Dinis-Ribeiro *et al.*^[26] examined and proposed a classification in 136 patients using ME after methylene blue (1%) spray and could identify IM and dysplasia with 84% and 83% accuracy respectively. The findings were externally validated at another centre in Portugal in forty two patients with AG with or without IM, and the results showed excellent reproducibility for the classification^[27]. In a tandem study with only thirty-three patients, Taghavi *et al.*^[28] compared conventional endoscopy against CE with methylene blue. The CE group yielded more IM lesions compared to conventional endoscopy.

Use of haematoxylin in stomach

Haematoxylin is a common stain used in histological assessment since it stains the nuclei of cells. To date, there is only a single study utilizing haematoxylin as CE on a heterogeneous sample of gastric abnormalities^[29]. Although high sensitivity (92.9%) and specificity (89.3%) for diagnosing gastric neoplasia were reported, there were only three cases of cancer.

Use of "acetic acid plus indigo carmine" in stomach

Acetic acid whitens the non-cancerous gastric mucosal epithelial cell while the cancerous cells remain unstained.

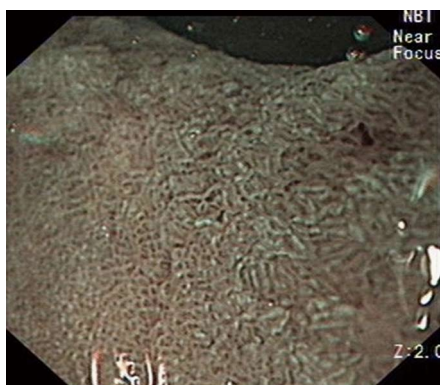


Figure 4 Gastric intestinal metaplasia highlighted by narrow band imaging using the EXERA III system with dual focus.

As detailed above, multiple studies have utilized acetic acid with ME in technique known EME. However, some authors believe that the use of ME may be cumbersome for neoplastic lesions (especially if lesion is large or located at a difficult position). Therefore, CE using a sequential combination of acetic acid spray followed by another spray with indigo carmine (AI) has been proposed for examination of a mucosal neoplastic lesion. Multiple studies have shown the efficacy of AI for delineating the margins of EGC before endoscopic resection. In the first published study on AI use with 114 patients, AI was much more effective in delineating the lateral spread of cancers as compared to indigo carmine alone^[30]. In another prospective comparative study, Sakai *et al.*^[31] used AI in 53 consecutive gastric lesions before endoscopic submucosal dissection and good interobserver agreement was reported between the two endoscopists ($\kappa = 0.764$). The diagnostic performance of AI was significantly better than either indigo carmine or acetic acid alone. In another prospective study on 108 EGC lesions, Kawahara *et al.*^[32] compared WLE, indigo-carmine and AI for delineation of margins before ESD. All endoscopic examinations were performed by one endoscopist. When correlated with pathological specimens, the diagnostic accuracy of AI was higher when compared to WLE or indigo-carmine (90.7% vs 50.0% vs 75.9%, respectively).

Overall, the studies with AI have shown an excellent efficacy in demarcation of EGC before endoscopic resection. The technique does not require additional equipment (*e.g.*, magnification endoscope).

NARROW BAND IMAGING

NBI is a proprietary optical image-enhancement technology launched by the Olympus Corporation (Tokyo, Japan) in year 2005. NBI is the most widely utilized electronic IEE technique with demonstrated scientific evidence for its efficacy in GI diseases. Normally, the wavelengths of white light range from 400 to 700 nm. During conventional WLE, the illuminating white light travels from the xenon lamp *via* a rotating red-green-blue (RGB) rotatory filter. In NBI, an additional filter is

placed between the xenon lamp and the RGB filter^[33]. This whole NBI system is simply activated by a push of button on the control handle of the endoscope without interrupting the views on monitor. By this additional NBI filter, the light is converted from a broad RGB into narrow bands of blue and green at 415 (± 15) nm and 540 (± 15) nm wavelengths respectively. The narrow wavelengths of illuminating light increase the saturation. Moreover, biological tissues behave differently at different wavelengths of light due to their characteristic patterns of absorption and scattering of light. Since haemoglobin molecule has two absorption peaks at 415 nm and 540 nm, the mucosal microvascular patterns are highlighted in extensive detail with NBI^[34].

NBI can diagnose the subtle and flat mucosal GI lesions which are often missed or remain uncharacterized on WLE. Since the sub-epithelial capillaries of stomach have minimum diameter of 8 μm ^[17], combining ME with NBI has been studied for detailed examination of capillary patterns in stomach. As described below, most of the published studies have utilized a simultaneous combination of ME and NBI. It must be recognized that there are two NBI systems in use, the EVIS EXERA and the EVIS LUCERA systems. For the EXERA system, the magnification achieved is by digital magnification and a specific technique called "Dual Focus" which allows near mode imaging; in contrast, the LUCERA system allows optical magnification and this is the main system used in prior studies of magnifying NBI. An overview of NBI studies are provided in Table 2.

NBI for screening of gastric pathologies

At narrow wavelengths of light with NBI, the intensity of illumination is compromised resulting in darker images when compared to images during WLE. This is especially relevant while examining the stomach, a capacious organ, where dark views result in NBI being not so useful for screening of focal gastric lesions. However, NBI can be utilized as a second-look method to focus on lesions detected upon screening with WLE. This technique appears to increase detection rate of gastric focal lesions. At least five prospective studies have studied NBI using this approach^[35-39]. In a prospective study on an unselected population, our group screened for focal gastric lesions using WLE followed by characterization of detected lesions by magnified NBI (M-NBI)^[34]. Additional 15% lesions (mostly IM) were detected with M-NBI (Figure 4). In another multicentre prospective study using the similar sequence (WLE followed by M-NBI), the accuracy of M-NBI for high confidence diagnoses of gastric lesions was 98%^[35]. In a recent prospective study with more than three thousands non-selected patients, gastric examinations were performed with high-definition white light (HD-WLE) followed by ME and then with M-NBI^[36]. Using such strategy to detect EGC, ME and M-NBI had significantly higher sensitivities when compared to HD-WLE. However, there were no differences among specificities of the techniques.

Table 2 Summary of studies using narrow band imaging in stomach

Use in stomach	Type of evidence	Description	Remarks
Screening of focal lesions in stomach	Five prospective studies ^[35-39] studied screening with WLE followed by characterization of detected lesions with NBI Single randomized prospective study with bright-NBI ^[40]	WLE followed by characterization with NBI seems to increase confidence in taking targeted biopsies New generation "bright-NBI" appears promising to increase yield of FGL as single step examination in stomach	Majority of the detected FGLs are intestinal metaplasia Due to small sample sizes in these studies, it is unclear whether such strategy will improve detection of subtle malignant gastric lesions
Diagnosis of <i>H. pylori</i> gastritis	Two prospective trials ^[41,42] using M-NBI with histology as comparator	Subjective classifications of mucosal microvascular patterns showed high sensitivity and specificity for real-time diagnosis of <i>H. pylori</i> gastritis	Inherent subjectivity in the classification is an issue
Diagnosis of IM	Multiple prospective studies and one recent meta-analysis ^[44] using M-NBI for diagnosis of IM	Multiple patterns have been assigned for diagnosis of IM. The most prevalent is the "LBC" sign The pooled sensitivity and specificity of LBC for diagnosis of IM are 84% and 93% respectively	LBC sign with M-NBI appears easy to learn and reliable for real-time diagnosis of IM
Characterization of an EGC	Multiple prospective studies including two recent meta-analyses ^[52,53] using M-NBI for characterization of an EGC	Various pattern-classification systems with M-NBI have been used in different studies to characterize a lesion as EGC. The pooled sensitivity: 0.83-0.85 The pooled specificity: 0.96	Inherent subjectivities in a variety of classifications remain an issue Significant heterogeneity were observed in both meta-analyses
Prediction of histological differentiation of an EGC	At least two prospective studies ^[54,55]	Subjective pattern assignments were given; Only moderate sensitivities and specificities to determine histological differentiation of an EGC	Inherent subjectivities in the classification system. Currently, histology is still required to determine histological differentiation of an EGC
Determination of horizontal extent of an EGC	Few studies with small sample sizes	One study ^[58] showed better accuracy than indigo carmine chromoendoscopy	Real-time estimation of an EGC is useful before endoscopic resection. However, the histology still remains the gold-standard
Determination of depth of an EGC	Two prospective ^[61,62] studies	Subjective classifications but with excellent accuracy	Inherent subjectivities in the classification system. Currently, histology is still required to determine depth of an EGC

FGL: Focal gastric lesion; *H. pylori*: *Helicobacter pylori*; EGC: Early gastric cancer; M-NBI: Magnifying narrow band imaging; IM: Intestinal metaplasia; LBC: Light blue-crest; WLE: White light endoscopy.

The new generation NBI system introduced in 2012 (e.g., the "EVIS EXERA III" or "EVIS LUCERA" from Olympus Corporation) attempt to overcome the drawback of dark views by having an upgraded xenon light source. Besides this, the new systems also have two filters for blue light and one filter for green light in contrast with previous NBI system where only one filter each is used for blue and green. Thus, this new generation NBI system (sometimes known as bright-NBI) produces brighter NBI images even from a distance. In a recent multicentre prospective randomized study, our group compared the HD-WLE with the new generation bright-NBI system (either 190-NBI or 290-NBI) for screening of focal gastric lesions (FGL)^[40]. The detection rate of FGL was higher with bright-NBI than with HD-WLE (41% vs 29%; $P = 0.003$).

Magnifying-NBI for diagnosis of *H. pylori* gastritis

Since *H. pylori* infection produces alterations in the microsurface structures and microvascular patterns of gastric mucosa, it is postulated that the magnified NBI views may be helpful for real-time diagnosis of *H. pylori* gastritis. For this pathology, there has been considerable interest by researchers for two reasons. First, the high-confidence real-time diagnosis of *H. pylori* may stimulate an endoscopist to be more vigilant

for concomitant pre-malignant and malignant lesions of stomach. Also, the real-time gastric mucosal pattern analyses may theoretically help in obtaining targeted biopsies instead of routine practice of blind-biopsies for *H. pylori* check. In a prospective study in 2009, Tahara *et al.*^[41] attempted to correlate gastric mucosal patterns on magnifying-NBI (M-NBI) with *H. pylori* gastritis. At M-NBI, the normal gastric corpus pattern was identified as small, round pits with regular subepithelial capillary networks (SECN). The abnormal patterns were classified into three (type 1 to 3) categories. The sensitivity and specificity of abnormal patterns (type 1 + 2 + 3) for *H. pylori* gastritis were 95.2% and 82.2%, respectively. In a comparative trial in 2014, Yagi *et al.*^[42] compared conventional WLE with M-NBI for detection of *H. pylori* gastritis in patients diagnosed with EGC. For diagnosis of *H. pylori* gastritis, the sensitivity and specificity in M-NBI group were higher than in WLE group.

M-NBI for diagnosis of AG and IM

AG and IM represent significant milestones in the sequence of gastric carcinogenesis^[14]. On conventional WLE, corpus AG is suspected based on a paucity of gastric rugae with more marked appearances of sub-mucosal vessels; while IM appears as patchy, white, raised or flat spots. However, WLE is considered

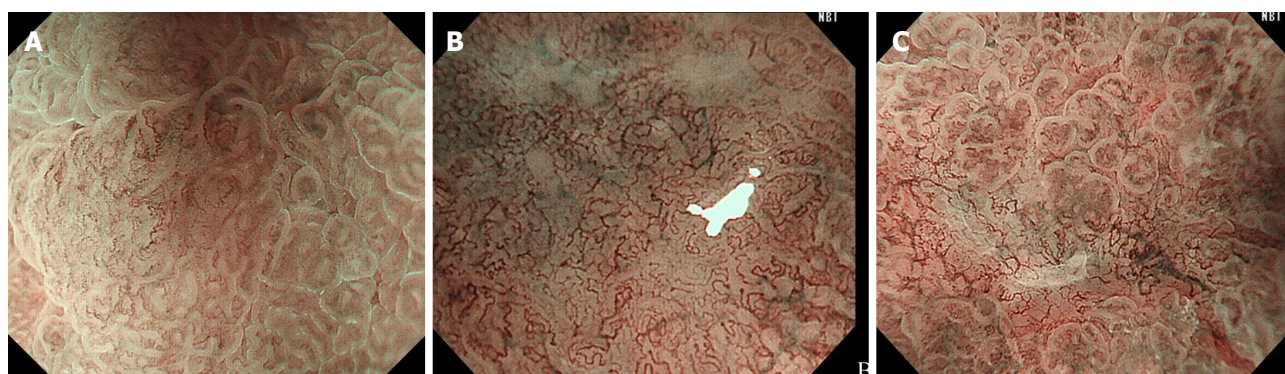


Figure 5 Best visualized with optical magnification. A: Magnifying narrow band image of gastric intestinal metaplasia showing, the light blue crest sign, surrounding central area of early gastric cancer; B: Magnifying narrow band image of early gastric cancer; C: Magnifying narrow band image of early gastric cancer.



Figure 6 Image of early gastric cancer visualized using narrow band imaging with digital magnification and dual focus imaging.

insensitive for diagnosis of AG and IM. On NBI, AG is characterized by a complete loss of pit-pattern and SECN, with presence of only collecting venules. In a randomized, prospective and crossover study by Dutta *et al*^[38] NBI was superior to WLE for detection of AG. With NBI various appearances have been proposed for characterization of IM. The most important of these is the identification of light blue crests (LBC).

In 2006, Uedo *et al*^[43] first described LBC as fine blue-white lines on the crests of the epithelial surface/gyri, similar to a light reflected from mirror. In this seminal study, the sensitivity and specificity of LBC for diagnosis of IM were 89% and 93% respectively. Similarly, high diagnostic values of LBC for characterization of IM have been shown by other authors (Figure 5A). A recent meta-analysis by Wang *et al*^[44], which included four prospective studies without significant heterogeneity, documented that the pooled sensitivity and specificity of LBC for diagnosis of IM were 84% and 93% respectively. In a pilot feasibility trial, Bansal *et al*^[45] found sensitivity and specificity of "ridge/villous pattern" for IM to be 80% and 100% respectively.

M-NBI for characterization of EGC

Perhaps the most important and most extensively investigated use of NBI in the stomach is for the characterization of EGC. The accurate identification

of EGC is important since endoscopic resection for such early cancers achieves > 90% five-year survival. Morphologically EGC are categorized mainly into three types by the Paris classification^[46]: Superficial elevated (0-IIa), superficial flat (0-IIb), and superficial depressed (0-IIc). EGCs often produce subtle mucosal changes (sometimes known as "gastritis-like cancers") and can be easily missed on conventional WLE. The major contribution of M-NBI lies in accurate differentiation of such lesions from normal or inflamed gastric mucosa.

The most widely studied and utilized classification is the "VS classification" by Yao *et al*^[47] where "V" stands for microvascular patterns while "S" stands for surface microstructures. In this classification, an EGC is accurately identified based on two features: (1) a demarcation line (DL) with loss of SECN; and (2) an irregular microvascular pattern (IMVP) or an irregular microstructural pattern. These features are best visualized with optical magnification (Figure 5). Digital magnification combined with dual focus imaging may provide an adequate view of the demarcation line and microstructural pattern, but will not be able to clearly visualize the microvascular pattern (Figure 6).

In 2010, Ezoe *et al*^[48] prospectively compared diagnostic efficacies of ME with M-NBI using VS classification in a sample of 57 depressed gastric lesions (including 27 malignant). For accurate diagnosis of EGC, the diagnostic accuracy and sensitivity were significantly higher for M-NBI as compared to ME. Subsequently, the same comparison was studied in much larger sample in a randomized and multicentre trial^[49]. Again for diagnosis of depressed-type EGC, the M-NBI was superior to ME. The sensitivity and specificity of M-NBI were 95.0% and 96.8% respectively.

In the recent post-hoc analysis of this study, a sequential strategy for diagnosing a cancerous gastric lesion was proposed^[50]. For a depressed gastric lesion on white-light examination, M-NBI was suggested to look for a DL first since presence of DL had high sensitivity and high negative predictive value for a malignant lesion. In lesions with DL, an absence of IMVP was proposed to rule out malignant lesions because of high specificity of IMVP. In another prospective study, Kato

et al.^[51] surveyed 111 high-risk patients for EGC based on a triad of findings on M-NBI: (1) disappearance of mucosal pattern; (2) microvascular dilatation; and (3) heterogeneity. Although only 14 gastric cancers were detected, the sensitivity and specificity of M-NBI (92.9% and 94.7% respectively) were superior to WLE (42.9% and 61.0% respectively).

In a recent meta-analysis by Zhang *et al.*^[52] the pooled sensitivity and specificity of M-NBI for diagnosis of EGC were 0.83 and 0.96 respectively. However, there were significant heterogeneity among the studies and also, a combination of retrospective and prospective studies were pooled together. Another recent meta-analysis, which only included six prospective studies, also showed high pooled sensitivity (0.85) and specificity (0.96) for M-NBI diagnosis of EGC^[53]. A significant heterogeneity among studies was also observed in this meta-analysis.

M-NBI for histological differentiation of EGC

Besides differentiating between cancerous and non-cancerous lesions, several studies have attempted to use M-NBI for prediction of histologic differentiation of EGC. During the early years of NBI technique, Nakayoshi *et al.*^[54] studied 165 depressed-type of EGC with M-NBI. The microvascular patterns were divided into three patterns: Fine network, corkscrew and unclassified. The fine network patterns were seen more commonly in differentiated EGC as compared to the undifferentiated type (66.1% vs 3.7%), whereas corkscrew patterns were seen more commonly in undifferentiated-type (85.7% vs 3.6%; $P = 0.0011$). However, the conclusion was that the real-time optical diagnosis with M-NBI, although beneficial, was still not sufficient to replace histopathological confirmation.

Similarly, Yokoyama *et al.*^[55] studied 257 consecutive EGC with M-NBI and divided the microvascular patterns into four categories: Fine-network, corkscrew, intra-lobular loop-1, and intra-lobular loop-2. When correlated with histopathology, differentiated-type EGC mostly had fine-network pattern or intra-lobular loop patterns. On the contrary, the undifferentiated-type of EGC had intra-lobular loop-2 pattern and corkscrew pattern in almost all patients (41.2% and 58.2% respectively).

M-NBI to determine the horizontal extent of EGC

Delineating the horizontal extent of EGC is important for margin-free endoscopic resection. Traditionally, CE with indigo-carmin has been used to highlight abnormal mucosal patterns before endoscopic resection. In 2002, Yao *et al.*^[56] published a case report where demarcation of a well-differentiated EGC was made with an image-enhanced technology using "hemoglobin index".

Subsequently in a sample of twelve EGC, Sumiyama *et al.*^[57] used a combination of M-NBI and a multibending endoscope for *en bloc* endoscopic mucosal resection. Using this combination, 91.7% (11/12) *en bloc* resections were made feasible as compared to 35% in conventional endoscopy group. However, authors stated

that it was unclear as to which of these factors (*i.e.*, either NBI or multibending endoscope or both) led to this satisfactory outcome.

Kiyotoki *et al.*^[58] compared M-NBI with indigo-carmin based CE in 118 EGC. For delineating margins of EGC, the accuracy was higher in M-NBI group as compared to the indigo-carmin (97.4% and 77.8% respectively; $P = 0.009$). Another prospective study by Nagahama *et al.*^[59] documented 72.6% accuracy for identifying margins of EGC which could not be delineated with acetic acid CE.

Overall, studies have shown beneficial results with M-NBI for delineation of margins only in the differentiated-type of EGC. Demarcation of undifferentiated-type of EGC is considered difficult since the malignant growth seems to creep more into the lamina propria which may not always produce endoscopically visible mucosal changes. For example in the study by Nagahama *et al.*^[59] the endoscopic delineation remained difficult for undifferentiated lesions. However one prospective study also showed high accuracy (81.6%) using M-NBI for demarcation of undifferentiated-type of EGC^[60].

It can be concluded that there is good evidence with prospective trials in support of M-NBI for demarcation of differentiated EGC before performing endoscopic resection. However it should also be noted that the trials have generally included a small number of patients in whom experts have performed endoscopic examination while utilizing various types of classification for pattern categorization. Although histopathology is still considered the gold-standard for retrospective confirmation of clearance of margins, the real-time estimation of horizontal margins with M-NBI is helpful as a prospective guide for accurate *en-bloc* resection.

M-NBI to determine the depth of EGC

According to the Japanese Gastric Cancer Handling Codes, the submucosal EGC are divided into three types (SM1 to SM3) based on the depth of cancer invasion. The differentiated-type of SM1 (*i.e.*, vertical depth up to 500 μ m) EGC can be considered as an expanded indication for endoscopic resection. But, surgical resection should be considered for SM2 and SM3 cancers as the probability of lymph node metastatic disease is high. Prospective estimation of the depth of invasion is difficult and therefore endoscopic resection is considered complete only after histopathological assessment of the resected specimen. Knowledge of deep invasion will avoid unwarranted endoscopic resection. Presence of ulceration on standard WLE suggests deep invasion. But, it may be especially difficult to estimate depth of invasion in flat (Paris 0-IIa, 0-IIb and 0-IIc) EGC.

In 2008, Yagi *et al.*^[61] correlated the M-NBI patterns of 72 differentiated-type EGC (10 elevated, 27 flat, and 35 depressed-type) with histopathology. All endoscopic examinations were performed by one expert and the patterns were classified into three types: Mesh, loop and interrupted. The mesh or loop pattern were seen

in 94.9% of mucosal EGC while 92.3% of submucosal EGC had interrupted patterns. In another prospective study from China, Li *et al.*^[62] reported findings of M-NBI in 164 suspected gastric lesions. The patterns of M-NBI were categorized into three groups (A, B and C) based on both surface pattern and microvascular architecture. Besides excellent diagnostic values for characterization and differentiation of EGC, M-NBI classification was able to accurately predict the depth of invasion in 37 out of 39 differentiated adenocarcinomas (95%).

Two retrospective studies have also attempted correlation of M-NBI images (taken before the resection) with histopathology of resected specimens. In the first study by Kobara *et al.*^[63] it was concluded that the presence of non-structure, scatterly vessels and multi-caliber vessels can possibly serve as indicators of SM2 invasion in differentiated-type of EGC. In the second study by Kikuchi *et al.*^[64] M-NBI images were examined for dilated vessels (D-vessels) which were defined as vessels with diameter 3 times larger than that of the irregular microvessels. The sensitivity and specificity of D-vessels for SM2 invasion were 37.5% and 88.3% respectively.

FICE

This technology is also known as "optimal band imaging" or "multi-band imaging". FICE was introduced by Fujinon (Tokyo, Japan) in year 2005 and is currently its proprietary technology. In FICE, the ordinary white-light images are captured by the CCD and are mathematically processed in the processor by assigning specific ranges of wavelengths. Thereafter, electronically enhanced and reconstructed color images are displayed on the monitor^[65]. This is in contrast with the NBI where raw and enhanced images are captured by putting an optical filter in the path of illuminating light. Since FICE processes well-illuminated white-light images, this means that the FICE can provide enhanced images without compromising on brightness. At present, there are ten pre-settings of FICE which can be instantaneously activated by pushing a button on an accompanying keyboard. A total of three presets can also be assigned to the buttons on the control handle of the endoscope to ease the switching of the different FICE images. In recent years, several studies have claimed superior efficacy of FICE as compared to WLE for various pathologies of esophagus, colon and stomach. Only a few studies have studied FICE in stomach, with most performed for delineation of margins of EGCs. However, a learning curve for pattern recognition, a requirement for separate endoscopic equipment and lack of consensus for objective diagnostic criteria has restricted use of FICE.

Use of FICE in EGC

In the management of EGC, the use of FICE has been limited to demarcation of already identified lesions.

FICE has not been objectively studied as a screening tool to pick up early malignant lesion. In 2008, Osawa *et al.*^[66] published the first clinical study in stomach. In this real-time prospective study with a small sample of twenty-seven patients, four endoscopists, in real-time demarcated the depressed type of EGC with accuracy of 96%. In the same year, another study by the same group claimed efficacy in demarcation of elevated and depressed type of EGC^[67]. However in this study, the objective results of efficacy of this method were not reported. In another study from the same group, it enabled delineation of elevated-type of EGC in the background of AG^[68].

Since a variety of wavelengths were being used for gastric examination with FICE, the most effective wavelength was studied in a retrospective fashion by another group in Japan^[69]. Previously captured white-light images of EGC were processed by the FICE processor and analysed. It was noted that the wavelength of 530 nm generated maximal difference in spectral reflectance between EGC and normal mucosa and there was significant improvement from the WLE images to the FICE images. FICE is proposed as a potential alternative to conventional CE because it provides contrast enhancement of tissue surface structures. However at present, the evidence for its support has come from a few studies with small sample. Since the technology requires a new set of equipment, further external and large-scale validation will be required before its widespread use.

Use of FICE for other gastric pathologies

In one study, FICE was studied for differentiation of non-neoplastic lesions, adenomas and cancers in the stomach^[70]. A total of 171 gastric lesions were examined and FICE performed better than magnifying-WLE. Another study examined the role of FICE for diagnosis of gastric intestinal metaplasia^[71]. FICE had sensitivity and specificity of IM diagnosis of 60% and 87% based on histological confirmation. Although this study might have diagnosed IM based on LBC, there is still no consensus on diagnostic criteria for IM on FICE.

Small-caliber gastroscope with FICE

Small-caliber endoscope has lower resolution but is more comfortable for the patients, especially if used as a screening tool for gastric pathologies. Theoretically, FICE combined with small-caliber gastroscope can enhance the color contrast of gastric pathologies. To date, there are two studies, from Japan, which have evaluated this hypothesis. Tanioka *et al.*^[72] retrospectively examined 50 gastric lesions which were previously identified on screening endoscopy with Ultraslim endoscope (Fujinon EG-530N2). After conversion into FICE images, superior visibility was seen in 54.7% upper GI lesions as compared to conventional images. In another study by Osawa *et al.*^[73] 82 depressed-type EGC (which were already diagnosed with conventional normal-caliber

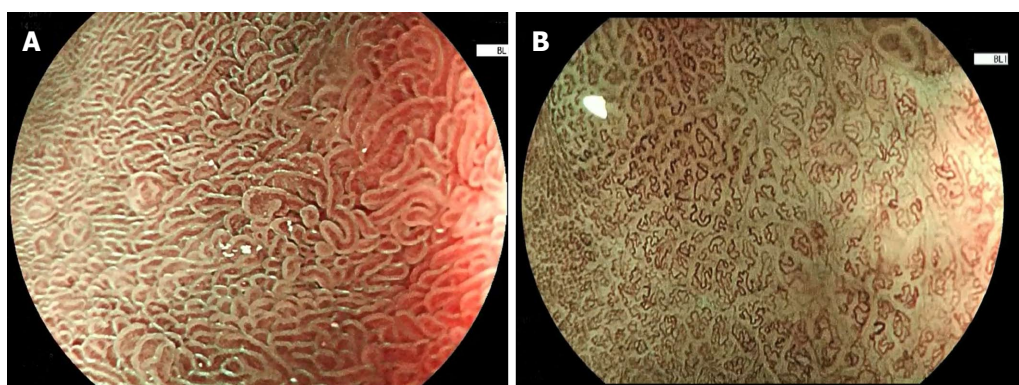


Figure 7 Performance characteristics. A: Image of gastric intestinal metaplasia visualized by blue laser imaging with optical magnification; B: Image of early gastric cancer visualized by blue laser imaging with optical magnification.

Table 3 Summary of image-enhanced endoscopy in stomach

Technique	Use	Evidence	Remarks
High-definition WLE	Standard of care for initial examination of gastric mucosa	Not available	
WLE with magnification	Helpful in describing normal mucosal patterns in corpus and antrum. Appears useful in predicting real-time diagnosis of <i>H. pylori</i> infection. Better than WLE for characterization of EGCs	Multiple prospective comparative studies for identifying <i>H. pylori</i> infection and for characterization of EGCs	A variety of classifications in describing the normal and abnormal mucosal pattern makes interpretation difficult for widespread use
Dye-based chromoendoscopy	Traditionally used for demarcation of EGC before resection	Few prospective studies are available, and more data will be needed	There are heterogeneity in the types of stain, technique of staining, classification in defining mucosal patterns
NBI	Good for characterization of a focal lesion detected on WLE May be useful for real-time diagnosis of <i>H. pylori</i> Appears reliable for diagnosis of intestinal metaplasia High specificity for characterization of EGCs May be useful for prediction of histological differentiation, prediction of depth of invasion, and in determination of horizontal extent of EGCs	Multiple prospective comparative study show good evidence in support of NBI for diagnosis of intestinal metaplasia and characterization of EGCs More evidence will be needed for other indications	Identifying intestinal metaplasia appears straightforward A variety of classifications for different mucosal pattern bring difficulty in generalization of NBI
FICE	May be useful for diagnosis of focal gastric lesions	Not much comparative prospective data is available	
I-SCAN		No comparative data for use of I-SCAN in stomach	
Blue-laser imaging	Is expected to be used in similar manner as NBI	Data mainly based on case series rather than comparative studies	Based on anecdotal experience it is similar to NBI and therefore would be expected to provide similar outcomes

WLE: White light endoscopy; EGC: Early gastric cancer; NBI: Narrow-band imaging; FICE: Flexible spectral imaging color enhancement; BNI: Narrow band imaging; *H. pylori*: *Helicobacter pylori*.

endoscopy) were examined with small-caliber (Fujinon EG-530N2) endoscopy and FICE by endoscopists who were blinded of the locations of the lesions. Most EGC could be detected as reddish lesions on FICE with clear demarcation.

FICE combined with indigo carmine in stomach

A single study from Japan has evaluated the usefulness of adding indigo-carmin to FICE examination (I-FICE)^[74]. In a small sample of 29 well-differentiated EGC, I-FICE

was superior for demarcation of the lesion when compared to WLE, FICE and indigo-carmin CE.

I-SCAN

Conceptually similar to FICE, I-SCAN is a post-processing image-enhancement technology introduced by Pentax Corporation (Tokyo, Japan) in year 2007, allowing detailed views of mucosal vascular patterns^[75]. Special processors (EPKi high-definition, Pentax)

are required for I-SCAN. The white-light images are processed arithmetically into three types of enhancements: Surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE). The SE and CE are suggested useful for screening of early GI lesions, while TE is proposed for further characterization of identified lesions. The modes can be switched back and forth by pressing a button on the endoscope, and two modes can be displayed simultaneously. A small number of studies have explored this technique for colonic and esophageal pathologies, where equivocal benefits have been seen. Till date, there is only one study of I-SCAN's use in stomach. Using magnified I-SCAN in a small sample of 43 patients, Li *et al.*^[76] performed a feasibility trial. Magnified I-SCAN was attempted to characterize a heterogeneous variety of small superficial gastric lesions. With histology as gold-standard, the specificity of real-time magnified I-SCAN was only 77% for neoplastic lesions. Therefore at present, the data for gastric use of I-SCAN is almost non-existent and further work will be required before routine use in stomach.

BLUE-LASER IMAGING

Introduced in year 2012 by Fujifilm Corporation (Tokyo, Japan), this is the latest addition to the field of IEE. Contrary to NBI which, in the process of producing a narrow bandwidth, darkens the image, blue-laser imaging (BLI) generates brighter and sharper images. BLI utilizes two laser sources: One at 410 nm for illumination of superficial mucosa and another at 450 nm to visualize deep vascular mucosal image. Therefore, BLI produces more vivid mucosal and microvascular architectural details. In 2014, first in-human clinical trial with BLI in stomach was reported by Kaneko *et al.*^[77] from Japan. Out of a variety of GI lesions, 14 patients had EGC. BLI-bright produced better far-field view as compared to the first generation NBI. Since the BLI technology is new, more extensive work is warranted before any conclusion can be drawn. However, it would appear to be very promising, and be similar to NBI in terms of performance characteristics (Figure 7).

CONCLUSION

Especially in last 15 years, there has been a proliferation of research for use of IEE in detection and characterization of gastric pathologies. The role of IEE in screening is still limited and WLE should still be used as first line method of examination. However, there is large amount of data in support of M-NBI for diagnosis, delineation and depth-estimation of EGC. M-NBI also has excellent diagnostic characteristics for IM. It is important to emphasize that almost all studies have been done by experts in IEE highlighting the importance of a proper training in pattern recognition before general use. The published data for other IEE techniques are more limited. Since the principle of BLI is the same as NBI, it would be expected to provide similar efficacy as

NBI, especially with optical magnification. In contrast, it is probably not possible to extrapolate the NBI data to FICE and I-SCAN, since these are processed images without optical magnification (Table 3).

ACKNOWLEDGMENTS

We would like to acknowledge Dr Noriya Uedo (Osaka, Japan) and FUJIFILM Asia Pacific Pte. Ltd., for contribution of images used in this paper.

REFERENCES

- 1 **Subramanian V**, Ragunath K. Advanced endoscopic imaging: a review of commercially available technologies. *Clin Gastroenterol Hepatol* 2014; **12**: 368-376.e1 [PMID: 23811245 DOI: 10.1016/j.cgh.2013.06.015]
- 2 **Miyahara R**, Niwa Y, Matsuura T, Maeda O, Ando T, Ohmiya N, Itoh A, Hirooka Y, Goto H. Prevalence and prognosis of gastric cancer detected by screening in a large Japanese population: data from a single institute over 30 years. *J Gastroenterol Hepatol* 2007; **22**: 1435-1442 [PMID: 17573829 DOI: 10.1111/j.1440-1746.2007.04991.x]
- 3 **Tajiri H**, Niwa H. Proposal for a consensus terminology in endoscopy: how should different endoscopic imaging techniques be grouped and defined? *Endoscopy* 2008; **40**: 775-778 [PMID: 18698532 DOI: 10.1055/s-2008-1077507]
- 4 **Kwon RS**, Adler DG, Chand B, Conway JD, Diehl DL, Kantsevoy SV, Mamula P, Rodriguez SA, Shah RJ, Wong Kee Song LM, Tierney WM. High-resolution and high-magnification endoscopes. *Gastrointest Endosc* 2009; **69**: 399-407 [PMID: 19231483 DOI: 10.1016/j.gie.2008.12.049]
- 5 **Subramanian V**, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011; **43**: 499-505 [PMID: 21360420 DOI: 10.1055/s-0030-1256207]
- 6 **Sakaki N**, Iida Y, Okazaki Y, Kawamura S, Takemoto T. Magnifying endoscopic observation of the gastric mucosa, particularly in patients with atrophic gastritis. *Endoscopy* 1978; **10**: 269-274 [PMID: 738222 DOI: 10.1055/s-0028-1098307]
- 7 **Yao K**, Oishi T. Microgastroscopic findings of mucosal microvascular architecture as visualized by magnifying endoscopy. *Dig Endosc* 2001; **13**: S27-S33
- 8 **Yagi K**, Nakamura A, Sekine A. Characteristic endoscopic and magnified endoscopic findings in the normal stomach without *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2002; **17**: 39-45 [PMID: 11895551 DOI: 10.1046/j.1440-1746.2002.02665.x]
- 9 **Yagi K**, Nakamura A, Sekine A. Comparison between magnifying endoscopy and histological, culture and urease test findings from the gastric mucosa of the corpus. *Endoscopy* 2002; **34**: 376-381 [PMID: 11972268 DOI: 10.1055/s-2002-25281]
- 10 **Gonen C**, Simsek I, Sarioglu S, Akpinar H. Comparison of high resolution magnifying endoscopy and standard videoendoscopy for the diagnosis of *Helicobacter pylori* gastritis in routine clinical practice: a prospective study. *Helicobacter* 2009; **14**: 12-21 [PMID: 19191891 DOI: 10.1111/j.1523-5378.2009.00650.x]
- 11 **Anagnostopoulos GK**, Yao K, Kaye P, Fogden E, Fortun P, Shonde A, Foley S, Sunil S, Atherton JJ, Hawkey C, Ragunath K. High-resolution magnification endoscopy can reliably identify normal gastric mucosa, *Helicobacter pylori*-associated gastritis, and gastric atrophy. *Endoscopy* 2007; **39**: 202-207 [PMID: 17273960 DOI: 10.1055/s-2006-945056]
- 12 **Yang JM**, Chen L, Fan YL, Li XH, Yu X, Fang DC. Endoscopic patterns of gastric mucosa and its clinicopathological significance. *World J Gastroenterol* 2003; **9**: 2552-2556 [PMID: 14606095 DOI: 10.3748/wjg.v9.i11.2552]
- 13 **Nakagawa S**, Kato M, Shimizu Y, Nakagawa M, Yamamoto J, Luis PA, Kodaira J, Kawarasaki M, Takeda H, Sugiyama T, Asaka M. Relationship between histopathologic gastritis and mucosal

- microvasculature: observations with magnifying endoscopy. *Gastrointest Endosc* 2003; **58**: 71-75 [PMID: 12838224 DOI: 10.1067/mge.2003.316]
- 14 **Correa P.** Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]
 - 15 **Tobita K.** Study on minute surface structures of the depressed-type early gastric cancer with magnifying endoscopy. *Dig Endosc* 2001; **13**: 121-126
 - 16 **Tajiri H,** Doi T, Endo H, Nishina T, Terao T, Hyodo I, Matsuda K, Yagi K. Routine endoscopy using a magnifying endoscope for gastric cancer diagnosis. *Endoscopy* 2002; **34**: 772-777 [PMID: 12244497 DOI: 10.1055/s-2002-34267]
 - 17 **Yao K,** Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. *Gastrointest Endosc* 2002; **56**: 279-284 [PMID: 12145613 DOI: 10.1016/S0016-5107(02)70194-6]
 - 18 **Yao K,** Iwashita A, Tanabe H, Nagahama T, Matsui T, Ueki T, Sou S, Kikuchi Y, Yorioka M. Novel zoom endoscopy technique for diagnosis of small flat gastric cancer: a prospective, blind study. *Clin Gastroenterol Hepatol* 2007; **5**: 869-878 [PMID: 17544872 DOI: 10.1016/j.cgh.2007.02.034]
 - 19 **Otsuka Y,** Niwa Y, Ohmiya N, Ando N, Ohashi A, Hirooka Y, Goto H. Usefulness of magnifying endoscopy in the diagnosis of early gastric cancer. *Endoscopy* 2004; **36**: 165-169 [PMID: 14765314 DOI: 10.1055/s-2004-814184]
 - 20 **Yoshida T,** Kawachi H, Sasajima K, Shiokawa A, Kudo SE. The clinical meaning of a nonstructural pattern in early gastric cancer on magnifying endoscopy. *Gastrointest Endosc* 2005; **62**: 48-54 [PMID: 15990819 DOI: 10.1016/S0016-5107(05)00373-1]
 - 21 **Kiesslich R,** Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003; **124**: 880-888 [PMID: 12671882 DOI: 10.1053/gast.2003.50146]
 - 22 **Yagi K,** Aruga Y, Nakamura A, Sekine A, Umezue H. The study of dynamic chemical magnifying endoscopy in gastric neoplasia. *Gastrointest Endosc* 2005; **62**: 963-969 [PMID: 16301045 DOI: 10.1016/j.gie.2005.08.050]
 - 23 **Tanaka K,** Toyoda H, Kadowaki S, Kosaka R, Shiraishi T, Imoto I, Shiku H, Adachi Y. Features of early gastric cancer and gastric adenoma by enhanced-magnification endoscopy. *J Gastroenterol* 2006; **41**: 332-338 [PMID: 16741612 DOI: 10.1007/s00535-005-1760-3]
 - 24 **Tanaka K,** Toyoda H, Kadowaki S, Hamada Y, Kosaka R, Matsuzaki S, Shiraishi T, Imoto I, Takei Y. Surface pattern classification by enhanced-magnification endoscopy for identifying early gastric cancers. *Gastrointest Endosc* 2008; **67**: 430-437 [PMID: 18294504 DOI: 10.1016/j.gie.2007.10.042]
 - 25 **Kohli Y,** Kato T, Ito S. Helicobacter pylori an chronic atrophic gastritis. *J Gastroenterol* 1994; **29** Suppl 7: 105-109 [PMID: 7921139]
 - 26 **Dinis-Ribeiro M,** da Costa-Pereira A, Lopes C, Lara-Santos L, Guilherme M, Moreira-Dias L, Lomba-Viana H, Ribeiro A, Santos C, Soares J, Mesquita N, Silva R, Lomba-Viana R. Magnification chromoendoscopy for the diagnosis of gastric intestinal metaplasia and dysplasia. *Gastrointest Endosc* 2003; **57**: 498-504 [PMID: 12665759 DOI: 10.1067/mge.2003.145]
 - 27 **Areia M,** Amaro P, Dinis-Ribeiro M, Cipriano MA, Marinho C, Costa-Pereira A, Lopes C, Moreira-Dias L, Romãozinho JM, Gouveia H, Freitas D, Leitão MC. External validation of a classification for methylene blue magnification chromoendoscopy in premalignant gastric lesions. *Gastrointest Endosc* 2008; **67**: 1011-1018 [PMID: 18178207 DOI: 10.1016/j.gie.2007.08.044]
 - 28 **Taghavi SA,** Membari ME, Eshraghian A, Dehghani SM, Hamidpour L, Khademalhosseini F. Comparison of chromoendoscopy and conventional endoscopy in the detection of premalignant gastric lesions. *Can J Gastroenterol* 2009; **23**: 105-108 [PMID: 19214285]
 - 29 **Mouzyka S,** Fedoseeva A. Chromoendoscopy with hematoxylin in the classification of gastric lesions. *Gastric Cancer* 2008; **11**: 15-21; discussion 21-22 [PMID: 18373173 DOI: 10.1007/s10120-007-0445-4]
 - 30 **Iizuka T,** Kikuchi D, Hoteya S, Yahagi N. The acetic acid + indigocarmine method in the delineation of gastric cancer. *J Gastroenterol Hepatol* 2008; **23**: 1358-1361 [PMID: 18853994 DOI: 10.1111/j.1440-1746.2008.05528.x]
 - 31 **Sakai Y,** Eto R, Kasanuki J, Kondo F, Kato K, Arai M, Suzuki T, Kobayashi M, Matsumura T, Bekku D, Ito K, Nakamoto S, Tanaka T, Yokosuka O. Chromoendoscopy with indigo carmine dye added to acetic acid in the diagnosis of gastric neoplasia: a prospective comparative study. *Gastrointest Endosc* 2008; **68**: 635-641 [PMID: 18561923 DOI: 10.1016/j.gie.2008.03.1065]
 - 32 **Kawahara Y,** Takenaka R, Okada H, Kawano S, Inoue M, Tsuzuki T, Tanioka D, Hori K, Yamamoto K. Novel chromoendoscopic method using an acetic acid-indigocarmine mixture for diagnostic accuracy in delineating the margin of early gastric cancers. *Dig Endosc* 2009; **21**: 14-19 [PMID: 19691795 DOI: 10.1111/j.1443-1661.2008.00824.x]
 - 33 **Gono K,** Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; **9**: 568-577 [PMID: 15189095]
 - 34 **Gono K.** Narrow Band Imaging: Technology Basis and Research and Development History. *Clin Endosc* 2015; **48**: 476-480 [PMID: 26668792 DOI: 10.5946/ce.2015.48.6.476]
 - 35 **Ang TL,** Fock KM, Teo EK, Tan J, Poh CH, Ong J, Ang D. The diagnostic utility of narrow band imaging magnifying endoscopy in clinical practice in a population with intermediate gastric cancer risk. *Eur J Gastroenterol Hepatol* 2012; **24**: 362-367 [PMID: 22198222 DOI: 10.1097/MEG.0b013e3283500968]
 - 36 **Yao K,** Doyama H, Gotoda T, Ishikawa H, Nagahama T, Yokoi C, Oda I, Machida H, Uchida K, Tabuchi M. Diagnostic performance and limitations of magnifying narrow-band imaging in screening endoscopy of early gastric cancer: a prospective multicenter feasibility study. *Gastric Cancer* 2014; **17**: 669-679 [PMID: 24407989 DOI: 10.1007/s10120-013-0332-0]
 - 37 **Yu H,** Yang AM, Lu XH, Zhou WX, Yao F, Fei GJ, Guo T, Yao LQ, He LP, Wang BM. Magnifying narrow-band imaging endoscopy is superior in diagnosis of early gastric cancer. *World J Gastroenterol* 2015; **21**: 9156-9162 [PMID: 26290643 DOI: 10.3748/wjg.v21.i30.9156]
 - 38 **Dutta AK,** Sajith KG, Pulimood AB, Chacko A. Narrow band imaging versus white light gastroscopy in detecting potentially premalignant gastric lesions: a randomized prospective crossover study. *Indian J Gastroenterol* 2013; **32**: 37-42 [PMID: 22983839 DOI: 10.1007/s12664-012-0246-5]
 - 39 **Xirouchakis E,** Laoudi F, Tsartsali L, Spiliadi C, Georgopoulos SD. Screening for gastric premalignant lesions with narrow band imaging, white light and updated Sydney protocol or both? *Dig Dis Sci* 2013; **58**: 1084-1090 [PMID: 23086114 DOI: 10.1007/s10620-012-2431-x]
 - 40 **Ang TL,** Pittayanon R, Lau JY, Rerkinmitr R, Ho SH, Singh R, Kwek AB, Ang DS, Chiu PW, Luk S, Goh KL, Ong JP, Tan JY, Teo EK, Fock KM. A multicenter randomized comparison between high-definition white light endoscopy and narrow band imaging for detection of gastric lesions. *Eur J Gastroenterol Hepatol* 2015; **27**: 1473-1478 [PMID: 26426836 DOI: 10.1097/meg.0000000000000478]
 - 41 **Tahara T,** Shibata T, Nakamura M, Yoshioka D, Okubo M, Arisawa T, Hirata I. Gastric mucosal pattern by using magnifying narrow-band imaging endoscopy clearly distinguishes histological and serological severity of chronic gastritis. *Gastrointest Endosc* 2009; **70**: 246-253 [PMID: 19386303 DOI: 10.1016/j.gie.2008.11.046]
 - 42 **Yagi K,** Saka A, Nozawa Y, Nakamura A. Prediction of Helicobacter pylori status by conventional endoscopy, narrow-band imaging magnifying endoscopy in stomach after endoscopic resection of gastric cancer. *Helicobacter* 2014; **19**: 111-115 [PMID: 24372729 DOI: 10.1111/hel.12104]
 - 43 **Uedo N,** Ishihara R, Iishi H, Yamamoto S, Yamamoto S, Yamada T,

- Imanaka K, Takeuchi Y, Higashino K, Ishiguro S, Tatsuta M. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy* 2006; **38**: 819-824 [PMID: 17001572 DOI: 10.1055/s-2006-944632]
- 44 **Wang L**, Huang W, Du J, Chen Y, Yang J. Diagnostic yield of the light blue crest sign in gastric intestinal metaplasia: a meta-analysis. *PLoS One* 2014; **9**: e92874 [PMID: 24658503 DOI: 10.1371/journal.pone.0092874]
 - 45 **Bansal A**, Ulusarac O, Mathur S, Sharma P. Correlation between narrow band imaging and nonneoplastic gastric pathology: a pilot feasibility trial. *Gastrointest Endosc* 2008; **67**: 210-216 [PMID: 18226682 DOI: 10.1016/j.gie.2007.06.009]
 - 46 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541 DOI: 10.1016/S0016-5107(03)02159-X]
 - 47 **Yao K**, Takaki Y, Matsui T, Iwashita A, Anagnostopoulos GK, Kaye P, Ragunath K. Clinical application of magnification endoscopy and narrow-band imaging in the upper gastrointestinal tract: new imaging techniques for detecting and characterizing gastrointestinal neoplasia. *Gastrointest Endosc Clin N Am* 2008; **18**: 415-433, vii-viii [PMID: 18674694 DOI: 10.1016/j.giec.2008.05.011]
 - 48 **Ezoe Y**, Muto M, Horimatsu T, Minashi K, Yano T, Sano Y, Chiba T, Ohtsu A. Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study. *Gastrointest Endosc* 2010; **71**: 477-484 [PMID: 20189506 DOI: 10.1016/j.gie.2009.10.036]
 - 49 **Ezoe Y**, Muto M, Uedo N, Doyama H, Yao K, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Takeuchi Y, Kaneko Y, Saito Y. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. *Gastroenterology* 2011; **141**: 2017-2025.e3 [PMID: 21856268 DOI: 10.1053/j.gastro.2011.08.007]
 - 50 **Yamada S**, Doyama H, Yao K, Uedo N, Ezoe Y, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Takeuchi Y, Saito Y, Muto M. An efficient diagnostic strategy for small, depressed early gastric cancer with magnifying narrow-band imaging: a post-hoc analysis of a prospective randomized controlled trial. *Gastrointest Endosc* 2014; **79**: 55-63 [PMID: 23932092 DOI: 10.1016/j.gie.2013.07.008]
 - 51 **Kato M**, Kaise M, Yonezawa J, Toyozumi H, Yoshimura N, Yoshida Y, Kawamura M, Tajiri H. Magnifying endoscopy with narrow-band imaging achieves superior accuracy in the differential diagnosis of superficial gastric lesions identified with white-light endoscopy: a prospective study. *Gastrointest Endosc* 2010; **72**: 523-529 [PMID: 20598685 DOI: 10.1016/j.gie.2010.04.041]
 - 52 **Zhang Q**, Wang F, Chen ZY, Wang Z, Zhi FC, Liu SD, Bai Y. Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis. *Gastric Cancer* 2016; **19**: 543-552 [PMID: 25920526 DOI: 10.1007/s10120-015-0500-5]
 - 53 **Lv X**, Wang C, Xie Y, Yan Z. Diagnostic efficacy of magnifying endoscopy with narrow-band imaging for gastric neoplasms: a meta-analysis. *PLoS One* 2015; **10**: e0123832 [PMID: 25856544 DOI: 10.1371/journal.pone.0123832]
 - 54 **Nakayoshi T**, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). *Endoscopy* 2004; **36**: 1080-1084 [PMID: 15578298 DOI: 10.1055/s-2004-825961]
 - 55 **Yokoyama A**, Inoue H, Minami H, Wada Y, Sato Y, Satodate H, Hamatani S, Kudo SE. Novel narrow-band imaging magnifying endoscopic classification for early gastric cancer. *Dig Liver Dis* 2010; **42**: 704-708 [PMID: 20462814 DOI: 10.1016/j.dld.2010.03.013]
 - 56 **Yao K**, Yao T, Iwashita A. Determining the horizontal extent of early gastric carcinoma: two modern techniques based on differences in the mucosal microvascular architecture and density between carcinomatous and non-carcinomatous mucosal. *Dig Endosc* 2002; **14**: S83-S87
 - 57 **Sumiyama K**, Kaise M, Nakayoshi T, Kato M, Mashiko T, Uchiyama Y, Goda K, Hino S, Nakamura Y, Matsuda K, Mochizuki K, Kawamura M, Tajiri H. Combined use of a magnifying endoscope with a narrow band imaging system and a multibending endoscope for en bloc EMR of early stage gastric cancer. *Gastrointest Endosc* 2004; **60**: 79-84 [PMID: 15229430 DOI: 10.1016/S0016-5107(04)01285-4]
 - 58 **Kiyotoki S**, Nishikawa J, Satake M, Fukagawa Y, Shirai Y, Hamabe K, Saito M, Okamoto T, Sakaida I. Usefulness of magnifying endoscopy with narrow-band imaging for determining gastric tumor margin. *J Gastroenterol Hepatol* 2010; **25**: 1636-1641 [PMID: 20880172 DOI: 10.1111/j.1440-1746.2010.06379.x]
 - 59 **Nagahama T**, Yao K, Maki S, Yasaka M, Takaki Y, Matsui T, Tanabe H, Iwashita A, Ota A. Usefulness of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy (with video). *Gastrointest Endosc* 2011; **74**: 1259-1267 [PMID: 22136775 DOI: 10.1016/j.gie.2011.09.005]
 - 60 **Horiuchi Y**, Fujisaki J, Yamamoto N, Shimizu T, Miyamoto Y, Tomida H, Omae M, Ishiyama A, Yoshio T, Hirasawa T, Yamamoto Y, Tsuchida T, Igarashi M, Takahashi H. Accuracy of diagnostic demarcation of undifferentiated-type early gastric cancers for magnifying endoscopy with narrow-band imaging: endoscopic submucosal dissection cases. *Gastric Cancer* 2016; **19**: 515-523 [PMID: 25744291 DOI: 10.1007/s10120-015-0488-x]
 - 61 **Yagi K**, Nakamura A, Sekine A, Umezumi H. Magnifying endoscopy with narrow band imaging for early differentiated gastric adenocarcinoma. *Dig Endosc* 2008; **20**: 115-122
 - 62 **Li HY**, Dai J, Xue HB, Zhao YJ, Chen XY, Gao YJ, Song Y, Ge ZZ, Li XB. Application of magnifying endoscopy with narrow-band imaging in diagnosing gastric lesions: a prospective study. *Gastrointest Endosc* 2012; **76**: 1124-1132 [PMID: 23025977 DOI: 10.1016/j.gie.2012.08.015]
 - 63 **Kobara H**, Mori H, Fujihara S, Kobayashi M, Nishiyama N, Nomura T, Kato K, Ishihara S, Morito T, Mizobuchi K, Iwama H, Masaki T. Prediction of invasion depth for submucosal differentiated gastric cancer by magnifying endoscopy with narrow-band imaging. *Oncol Rep* 2012; **28**: 841-847 [PMID: 22752002 DOI: 10.3892/or.2012.1889]
 - 64 **Kikuchi D**, Iizuka T, Hoteya S, Yamada A, Furuhashi T, Yamashita S, Domon K, Nakamura M, Matsui A, Mitani T, Ogawa O, Watanabe S, Kaise M. Usefulness of magnifying endoscopy with narrow-band imaging for determining tumor invasion depth in early gastric cancer. *Gastroenterol Res Pract* 2013; **2013**: 217695 [PMID: 23401676 DOI: 10.1155/2013/217695]
 - 65 **Cho JH**. Advanced Imaging Technology Other than Narrow Band Imaging. *Clin Endosc* 2015; **48**: 503-510 [PMID: 26668796 DOI: 10.5946/ce.2015.48.6.503]
 - 66 **Osawa H**, Yoshizawa M, Yamamoto H, Kita H, Satoh K, Ohnishi H, Nakano H, Wada M, Arashiro M, Tsukui M, Ido K, Sugano K. Optimal band imaging system can facilitate detection of changes in depressed-type early gastric cancer. *Gastrointest Endosc* 2008; **67**: 226-234 [PMID: 18061596 DOI: 10.1016/j.gie.2007.06.067]
 - 67 **Yoshizawa M**, Osawa H, Yamamoto H, Satoh K, Nakano H, Tsukui M, Sugano K. Newly developed optimal band imaging system for the diagnosis of early gastric cancer. *Dig Endosc* 2008; **20**: 194-197
 - 68 **Yoshizawa M**, Osawa H, Yamamoto H, Kita H, Nakano H, Satoh K, Shigemori M, Tsukui M, Sugano K. Diagnosis of elevated-type early gastric cancers by the optimal band imaging system. *Gastrointest Endosc* 2009; **69**: 19-28 [PMID: 19111685 DOI: 10.1016/j.gie.2008.09.007]
 - 69 **Mouri R**, Yoshida S, Tanaka S, Oka S, Yoshihara M, Chayama K. Evaluation and validation of computed virtual chromoendoscopy in early gastric cancer. *Gastrointest Endosc* 2009; **69**: 1052-1058 [PMID: 19152892 DOI: 10.1016/j.gie.2008.08.032]
 - 70 **Jung SW**, Lim KS, Lim JU, Jeon JW, Shin HP, Kim SH, Lee EK, Park JJ, Cha JM, Joo KR, Lee JI. Flexible spectral imaging color enhancement (FICE) is useful to discriminate among non-neoplastic lesion, adenoma, and cancer of stomach. *Dig Dis Sci* 2011; **56**: 2879-2886 [PMID: 21800158 DOI: 10.1007/s10620-011-1831-7]
 - 71 **Kikuste I**, Stirna D, Liepniece-Karele I, Leja M, Dinis-Ribeiro

- M. The accuracy of flexible spectral imaging colour enhancement for the diagnosis of gastric intestinal metaplasia: do we still need histology to select individuals at risk for adenocarcinoma? *Eur J Gastroenterol Hepatol* 2014; **26**: 704-709 [PMID: 24901816 DOI: 10.1097/MEG.000000000000108]
- 72 **Tanioka Y**, Yanai H, Sakaguchi E. Ultraslim endoscopy with flexible spectral imaging color enhancement for upper gastrointestinal neoplasms. *World J Gastrointest Endosc* 2011; **3**: 11-15 [PMID: 21258601 DOI: 10.4253/wjge.v3.i1.11]
- 73 **Osawa H**, Yamamoto H, Miura Y, Ajibe H, Shinhata H, Yoshizawa M, Sunada K, Toma S, Satoh K, Sugano K. Diagnosis of depressed-type early gastric cancer using small-caliber endoscopy with flexible spectral imaging color enhancement. *Dig Endosc* 2012; **24**: 231-236 [PMID: 22725107 DOI: 10.1111/j.1443-1661.2011.01224.x]
- 74 **Dohi O**, Yagi N, Wada T, Yamada N, Bito N, Yamada S, Gen Y, Yoshida N, Uchiyama K, Ishikawa T, Takagi T, Handa O, Konishi H, Wakabayashi N, Kokura S, Naito Y, Yoshikawa T. Recognition of endoscopic diagnosis in differentiated-type early gastric cancer by flexible spectral imaging color enhancement with indigo carmine. *Digestion* 2012; **86**: 161-170 [PMID: 22889937 DOI: 10.1159/000339878]
- 75 **Kodashima S**, Fujishiro M. Novel image-enhanced endoscopy with i-scan technology. *World J Gastroenterol* 2010; **16**: 1043-1049 [PMID: 20205272 DOI: 10.3748/wjg.v16.i9.1043]
- 76 **Li CQ**, Li Y, Zuo XL, Ji R, Li Z, Gu XM, Yu T, Qi QQ, Zhou CJ, Li YQ. Magnified and enhanced computed virtual chromoendoscopy in gastric neoplasia: a feasibility study. *World J Gastroenterol* 2013; **19**: 4221-4227 [PMID: 23864787 DOI: 10.3748/wjg.v19.i26.4221]
- 77 **Kaneko K**, Oono Y, Yano T, Ikematsu H, Odagaki T, Yoda Y, Yagishita A, Sato A, Nomura S. Effect of novel bright image enhanced endoscopy using blue laser imaging (BLI). *Endosc Int Open* 2014; **2**: E212-E219 [PMID: 26135095 DOI: 10.1055/s-0034-1390707]

P- Reviewer: Tham TCK

S- Editor: Qiu S L- Editor: A E- Editor: Wu HL



Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms

Toshiyuki Yoshio, Tsutomu Nishida, Yoshito Hayashi, Hideki Iijima, Masahiko Tsujii, Junko Fujisaki, Tetsuo Takehara

Toshiyuki Yoshio, Junko Fujisaki, Department of Gastroenterology, Cancer Institute Hospital, Tokyo 135-8550, Japan

Toshiyuki Yoshio, Department of Gastroenterology, Osaka National Hospital, National Hospital Organization, Osaka 560-8565, Japan

Tsutomu Nishida, Department of Gastroenterology, Toyonaka Municipal Hospital, Osaka 560-8565, Japan

Yoshito Hayashi, Hideki Iijima, Masahiko Tsujii, Tetsuo Takehara, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka 560-8565, Japan

Masahiko Tsujii, Department of Gastroenterology, Higashiosaka City General Hospital, Osaka 560-8565, Japan

Author contributions: Yoshio T contributed to the conception, collected materials and wrote the manuscript; Nishida T contributed to the conception and supervised; Hayashi Y, Iijima H, Tsujii M, Fujisaki J and Takehara T made critical revisions related to important intellectual content of the manuscript.

Conflict-of-interest statement: The authors reported no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Tsutomu Nishida, MD, PhD, Department of Gastroenterology, Toyonaka Municipal Hospital, 4-14-1 Shibahara, Toyonaka, Osaka 560-8565, Japan. tnishida.gastro@gmail.com

Telephone: +81-6-68430101
Fax: +81-6-68583531

Received: June 6, 2016
Peer-review started: June 11, 2016
First decision: July 20, 2016
Revised: August 12, 2016
Accepted: September 21, 2016
Article in press: September 22, 2016
Published online: December 16, 2016

Abstract

Endoscopic submucosal dissection (ESD) is minimally invasive and thus has become a widely accepted treatment for gastric neoplasms, particularly for patients with comorbidities. Antithrombotic agents are used to prevent thrombotic events in patients with comorbidities such as cardio-cerebrovascular diseases and atrial fibrillation. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Dual antiplatelet therapy (DAPT), a representative combination therapy, is frequently used after placement of drug-eluting stents and has a high risk of delayed bleeding. In patients receiving DAPT, gastric ESD may be postponed until DAPT is no longer required. HBT is often required for patients treated with anticoagulants and has an extremely high bleeding risk. The continuous use of warfarin or direct oral anticoagulants may be possible alternatives. Here, we show that some antithrombotic therapies in high thrombosis-risk patients increase delayed bleeding after gastric ESD, whereas most antithrombotic therapies do not. The management of high thrombosis-risk patients is crucial for improved

outcomes.

Key words: Antithrombotic therapy; Endoscopic submucosal dissection; Heparin bridge therapy; Dual antiplatelet therapy; Delayed bleeding

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: It is unclear if antithrombotic therapy increases delayed bleeding after endoscopic submucosal dissection (ESD) of gastric neoplasms. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents, such as dual antiplatelet therapy (DAPT), and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Both patients with DAPT and HBT have a high risk of delayed bleeding. The management of these antithrombotic therapies is important in the perioperative period of ESD.

Yoshio T, Nishida T, Hayashi Y, Iijima H, Tsujii M, Fujisaki J, Takehara T. Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms. *World J Gastrointest Endosc* 2016; 8(20): 756-762 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/756.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.756>

INTRODUCTION

Endoscopic resection of early gastric cancer (EGC) has been developed and applied to many patients since the establishment of criteria for node-negative cancers^[1] and the advancement of endoscopic submucosal dissection (ESD)^[2,3]. In multicenter studies, we have reported that ESD is a feasible method for the treatment of EGC^[4] and that the long-term outcome of gastric ESD is satisfactory^[5]. A risk of metachronous gastric cancer exists following ESD or endoscopic mucosal resection, even when the procedure is curative^[6,7]. The cumulative 3-year risk is 5.9%^[7]. However, we also demonstrated that nearly all secondary cancers after ESD (97%) were treatable by repeated ESD following scheduled endoscopic surveillance^[5]. Consequently, ESD can preserve the entire stomach and improve patient post-operative quality of life. Therefore, ESD has become a more acceptable treatment option for EGC than gastrectomy, particularly for patients with comorbidities^[8].

Delayed bleeding is one of the major complications of gastric ESD, and the delayed bleeding rate is 3.1%-6.5%^[4,9,10]. In most cases, delayed bleeding is treated successfully by endoscopic hemostasis; however, some patients require transfusion or surgery, and these situations can be fatal^[11]. The reported risk

factors for delayed bleeding include larger lesions^[10], lesions with ulceration^[10,12], and longer procedure time^[1,13]. The risk is highest for lesions in the middle and lower third^[9]. Electronic coagulation of vessels in the ulcer bed after ESD was reported to decrease delayed bleeding^[9]. In our analysis, half of delayed bleeding occurred the day of ESD or the next day, and the remainder occurred within 2 wk, with the exception of 1 case that occurred 22 d after ESD^[14]. It has been argued that second-look endoscopy after ESD prevents delayed bleeding. However, Goto *et al.*^[15] showed that second-look endoscopy did not decrease delayed bleeding in a retrospective analysis. A prospective randomized control study also denied a preventive effect of second-look endoscopy for delayed bleeding^[16].

Antithrombotic therapy, including antiplatelet agents and anticoagulants, is increasingly used worldwide to prevent cerebro-cardiovascular events^[17,18]. These prophylactic agents reduce the risks of thromboembolic events but simultaneously increase the risk of bleeding complications. Most patients with EGC are elderly, and these patients commonly exhibit several comorbidities that require medical treatment, particularly antithrombotic therapy. Risks for delayed bleeding after ESD in patients with antithrombotic therapy depend on the type of endoscopic treatment and the use of antithrombotic therapy.

In this review, we discuss the problems of antithrombotic therapy associated with delayed bleeding after gastric ESD. This review is not a systematic review because of the limited evidence and the variety of patients with various comorbidities receiving many types of antithrombotic agents. However, we searched the entire MEDLINE database to identify the literature on antithrombotic therapy and gastric ESD and included as many studies as possible.

EFFECT OF ANTIPLATELET AGENTS ON GASTRIC ESD

Antiplatelet agents are used to prevent platelet aggregation for prophylaxis of secondary cerebro-cardioembolic events after the occurrence of stroke or ischemic heart disease^[19]. Antiplatelet agents include thienopyridines, protease-activated receptor-1 inhibitors, glycoprotein IIb/IIIa receptor inhibitors, aspirin and non-steroidal anti-inflammatory drugs. When patients exhibit a low risk of thrombosis, antithrombotic agents can be discontinued. Antithrombotic therapy with appropriate cessation is not considered to increase delayed bleeding rates^[14,20]. In some high thrombosis-risk patients, it is difficult to discontinue antithrombotic therapy during the perioperative period of ESD. Administration of these antithrombotic agents in combination further complicates the management of these agents. In these patients, the continuous use of minimum antithrombotic agents during ESD is an option.

The recent guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) in 2016^[21] and

the Japan Gastroenterological Endoscopy Society in 2014^[22] recommend the continuous use of aspirin during endoscopic procedures in high thrombosis-risk patients, even if the procedures carry a high risk of bleeding. For gastric ESD, a multivariate analysis^[23-25] found that the continuous use of aspirin did not increase delayed bleeding, supporting the application of this treatment; however, the delayed bleeding rate was slightly increased (3.6%-21.1%)^[23-26]. Moreover, the delayed bleeding rate was considerably higher in patients receiving dual antiplatelet therapy (DAPT) with continuous aspirin and cessation of thienopyridines (35.5%) than in patients who did not receive antithrombotic medications^[25].

For patients with coronary artery stents, DAPT with aspirin plus thienopyridines is recommended for 30 d after placement of a bare metal stent and for one year after placement of a drug-eluting stent (DES)^[27]. Cessation of these agents within the period resulted in a high risk of stent thrombosis^[28]. Thus, according to the consensus statement from the American College of Cardiology Foundation and the American College of Gastroenterology, it is recommended to defer elective endoscopic procedures up to 12 mo from the time of DES placement and perform endoscopic procedures 5 to 7 d after thienopyridine cessation^[29]. In addition, aspirin should be continued throughout the perioperative period, and thienopyridine should be resumed once hemostasis is achieved^[29]. The timing of ESD for EGC should be decided based on the balance of cancer progression and bleeding risk. EGC often remains in the early stage for a period^[30]. Thus, ESD can be delayed in patients with DES placement, provided that the EGC lesion is still considered resectable after the completion of required DAPT.

The management of patients with DAPT for ESD is difficult. A delayed bleeding rate as high as 35.5%^[25] was reported when ESD was performed with continuous aspirin and cessation of thienopyridines following the guidelines^[21,22,29]. Moreover, patients receiving DAPT for ESD face thrombotic risk from the cessation of thienopyridines, and this thrombotic risk can be increased if delayed bleeding occurs^[11,14]. However, it is sometimes necessary to perform ESD in patients with DAPT with continuous aspirin and cessation of thienopyridines who have a risk of delayed bleeding and thrombosis. Care must be taken to identify the initial symptoms of delayed bleeding and thrombotic events. There is insufficient evidence for methods to minimize both bleeding risk and thrombotic risk during DAPT, and we have no data on cases of continuous administration of both aspirin and thienopyridines or cessation of aspirin and continuous thienopyridines.

EFFECTS OF ANTICOAGULANTS ON GASTRIC ESD

Anticoagulants prevent thrombotic events in patients with conditions such as arterial fibrillation (AF) and deep

vein thrombosis by interfering with the native clotting cascade. Anticoagulants include oral warfarin, direct oral anticoagulants (DOACs: Dabigatran, rivaroxaban, apixaban, and edoxaban), and heparin derivatives.

The risk of thromboembolism associated with withdrawal of anticoagulants varies considerably. AF is the most common reason for the use of anticoagulant therapy, and the risk of thrombotic events is approximately 1% when anticoagulation is interrupted for 4 to 7 d^[31,32]. Thrombotic events can cause serious complications and can be fatal. Thus, all patients on anticoagulant therapy are recommended to be treated as having a high risk of thrombosis^[22]. Thus, for the cessation of anticoagulants, heparin bridge therapy (HBT) is required to prevent thrombotic events during the perioperative period^[33-35]. However, ESD with HBT carries an extremely high risk of delayed bleeding, with a delayed bleeding rate of 23.8%-37.5% as we previously reported^[14,36-38].

DOACs are administered without the need to monitor their effects due to their rapid action and effectiveness in preventing cerebrovascular events^[39-42]. Before endoscopic procedures, 1 to 3 d of cessation is recommended in patients without renal dysfunction according to the ASGE guideline^[21] based on the half-lives of the agents (8-15 h)^[39-42]. According to the British Society of Gastroenterology and ASGE guidelines, at least 2 d of cessation is recommended before endoscopic procedures^[43]. By contrast, warfarin requires 5 d of cessation to cancel the effect^[44], and HBT is required during this period. After the procedure, DOACs should be re-administered without heparin because DOACs achieve their maximum effect shortly (1-4 h) after re-administration, in contrast to warfarin^[39-42,45]. Thus, shorter perioperative periods of controlling anticoagulant effects can be applied for DOACs compared with warfarin.

Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper. For gastric ESD for patients, we observed a delayed bleeding rate of 16.7% (3/18) in patients using DOACs, which did not differ significantly from the delayed bleeding rate of 23.5% (4/17) observed in patients using warfarin during the same period^[46]. However, the hospitalization period was significantly shorter in patients on DOACs compared with those on warfarin (8 d vs 14 d: $P < 0.01$) because the period of HBT was shorter^[46]. Further investigations are needed to understand the effect of DOACs on endoscopic procedures.

In high thrombosis-risk patients with comorbidities, combination use of antiplatelet agents and anticoagulants is occasionally required, which also increases delayed bleeding^[14].

TIMING OF DELAYED BLEEDING

Koh *et al.*^[47] reported that antithrombotic therapy was a risk factor for late bleeding [later than post-operative

Table 1 Multivariate analysis of risk factors for delayed bleeding: Antithrombotic therapy and patient and lesion characteristics

Ref.	No. of patients	Risk factor identified by multivariate analysis	OR (95%CI)	Risk factors identified by univariate analysis
Furuhata <i>et al</i> ^[36]	1781	HBT	10.04 (4.35-23.16)	HBT, multiple antithrombotic agents, tumor size greater than 20 mm, lower third location, UL+ tumors, operation time longer than 100 min, and cardiovascular disease
		Multiple antithrombotic agents	5.44 (2.00-14.79)	
		Lower third location	2.17 (1.32-3.58)	
		Operation time longer than 100 min	2.00 (1.25-3.20)	
Matsumura <i>et al</i> ^[37]	413	CKD undergoing hemodialysis	33.86 (4.72-242.74)	HBT, tumor size over 40 mm, CKD undergoing hemodialysis
		HBT	5.77 (1.67-19.96)	
		Lesion size greater than 40 mm	3.70 (1.09-12.52)	

HBT: Heparin bridge therapy; CKD: Chronic kidney disease.

day (POD) 5]. Tounou *et al*^[25] reported late bleeding (later than POD 8) was significantly more frequent in cases with DAPT but not cases with single aspirin therapy. In cases with HBT, the timing of delayed bleeding was later than in cases without HBT (POD 3.8 ± 4.1 vs POD 8.0 ± 5.7 , $P < 0.05$)^[14]. In cases without HBT, half of delayed bleeding cases occurred on POD 0 and 1; however, in cases with HBT, only 10% of the cases occurred on POD 0 and 1^[14].

IS HBT FEASIBLE FOR GASTRIC ESD?

A recent, randomized control study compared discontinued anticoagulant use with or without HBT in 1884 surgical cases and revealed that HBT did not reduce perioperative arterial thromboembolism but significantly increased major bleeding complications^[48]. A meta-analysis of studies of elective invasive procedures or surgeries revealed that warfarin-treated patients receiving bridge therapy with low-molecular-weight heparin appear to be at an increased risk of both overall and major bleeding and exhibited a similar risk of thromboembolic events as non-bridged patients^[49].

Another randomized control study involving 681 cases of pacemaker or defibrillator surgery revealed that bleeding complications occurred less frequently in patients with continuous warfarin use than in patients in whom warfarin was discontinued with HBT^[50]. Additional meta-analyses supported these results^[51].

Considering these findings together, continuous use of warfarin throughout the perioperative period is a better choice than HBT because continuous use of warfarin likely does not increase bleeding complications and exhibits the same risk for thrombosis. None of them are originated of the outcome of endoscopic procedures nor gastric ESD, these results will change our treatment. Tounou *et al*^[52] reported a case of gastric ESD safely performed with continuous use of warfarin; however, further investigation is needed, such as a randomized study comparing gastric ESD with continuous ESD and with HBT.

For patients requiring HBT, continuous use of warfarin and switching warfarin to DOACs are candidate new strategies, although data to support their use are lacking.

ANALYSIS OF BLEEDING RISK IN ANTITHROMBOTIC THERAPY BY COMPARING PATIENT AND LESION CHARACTERISTICS

High thrombosis-risk patients are often at a high risk of delayed bleeding under antithrombotic therapy with multiple agents, particularly patients with HBT and accompanying comorbidities. The antithrombotic therapies, patient comorbidities and EGC characteristics with the highest risks for delayed bleeding remain unclear.

Furuhata *et al*^[36] conducted a multivariate analysis of these factors and identified HBT (OR = 10.04), multiple antithrombotic agents (OR = 5.44), the lower third of the stomach (OR = 2.17), and an operation time longer than 100 min (OR = 2.00) as independent risk factors. Matsumura *et al*^[37] identified chronic kidney disease (CKD) undergoing hemodialysis (OR = 33.86), HBT (OR = 5.77) and a lesion size greater than 40 mm (OR = 3.70) as risk factors (Table 1).

We performed a bleeding risk analysis in 1563 consecutive patients with 1671 gastric neoplasms treated by ESD^[53] as an extended analysis of our previous study^[11] (unpublished data). This study included 283 (18%) patients receiving antithrombotic agents who all discontinued the agents before ESD. The delayed bleeding rates were similar between patients receiving no antithrombotic therapy and those who discontinued antithrombotic agents without HBT (5.6% vs 4.9%); however, the delayed bleeding rate was significantly higher (21.9%) in patients with HBT ($P < 0.01$). Moreover, the delayed bleeding rate increased in proportion to the number of discontinued drugs (two drugs: 15.6%, $P < 0.01$; three drugs: 27.3%, $P < 0.05$). Patients on warfarin or ticlopidine had a significant risk of delayed bleeding compared with patients receiving no antithrombotic agent. In a univariate analysis of tumor and patient factors, tumor size greater than 30 mm, tumor in the middle third of the stomach, tumor with ulceration, patients with CKD and male gender were identified as risk factors for delayed bleeding.

Multivariate analysis showed that HBT (OR = 6.14), lesion in the middle third of the stomach (OR = 2.21),

ulceration in tumor (OR = 1.97) and tumor size greater than 30 mm (OR = 1.75) were significant, independent risk factors for delayed bleeding. HBT (OR = 16.43) and CKD (OR = 6.34) were identified as significant risk factors for blood transfusions by multivariate analysis.

The results of these studies show that HBT is the most significant independent factor for delayed bleeding compared with other factors involving patient and lesion characteristics.

THROMBOTIC EVENTS

Few studies of the relationship between thrombotic events and endoscopic procedures have been conducted, and incidence rates of thrombotic events related to gastric ESD of 0%–4.2% have been reported^[14,20,23,54]. We observed one patient who developed a thrombotic event^[14]. This patient received HBT during the peri-operative period and exhibited delayed bleeding on POD 10. After successful endoscopic hemostasis, we restarted heparin, and his activated partial thromboplastin time was sufficiently prolonged on POD 11. However, a cerebral infarction developed on POD 13. This case suggests that delayed bleeding can lead to thrombotic events by reducing intravascular volume and causing hypercoagulability after bleeding. Numata *et al.*^[11] also reported a case of femoral artery infarction consequent to delayed bleeding after gastric ESD that led to death. These findings suggest that the prevention of delayed bleeding is important for preventing thrombotic events in patients at a high risk for thromboembolism.

CONCLUSION

Most antithrombotic therapies do not increase the risk of delayed bleeding during gastric ESD; however, patients receiving multiple antithrombotic agents, including DAPT, and patients on anticoagulants requiring HBT have a high risk for delayed bleeding. These high thrombosis-risk patients with accompanying comorbidities may have a high risk of delayed bleeding under strong antithrombotic therapy.

To prevent the exposure of these patients to a serious risk of acute ischemic events, new strategies should be developed to replace HBT and to address DAPT. Well-designed prospective and comparative clinical studies are needed to obtain further evidence regarding the management of antithrombotic therapy.

ACKNOWLEDGMENTS

We are deeply grateful to those who assisted with our study, including Kawai N (Osaka Police Hospital, Osaka, Japan); Yuguchi K (Suita Municipal Hospital, Osaka, Japan); Yamada T, Iwasaki T, Iwasaki R and Mita E (Osaka National Hospital, Osaka, Japan); Yabuta T and Kitamura S (Sakai City Hospital, Osaka, Japan); Komori M (Osaka Rosai Hospital, Osaka, Japan); Kato M (Tokyo Medical Center, Tokyo, Japan); and Michida T (Teikyo

University Chiba Medical Center, Chiba, Japan).

REFERENCES

- 1 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/PL00011720]
- 2 **Yamamoto H**, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, Sugano K. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointest Endosc* 2002; **56**: 507-512 [PMID: 12297765 DOI: 10.1067/mge.2002.128108]
- 3 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002 DOI: 10.1016/S1542-3565(05)00291-0]
- 4 **Akasaka T**, Nishida T, Tsutsui S, Michida T, Yamada T, Ogiyama H, Kitamura S, Ichiba M, Komori M, Nishiyama O, Nakanishi F, Zushi S, Nishihara A, Iijima H, Tsujii M, Hayashi N. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by osaka university ESD study group. *Dig Endosc* 2011; **23**: 73-77 [PMID: 21198921 DOI: 10.1111/j.1443-1661.2010.01062.x]
- 5 **Kato M**, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, Yoshio T, Nakamura T, Komori M, Kawai N, Nishihara A, Nakanishi F, Nakahara M, Ogiyama H, Kinoshita K, Yamada T, Iijima H, Tsujii M, Takehara T. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013; **62**: 1425-1432 [PMID: 22914298 DOI: 10.1136/gutjnl-2011-301647]
- 6 **Nasu J**, Doi T, Endo H, Nishina T, Hirasaki S, Hyodo I. Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection. *Endoscopy* 2005; **37**: 990-993 [PMID: 16189772 DOI: 10.1055/s-2005-870198]
- 7 **Nakajima T**, Oda I, Gotoda T, Hamanaka H, Eguchi T, Yokoi C, Saito D. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? *Gastric Cancer* 2006; **9**: 93-98 [PMID: 16767364 DOI: 10.1007/s10120-006-0372-9]
- 8 **Nishida T**, Kato M, Yoshio T, Akasaka T, Yoshioka T, Michida T, Yamamoto M, Hayashi S, Hayashi Y, Tsujii M, Takehara T. Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J Gastrointest Endosc* 2015; **7**: 524-531 [PMID: 25992191 DOI: 10.4253/wjge.v7.i5.524]
- 9 **Takizawa K**, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy* 2008; **40**: 179-183 [PMID: 18322872 DOI: 10.1055/s-2007-995530]
- 10 **Okada K**, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]
- 11 **Numata N**, Oka S, Tanaka S, Higashiyama M, Sanomura Y, Yoshida S, Arihiro K, Chayama K. Clinical outcomes of endoscopic submucosal dissection for early gastric cancer in patients with chronic kidney disease. *J Gastroenterol Hepatol* 2013; **28**: 1632-1637 [PMID: 23808356 DOI: 10.1111/jgh.12320]
- 12 **Mukai S**, Cho S, Kotachi T, Shimizu A, Matuura G, Nonaka M, Hamada T, Hirata K, Nakanishi T. Analysis of delayed bleeding after endoscopic submucosal dissection for gastric epithelial neoplasms. *Gastroenterol Res Pract* 2012; **2012**: 875323 [PMID: 22536221 DOI: 10.1155/2012/875323]
- 13 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for

- early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]
- 14 **Yoshio T**, Nishida T, Kawai N, Yuguchi K, Yamada T, Yabuta T, Komori M, Yamaguchi S, Kitamura S, Iijima H, Tsutsui S, Michida T, Mita E, Tsujii M, Takehara T. Gastric ESD under Heparin Replacement at High-Risk Patients of Thromboembolism Is Technically Feasible but Has a High Risk of Delayed Bleeding: Osaka University ESD Study Group. *Gastroenterol Res Pract* 2013; **2013**: 365830 [PMID: 23843783 DOI: 10.1155/2013/365830]
 - 15 **Goto O**, Fujishiro M, Kodashima S, Ono S, Niimi K, Hirano K, Yamamichi N, Koike K. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest Endosc* 2010; **71**: 241-248 [PMID: 19922919 DOI: 10.1016/j.gie.2009.08.030]
 - 16 **Mochizuki S**, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut* 2015; **64**: 397-405 [PMID: 25301853 DOI: 10.1136/gutjnl-2014-307552]
 - 17 **Lansberg MG**, O'Donnell MJ, Khatir P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e601S-e636S [PMID: 22315273 DOI: 10.1378/chest.11-2302]
 - 18 **Levine GN**, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011; **58**: e44-122 [PMID: 22070834 DOI: 10.1016/j.jacc.2011.08.007]
 - 19 **D'Agostino RB**, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; **117**: 743-753 [PMID: 18212285 DOI: 10.1161/CIRCULATIONAHA.107.699579]
 - 20 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or anti-platelet agents. *Dig Liver Dis* 2009; **41**: 725-728 [PMID: 19230799 DOI: 10.1016/j.dld.2009.01.007]
 - 21 **Acosta RD**, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaikat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016; **83**: 3-16 [PMID: 26621548 DOI: 10.1016/j.gie.2015.09.035]
 - 22 **Fujimoto K**, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, Mine T, Yoshino J, Kinoshita Y, Ichinose M, Matsui T. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; **26**: 1-14 [PMID: 24215155 DOI: 10.1111/den.12183]
 - 23 **Lim JH**, Kim SG, Kim JW, Choi YJ, Kwon J, Kim JY, Lee YB, Choi J, Im JP, Kim JS, Jung HC, Song IS. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; **75**: 719-727 [PMID: 22317881 DOI: 10.1016/j.gie.2011.11.034]
 - 24 **Cho SJ**, Choi IJ, Kim CG, Lee JY, Nam BH, Kwak MH, Kim HJ, Ryu KW, Lee JH, Kim YW. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; **44**: 114-121 [PMID: 22271021 DOI: 10.1055/s-0031-1291459]
 - 25 **Tounou S**, Morita Y, Hosono T. Continuous aspirin use does not increase post-endoscopic dissection bleeding risk for gastric neoplasms in patients on antiplatelet therapy. *Endosc Int Open* 2015; **3**: E31-E38 [PMID: 26134769 DOI: 10.1055/s-0034-1390764]
 - 26 **Sanomura Y**, Oka S, Tanaka S, Numata N, Higashiyama M, Kanao H, Yoshida S, Ueno Y, Chayama K. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2014; **17**: 489-496 [PMID: 24142107 DOI: 10.1007/s10120-013-0305-3]
 - 27 **Grines CL**, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007; **115**: 813-818 [PMID: 17224480 DOI: 10.1161/CIRCULATIONAHA.106.180944]
 - 28 **Eisenberg MJ**, Richard PR, Libersan D, Filion KB. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation* 2009; **119**: 1634-1642 [PMID: 19289638 DOI: 10.1161/CIRCULATIONAHA.108.813667]
 - 29 **Becker RC**, Scheiman J, Dauerman HL, Spencer F, Rao S, Sabatine M, Johnson DA, Chan F, Abraham NS, Quigley EM. Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. *Am J Gastroenterol* 2009; **104**: 2903-2917 [PMID: 19935784 DOI: 10.1038/ajg.2009.667]
 - 30 **Tsukuma H**, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: a non-concurrent, long term, follow up study. *Gut* 2000; **47**: 618-621 [PMID: 11034575 DOI: 10.1136/gut.47.5.618]
 - 31 **Garcia DA**, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, Hylek EM. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008; **168**: 63-69 [PMID: 18195197 DOI: 10.1001/archinternmed.2007.23]
 - 32 **Blacker DJ**, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology* 2003; **61**: 964-968 [PMID: 14557569 DOI: 10.1212/01.WNL.0000086817.54076.EB]
 - 33 **Keaton C**, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med* 1997; **336**: 1506-1511 [PMID: 9154771 DOI: 10.1056/NEJM199705223362107]
 - 34 **Hirsh J**, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol* 2003; **41**: 1633-1652 [PMID: 12742309 DOI: 10.1016/S0735-1097(03)00416-9]
 - 35 **Hirsh J**, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy: Heparin : a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; **103**: 2994-3018 [PMID: 11413093 DOI: 10.1161/01.CIR.103.24.2994]
 - 36 **Furuhata T**, Kaise M, Hoteya S, Iizuka T, Yamada A, Nomura K, Kuribayashi Y, Kikuchi D, Matsui A, Ogawa O, Yamashta S, Mitani T. Postoperative bleeding after gastric endoscopic submucosal dissection in patients receiving antithrombotic therapy. *Gastric Cancer* 2016 Jan 11; Epub ahead of print [PMID: 26754296 DOI: 10.1007/s10120-015-0588-7]
 - 37 **Matsumura T**, Arai M, Maruoka D, Okimoto K, Minemura S, Ishigami H, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. *BMC Gastroenterol* 2014; **14**: 172 [PMID: 25280756 DOI: 10.1186/1471-230X-14-172]
 - 38 **Matsumoto M**, Mabe K, Tsuda M, Ono M, Omori S, Takahashi M, Yoshida T, Ono S, Nakagawa M, Nakagawa S, Shimizu Y, Kudo T, Sakamoto N, Kato M. Multicenter study on hemorrhagic risk of

- heparin bridging therapy for periendoscopic thromboprophylaxis. *BMC Gastroenterol* 2015; **15**: 89 [PMID: 26215103 DOI: 10.1186/s12876-015-0315-1]
- 39 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]
 - 40 **Patel MR**, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]
 - 41 **Granger CB**, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Gerdas M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981-992 [PMID: 21870978 DOI: 10.1056/NEJMoa1107039]
 - 42 **Giugliano RP**, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104 [PMID: 24251359 DOI: 10.1056/NEJMoa1310907]
 - 43 **Veitch AM**, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Endoscopy* 2016; **48**: 385-402 [PMID: 26890676 DOI: 10.1055/s-0042-102652]
 - 44 **Schulman S**, Elbazi R, Zondag M, O'Donnell M. Clinical factors influencing normalization of prothrombin time after stopping warfarin: a retrospective cohort study. *Thromb J* 2008; **6**: 15 [PMID: 18925967 DOI: 10.1186/1477-9560-6-15]
 - 45 **Vanassche T**, Hirsh J, Eikelboom JW, Ginsberg JS. Organ-specific bleeding patterns of anticoagulant therapy: lessons from clinical trials. *Thromb Haemost* 2014; **112**: 918-923 [PMID: 25187203 DOI: 10.1160/TH14-04-0346]
 - 46 **Tomida H**, Yoshio T, Ninomiya T, Michitaka K, Fujisaki J, Igarashi M. The effects of anticoagulants on the clinical outcome of endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2015; **30**: 303
 - 47 **Koh R**, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]
 - 48 **Douketis JD**, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med* 2015; **373**: 823-833 [PMID: 26095867 DOI: 10.1056/NEJMoa1501035]
 - 49 **Siegal D**, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012; **126**: 1630-1639 [PMID: 22912386 DOI: 10.1161/CIRCULATIONAHA.112.105221]
 - 50 **Birnie DH**, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, Simpson CS, Ayala-Paredes F, Coutu B, Leiria TL, Essebag V. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013; **368**: 2084-2093 [PMID: 23659733 DOI: 10.1056/NEJMoa1302946]
 - 51 **Ghanbari H**, Phard WS, Al-Ameri H, Latchamsetty R, Jongnamgsin K, Crawford T, Good E, Chugh A, Oral H, Bogun F, Morady F, Pelosi F. Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices. *Am J Cardiol* 2012; **110**: 1482-1488 [PMID: 22906894 DOI: 10.1016/j.amjcard.2012.06.057]
 - 52 **Tounou S**, Morita Y, Hosono T, Harada H, Hayasaka K, Katsuyama Y, Suehiro S, Nagano S, Shimizu T. Endoscopic submucosal dissection for early gastric cancer without interruption of warfarin and aspirin. *Endosc Int Open* 2015; **3**: E307-E310 [PMID: 26357675 DOI: 10.1055/s-0034-1392018]
 - 53 **Yoshio T**, Nishida T, Kawai N, Yuguchi K, Yamada T, Kitamura S, Komori M, Michida T, Iijima H, Tsujii M, Takehara T. Sa1564 heparin replacement was the most significant risk of delayed bleeding in gastric ESD by multivariate analysis of anti-thrombotic therapy, comorbidities and characteristics of tumors: a multicenter study by Osaka University ESD Study Group. *Gastrointest Endosc* 2013; **77**: AB252 [DOI: 10.1016/j.gie.2013.03.615]
 - 54 **Takeuchi T**, Ota K, Harada S, Edogawa S, Kojima Y, Tokioka S, Umegaki E, Higuchi K. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol* 2013; **13**: 136 [PMID: 24010587 DOI: 10.1186/1471-230X-13-136]

P- Reviewer: Arai M, Hirasawa K, Iizuka T, Toyokawa T
S- Editor: Gong ZM **L- Editor:** A **E- Editor:** Wu HL



Retrospective Study

Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection

Darren D Ballard, Neel Choksi, Jingmei Lin, Eun-Young Choi, B Joseph Elmunzer, Henry Appelman, Douglas K Rex, Hala Fatima, William Kessler, John M DeWitt

Darren D Ballard, Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI 53226, United States

Neel Choksi, Division of Gastroenterology, University of Michigan, Ann Arbor, MI 48109, United States

Jingmei Lin, Department of Pathology, Indiana University, Indianapolis, IN 46202, United States

Eun-Young Choi, Henry Appelman, Department of Pathology, University of Michigan, Ann Arbor, MI 48109, United States

B Joseph Elmunzer, Division of Gastroenterology and Hepatology, University of South Carolina, Charleston, SC 29425, United States

Douglas K Rex, Hala Fatima, William Kessler, John M DeWitt, Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, IN 46202, United States

Author contributions: Ballard DD and DeWitt JM designed the research; Ballard DD, Choksi N, Lin J, Choi EY, Elmunzer BJ, Appelman H, Rex DK, Fatima H, Kessler W and DeWitt JM performed the research; Ballard DD and DeWitt JM analyzed the data; Ballard DD and DeWitt JM wrote the manuscript; Choksi N, Lin J, Choi EY, Elmunzer BJ, Appelman H, Rex DK, Fatima H and Kessler W critically reviewed the manuscript.

Institutional review board statement: The study was reviewed and approved by the IRB at Indiana University and the University of Michigan.

Informed consent statement: No informed consent was required as this was a retrospective study approved by the IRB.

Conflict-of-interest statement: There are no conflicts of interest for any of the authors of this study.

Data sharing statement: Dataset is available from the corresponding author at dballard@mcw.edu.

Open-Access: This article is an open-access article which was

selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Darren D Ballard, Assistant Professor, Division of Gastroenterology and Hepatology, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226, United States. dballard@mcw.edu

Telephone: +1-414-9556821

Fax: +1-414-9556215

Received: May 20, 2016

Peer-review started: May 20, 2016

First decision: July 20, 2016

Revised: August 23, 2016

Accepted: September 13, 2016

Article in press: September 18, 2016

Published online: December 16, 2016

Abstract

AIM

To investigate the outcomes and recurrences of pT1b esophageal adenocarcinoma (EAC) following endoscopic mucosal resection (EMR) and associated treatments.

METHODS

Patients undergoing EMR with pathologically confirmed T1b EAC at two academic referral centers were retrospectively identified. Patients were divided into 4 groups based on treatment following EMR: Endoscopic therapy alone (group A), endoscopic therapy with either chemotherapy, radiation or both (group B), surgical

resection (group C) or no further treatment/lost to follow-up (< 12 mo) (group D). Pathology specimens were reviewed by a central pathologist. Follow-up data was obtained from the academic centers, primary care physicians and/or referring physicians. Univariate analysis was performed to identify factors predicting recurrence of EAC.

RESULTS

Fifty-three patients with T1b EAC underwent EMR, of which 32 (60%) had adequate follow-up \geq 12 mo (median 34 mo, range 12-103). There were 16 patients in group A, 9 in group B, 7 in group C and 21 in group D. Median follow-up in groups A to C was 34 mo (range 12-103). Recurrent EAC developed overall in 9 patients (28%) including 6 (38%) in group A (median: 21 mo, range: 6-73), 1 (11%) in group B (median: 30 mo, range: 30-30) and 2 (29%) in group C (median 21 mo, range: 7-35). Six of 9 recurrences were local; of the 6 recurrences, 5 were treated with endoscopy alone. No predictors of recurrence of EAC were identified.

CONCLUSION

Endoscopic therapy of T1b EAC may be a reasonable strategy for a subset of patients including those either refusing or medically unfit for esophagectomy.

Key words: Esophageal cancer; Submucosal; T1b; Endoscopic mucosal resection; Chemotherapy; Esophagectomy

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Endoscopic eradication therapy (EET) is reported as safe and effective for low risk T1b esophageal adenocarcinomas (EAC), but overall data is lacking. We retrospectively evaluated patients with T1b EAC treated with EET, EET with chemotherapy and/or radiation therapy and surgical resection. The overall recurrence rate was 28% at median 21 mo (range: 6-73) following EMR. In those treated with endoscopic mucosal resection alone, recurrence rate was 38% at median 21 mo (range: 6-73). Six of the 9 recurrences were local; 5 were treated with endoscopy alone. EET of T1b EAC may be a reasonable treatment strategy for a subset of these patients.

Ballard DD, Choksi N, Lin J, Choi EY, Elmunzer BJ, Appelman H, Rex DK, Fatima H, Kessler W, DeWitt JM. Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection. *World J Gastrointest Endosc* 2016; 8(20): 763-769 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/763.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.763>

INTRODUCTION

Due to the inherent morbidity and rare mortality associated with esophagectomy and lymph node

dissection, endoscopic eradication therapy [including endoscopic mucosal resection (EMR) and ablative techniques] has been increasingly used as a safe, effective and potentially curative organ-sparing procedure to treat high grade dysplasia (Tis lesions) and intramucosal esophageal cancer (T1a lesions)^[1-5]. When complete resection or eradication of T1a cancers is confirmed, disease is generally considered cured due to the low rate of reported lymph node metastasis (< 2%) in these patients^[6]. Tumors that penetrate the submucosa of the esophagus (T1b cancers), however metastasize to regional lymph nodes in up to 30% of cases and the likelihood for metastases increases the further the tumor penetrates from the first third (sm1) into the lower two thirds (sm2 and sm3) of the submucosal layer^[7-11]. Therefore, endoscopic eradication therapies (EET) have generally not been employed in patients with T1b cancers.

The use of EET for primary treatment of T1b tumors was initially reported in patients with "low risk" submucosal esophageal cancers (macroscopically polypoid or flat, invasion limited to the upper 1/3 of the submucosa, no invasion of the vessels or lymphatic system, well to moderate tumor differentiation); this has more recently been updated in a larger series ($n = 66$) from the same group with similar characteristics showing recurrent or metachronous carcinomas developed in 19% of patients with an estimated 5 year survival rate of 84%^[12,13]. A study from two referral centers in the Netherlands examined EET of deep T1a and T1b EAC ($n = 75$) with an overall recurrence rate of 9%^[14]. A study from a tertiary center in the United States reported a group of patients ($n = 29$) with T1b EAC with sm1 (46%) and sm2-3 (54%) invasion that underwent either EET, chemo/radiation or a combination of both and showed mean survival of 34.8 mo with a 38% mortality rate^[15].

To our knowledge, there are no studies examining the outcomes and predictors of disease recurrence in patients with pathologically staged T1b esophageal cancer treated with EET alone, surgery, or adjuvant therapy following endoscopic resection. Identification of predictive factors for recurrence and outcomes following endoscopic therapy in this population would help to identify and tailor appropriate treatment. For this reason, we aimed to (1) retrospectively evaluate the clinical outcomes of pT1b esophageal cancers following EMR; (2) to compare the recurrence rates of cancer when patients are treated with EET alone, EET in association with chemotherapy, radiation therapy or both and surgical resection; and (3) to evaluate the predictors of recurrence of T1b esophageal cancer following EMR.

MATERIALS AND METHODS

Study population and design

All patients age \geq 18 years of age who underwent EMR of the esophagus from 2001 to 2013 at India-

na University Medical Center and the University of Michigan were retrospectively identified from institutional endoscopic databases. Patient charts were then reviewed to identify the subset of patients with pathologically (p) staged T1b esophageal cancer that comprised the study population. Patients with treatment by endoscopic submucosal dissection or ≤ 12 mo of follow-up after resection were excluded. Approval for this study was obtained by the institutional review boards at both participating institutions prior to any study activities.

Pre-procedure imaging with CT and/or PET scans was initially obtained in all patients to exclude distant metastasis. Endoscopic ultrasound (EUS) was also used in selected patients to assess the depth of any visualized mass or detect and sample any suspicious lymph nodes. Prior to EMR, all patients underwent EGD with a detailed exam of the mucosa of the esophagus and gastric cardia. The use of advanced imaging techniques such as narrow band imaging and chromoendoscopy was at the discretion of the endoscopist. After identification of the site(s) for resection, either cap-assisted (Olympus America Inc., Center Valley, PA) or band ligation-assisted EMR (Cook Medical Inc., Winston Salem, NC) was performed. The specimens retrieved were placed into formalin and sent to pathology for evaluation for examination by an experienced gastrointestinal pathologist.

Treatment groups

Treatment after identification of a pT1b esophageal cancer at each institution was at the discretion of the endoscopist as well as referring physicians based on the pathology findings, patient comorbidities and patient wishes. For study purposes, treatment after EMR was classified as utilizing endoscopy alone (group A), endoscopy with either chemotherapy, radiation or both (group B), surgical resection alone (group C), or no further treatment or lost to follow-up (group D). Patients in group A underwent additional EMR with or without ablation, surveillance endoscopies and cross-sectional imaging as determined by the treating physicians.

Pathology assessment

Endoscopic resection specimens from both institutions were initially reviewed by local pathologists. For the current study, slides from both institutions were re-reviewed by a single gastrointestinal pathologist at Indiana University for the following characteristics: Depth of tumor invasion (sm1 vs sm2/3), tumor differentiation (well, moderate and poor), presence or absence of lymphatic or perineural invasion (LPI) and the status of deep and lateral margins following resection. A T1b esophageal cancer was defined as tumor extending beyond the muscularis mucosa and into tissue which contains submucosal glands or tumor adjacent to large caliber arteries which would not be present in the mucosa. Tumors classified as sm1 had invasion of tumor into the upper 1/3 of the submucosa and sm2/3 depth

of invasion was defined as invasion into the lower 2/3 of the submucosa. Tumor differentiation was determined based on standard histologic features such as growth pattern, gland formation and degree of atypia. LPI was defined as the presence of malignant tumor cells within a lymphatic channel or neural bundle.

Follow-up

Follow-up cross-sectional imaging and endoscopy were performed at the discretion of the endoscopist and consulting physicians at each institution. These data on the study population were obtained both from the treating institution as well as referring physicians and primary care physicians and consisted of endoscopic procedures, imaging studies and clinic visits. The end point of follow-up for study patients included: Death, surgery for esophageal cancer, or loss of patient contact. Patient death was identified by reviewing medical records or by searching the Social Security Death Index. Tumor recurrence was diagnosed when biopsies from the previous or adjacent esophageal EMR site or from either regional or metastatic sites demonstrated pathology consistent with the primary cancer. A univariate analysis was performed in order to identify factors predicting recurrence of cancer after EMR and associated treatment. Variables analyzed in the analysis included: method of EMR (cap vs band), pathology depth (sm1 vs sm2/3), initial tumor location (proximal 2/3 vs distal 1/3 of the esophagus), lymphovascular and/or perineural invasion, degree of tumor differentiation, positive vs negative deep and lateral EMR margins, and primary treatment modality (endoscopic \pm chemotherapy and/or radiation therapy vs surgery).

Statistical analysis

The data were analyzed descriptively using means, medians, ranges and standard deviations. The variables between groups were compared using Fisher's exact tests (GraphPad). $P < 0.05$ was considered statistically significant.

RESULTS

Sixty patients who underwent EMR were found to have pT1b esophageal cancer, including 53 (88%) with adenocarcinoma and 7 (12%) with squamous cell carcinoma. Of the 53 patients with adenocarcinomas, 32 patients (60%) had adequate follow-up after EMR of ≥ 12 mo (median 34 mo, range 12-103). There were 16 patients in group A, 9 patients in group B, 7 patients in group C and 21 patients in group D (8 with no further treatment and 13 without required 12 mo follow-up). Demographics, EMR method (cap vs band), pathology findings and follow-up are summarized in Table 1. Pathology in patients who underwent esophagectomy (group C) showed no residual dysplasia or malignancy in 2, adenocarcinoma with negative nodes in 1, dysplasia in 3 and 1 with unknown findings.

No recurrence of carcinoma developed in 23 patients

Table 1 Characteristics of T1b esophageal adenocarcinoma by treatment modality following endoscopic mucosal resection

	Group A (n = 16)	Group B (n = 9)	Group C (n = 7)	Group D (n = 21)	Overall (n = 53)
Average age, yr	75 ± 78	70 ± 14	62 ± 5	72 ± 13	71 ± 12
Median follow-up after EMR, mo (range)	34 (12-102)	27 (12-56)	49 (13-103)	N/A	34 (12-103) (for groups A-C, n = 32)
EMR method, n (%)					
Cap	6 (38)	0 (0)	2 (29)	4 (19)	12 (23)
Band	10 (62)	9 (100)	5 (71)	17 (81)	41 (77)
Pathology depth, n (%)					
sm1	6 (38)	4 (44)	1 (14)	2 (10)	13 (25)
sm2/3	10 (62)	5 (56)	6 (86)	19 (90)	40 (75)
Tumor location, n (%)					
Proximal two-thirds	2 (13)	1 (11)	1 (14)	5 (24)	9 (17)
Distal one-third	14 (88)	8 (89)	6 (86)	16 (76)	44 (83)
LPI, n (%)					
Yes	1 (6)	1 (11)	0 (0)	3 (14)	5 (9)
No	15 (94)	8 (89)	7 (100)	18 (86)	48 (91)
Differentiation, n (%)					
Well-moderate	14 (88)	6 (67)	7 (100)	15 (71)	42 (79)
Poor	2 (13)	3 (33)	0 (0)	6 (29)	11 (21)
EMR margins for cancer, n (%)					
Deep -/lateral -	6 (38)	2 (22)	1 (14)	2 (10)	11 (21)
Deep -/lateral +	5 (31)	1 (11)	1 (14)	4 (19)	11 (21)
Deep +/lateral +	4 (25)	6 (66)	5 (71)	13 (62)	28 (53)
Deep +/lateral -	1 (6)	0 (0)	0 (0)	2 (10)	3 (6)
Recurrences, n (%)					
Yes	6 (38)	1 (11)	2 (29)	N/A	9 (28)
No	10 (63)	8 (88)	5 (71)		23 (72)
Median time to recurrence (mo, range)	21 (6-73)	30 (30-30)	21 (7-35)		21 (6-73) (for groups A-C, n = 32)
Location of recurrence					
Local	5	0	1	N/A	6
Metastatic	1	1	1		3

EMR: Endoscopic mucosal resection; LPI: Lymphatic/perineural invasion.

Table 2 Recurrence rates of esophageal adenocarcinoma investigated risk factors of esophageal adenocarcinoma (n = 3 n (%))

Variable	Recurrence rates	P value
EMR method		
Cap	4/8 (50)	0.18
Band	5/24 (21)	
Pathology depth		
sm1	3/11 (27)	0.11
sm2/3	6/21 (29)	
Tumor location		
Proximal 2/3 esophagus	2/4 (50)	0.56
Distal 1/3 esophagus	7/28 (25)	
LPI		
Yes	0/2 (0)	1.00
No	9/30 (30)	
Differentiation		
Well-moderate	8/27 (30)	1.00
Poor	1/5 (20)	
Deep EMR margins		
Positive	4/16 (25)	1.00
Negative	5/16 (31)	
Lateral EMR margins		
Positive	6/22 (27)	1.00
Negative	3/10 (30)	
Primary treatment		
Endoscopic +/- CRT	7/25 (28)	1.00
Surgical	2/7 (29)	

EMR: Endoscopic mucosal resection; LPI: Lymphatic/perineural invasion; CRT: Chemoradiation.

Table 3 Endoscopic ultrasound staging/path accuracy for T1b esophageal adenocarcinoma

EUS staging (n = 51)	Pathologic staging		
	pT1sm1 (n = 12)	pT1sm2/3 (n = 39)	Overall (all pT1b) (n = 51)
uT0 Nx	0	1	1
uT1 Nx	11	36	47
uT2 Nx	1	2	3
T staging accuracy	91.7%	92.3%	92.2%

(72%) during a median follow-up of 31 mo (range 12-103). Recurrent adenocarcinoma developed in 9 (28%) patients among all 3 groups. There was no statistically significant differences between recurrences in group A (n = 6; 38%), group B (n = 1; 11%) and group C (n = 2; 29%). Median time to recurrence was 21 mo (range 6-73) in group A, 30 mo in group B, and 9 mo (range 8-10) in group C. Of the recurrences in group A, 5 were local and 1 was metastatic. These local recurrences in group A were treated with further EET alone in two, EET and radiation in one, EET with chemotherapy with radiation in one and radiation in one. The single metastatic recurrence in group A was treated with chemotherapy and radiation. The single recurrence in group B was metastatic and had no further treatment. The two recurrences in group C were

Table 4 Studies evaluating endoscopic management of T1b esophageal adenocarcinoma

Ref.	# Patients	Depth of invasion	Histology	Margins	Remission	Recurrence	Survival
Manner <i>et al</i> ^[12]	21	sm1	Well to moderately differentiated, no lymphovascular invasion	Lateral margins negative in 12	95% at mean 5.3 mo	28% at mean 62 mo (range 45-89)	67% estimated 5-yr survival
Alvarez Herrero <i>et al</i> ^[14]	18	sm1 and sm2/3	Well, moderately and poorly differentiated, some with lymphovascular invasion	Not reported	Not reported	17%	Not reported
Tian <i>et al</i> ^[15]	29	sm1 and sm2-3	Not reported	Not reported	Not reported	Not reported	62% with median duration 34.8 mo
Manner <i>et al</i> ^[13]	66	sm1	Well to moderately differentiated, no lymphovascular invasion	Not reported	84% at mean 4.5 mo	21% at mean 22 mo (range 6-60)	84% estimated 5-yr survival

local in one and metastatic in one. The local recurrence in group C was treated with chemotherapy and the metastatic recurrence in group C was treated with local resection of a hepatic metastasis. No predictors of recurrence of adenocarcinoma were identified on univariate analysis (Table 2).

Of the 32 patients in groups A, B and C, 7 died within 3 years of EMR giving an overall 3 year mortality for all causes of 22%. Specifically within each group, 3 year mortality rates were 13% in group A (2/16), 44% in group B (4/9), and 14% in group C (1/7).

EUS was performed prior to EMR in 51 (96%) of the 53 patients with T1b EAC. T staging accuracy (for T1 malignancy) on EUS for pT1b tumors overall was 92%; specifically for pT1sm1 tumors was 92% and for pT1sm2/3 tumors was 92% (Table 3).

DISCUSSION

Endoscopic therapy is an alternative to esophagectomy for mucosal EAC in select populations^[1] and has been included in national guidelines as a curative form of treatment^[16]. More recently, "low risk" T1b EAC have been treated with EET as primary therapy in Germany with recurrence rates ranging from 19% to 28% and estimated five-year survival rates up to 84%^[12,13]. Two small studies from the United States ($n = 15$) and the Netherlands ($n = 18$) showed a recurrence rate of 21% and 17% respectively, with all recurrences in the latter study having initial sm2/3 depth of invasion^[14,15].

In our study, we aimed to retrospectively evaluate and compare outcomes of various treatments for T1b EAC after EMR and to evaluate predictors of recurrence after those treatments. We found an overall recurrence rate of 28%, which was not statistically different between those treated with endotherapy alone (38%), chemotherapy, radiation or both (11%) or those undergoing esophagectomy (29%). The overall observed rate of recurrence in our study for those undergoing EET alone is higher than previously reported in patients undergoing EET as primary therapy (Table 4). These differences likely reflect differences in population between most other series (which included primarily

low risk T1bsm1 EAC) and our study which evaluated outcomes for all T1b patients. The rate of recurrence in our study does compare favorably to that previously reported for a small cohort of patients with sm2/3 invasion of 33%^[14].

We found that most recurrences following EMR in those treated at least partly endoscopically (groups A and B) were localized. Of the patients who underwent EET alone, there were 6 recurrences (38%), five of which were localized to the esophagus with only 1 having metastatic disease 21 mo following EMR. Of the patients who underwent EET + chemotherapy and/or radiation, 1 (11%) had metastatic recurrence 30 mo after resection. Therefore, EET with or without chemotherapy or radiation, may be a reasonable initial treatment strategy for a subset of patients with T1b EAC, especially those that refuse or are unfit for surgical intervention due to medical comorbidities or home support since most recurrences appear to be localized.

In those that underwent esophagectomy, we identified 2 recurrences out of 7 patients (29%). Our recurrence rate is similar to a recent retrospective study including 26 patients with T1b EAC undergoing surgical resection which showed a 23% recurrence rate^[17]. Recurrence or metastatic disease discovered after resection may be related to micrometastatic disease that was unable to be identified prior to esophagectomy.

Overall, we found a 3-year survival rate of 78% when evaluating the patients in our study; more specifically a rate of 87% in those treated with EET only and 56% in those treated with EET + chemotherapy and/or radiation. When combining those treated at least partly endoscopically, the survival rate at 3 years was 76%. Manner *et al*^[13] previously have shown an estimated 5-year survival rate of 84% in those treated with EET with "low risk" T1b. Our lower survival rate is likely reflected in our patient population, as we evaluated all patients with T1b EAC and not only those with "low risk" disease. Tian *et al*^[15] reported on a group of patients ($n = 29$) more similar to our cohort including "low risk" and higher risk T1b EAC patients [sm1 (46%) and sm2-3 (54%) invasion] that underwent either EET, chemo/radiation or a combination of both and showed a

survival rate of 72% at mean 34.8 mo.

We failed to identify any individual predictors of cancer recurrence in this population. A previous retrospective study with 39 patients with T1b EAC treated with EET alone showed decreased survival in patients with older age and lymphovascular invasion, although it did not specifically assess for predictors of cancer recurrence^[18]. In our study, we were unable to identify lymphatic and perineural invasion as predictors of recurrence.

A recent prospective study from Germany evaluated the risk of lymph node metastases when comparing "low risk" (sm1 invasion) to "high risk" (sm2/3 invasion) T1b EAC in patients treated both surgically and with EET, and found a 2% risk of lymph node metastasis in pT1bsm1 tumors and 9% in pT1bsm2/3 tumors, which is lower than has generally been reported in prior studies^[19]. In our study which includes both sm1 and sm2/3 invasion, we similarly found 6% of patients with metastatic lymph nodes either on initial staging or on surveillance (one each with sm1 and sm2/3 tumors).

Previous studies have shown excellent accuracy for staging both T1a and T1b esophageal cancers. Specifically, a previous meta-analysis showed good accuracy with area under the curve > 0.93 for both T1a and T1b esophageal cancers^[20]. We also demonstrated overall diagnostic accuracy of 91% for pT1 lesions in our cohort.

Our study has several strengths including data from all T1b cancers removed by EMR from two tertiary care referral centers, re-review of all pathology by a single pathologist, and evaluation of outcomes of medical and surgical therapy for these patients. However, our study is limited by the number of patients who refused further therapy or were lost to follow-up which may limit the ability to compare outcomes from various treatments after resection.

In conclusion, our study shows that endoscopic therapy alone following EMR of a T1b cancer is associated with a recurrence rate of 38%. Therefore, treatment with adjuvant therapy appears reasonable in this population when possible. No particular variable is predictive of recurrence following EMR of T1b adenocarcinomas. Therefore, future research into the management and risk stratification of these patients after EMR is warranted.

COMMENTS

Background

Endoscopic eradication therapy (EET) (including endoscopic mucosal resection and ablative techniques) have become standard of care for high grade dysplasia and T1a esophageal cancer. The use of EET for T1b cancers is more controversial due to the higher risk of lymph node involvement and data is lacking.

Research frontiers

Recent studies have shown that "low risk" T1b esophageal cancer can be treated safely and effectively with EET. Many of these studies include relatively small numbers of patients, and do not address higher risk T1b esophageal

cancers or the use of EET in conjunction with other treatment modalities such as chemotherapy or radiation.

Innovations and breakthroughs

In the current study, the authors attempted to evaluate the clinical outcomes and recurrence rates of T1b esophageal cancers treated with EET alone, as well as those treated with EET in conjunction with chemotherapy and/or radiation as well as those undergoing surgical resection. In addition, the authors attempted to identify factors that may predict recurrence.

Applications

For patients with T1b esophageal cancer and treated with EET alone, the recurrence rate was 38%; therefore treatment with adjuvant therapy in conjunction with EET seems reasonable in patients that are either unable to or refuse to undergo esophagectomy. No particular variables were identified that predict recurrence of cancer in this population following EMR. Further research in these areas regarding management and risk stratification will be required.

Terminology

T1b esophageal adenocarcinoma - cancer which invades into but not through the submucosal layer; Endoscopic eradication therapy - Endoscopic treatment including endoscopic mucosal resection and ablative techniques such as radiofrequency ablation and cryotherapy.

Peer-review

A retrospective study is reported to investigate outcomes and recurrences of T1b esophageal adenocarcinomas following EMR. The topic is relevant, and the data collection done by the authors are very useful.

REFERENCES

- 1 Pech O, May A, Manner H, Behrens A, Pohl J, Weferling M, Hartmann U, Manner N, Huijsmans J, Gossner L, Rabenstein T, Vieth M, Stolte M, Ell C. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology* 2014; **146**: 652-660.e1 [PMID: 24269290 DOI: 10.1053/j.gastro.2013.11.006]
- 2 Moss A, Bourke MJ, Hourigan LF, Gupta S, Williams SJ, Tran K, Swan MP, Hopper AD, Kwan V, Bailey AA. Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. *Am J Gastroenterol* 2010; **105**: 1276-1283 [PMID: 20179694 DOI: 10.1038/ajg.2010.1]
- 3 Ngamruengphong S, Wolfsen HC, Wallace MB. Survival of patients with superficial esophageal adenocarcinoma after endoscopic treatment vs surgery. *Clin Gastroenterol Hepatol* 2013; **11**: 1424-1429.e2; quiz e81 [PMID: 23735443 DOI: 10.1016/j.cgh.2013.05.025]
- 4 Pech O, Bollschweiler E, Manner H, Leers J, Ell C, Holscher AH. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. *Ann Surg* 2011; **254**: 67-72 [PMID: 21532466 DOI: 10.1097/SLA.0b013e31821d4bf6]
- 5 Das A, Singh V, Fleischer DE, Sharma VK. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. *Am J Gastroenterol* 2008; **103**: 1340-1345 [PMID: 18510606 DOI: 10.1111/j.1572-0241.2008.01889.x]
- 6 Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol* 2012; **107**: 850-862; quiz 863 [PMID: 22488081 DOI: 10.1038/ajg.2012.78]
- 7 Leers JM, DeMeester SR, Oezcelik A, Klipfel N, Ayazi S, Abate E, Zehetner J, Lipham JC, Chan L, Hagen JA, DeMeester TR. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. *Ann Surg* 2011; **253**: 271-278 [PMID: 21119508 DOI: 10.1097/SLA.0b013e3181fbad42]

- 8 **Dubecz A**, Kern M, Solymosi N, Schweigert M, Stein HJ. Predictors of Lymph Node Metastasis in Surgically Resected T1 Esophageal Cancer. *Ann Thorac Surg* 2015; **99**: 1879-1885; discussion 1886 [PMID: 25929888 DOI: 10.1016/j.athoracsur.2015.02.112]
- 9 **Bollschweiler E**, Baldus SE, Schröder W, Prenzel K, Gutschow C, Schneider PM, Hölscher AH. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. *Endoscopy* 2006; **38**: 149-156 [PMID: 16479422 DOI: 10.1055/s-2006-924993]
- 10 **Stein HJ**, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann Surg* 2005; **242**: 566-573; discussion 573-575 [PMID: 16192817]
- 11 **Badreddine RJ**, Prasad GA, Lewis JT, Lutzke LS, Borkenhagen LS, Dunagan KT, Wang KK. Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma. *Clin Gastroenterol Hepatol* 2010; **8**: 248-253 [PMID: 19948247 DOI: 10.1016/j.cgh.2009.11.016]
- 12 **Manner H**, May A, Pech O, Gossner L, Rabenstein T, Günter E, Vieth M, Stolte M, Ell C. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. *Am J Gastroenterol* 2008; **103**: 2589-2597 [PMID: 18785950 DOI: 10.1111/j.1572-0241.2008.02083.x]
- 13 **Manner H**, Pech O, Heldmann Y, May A, Pohl J, Behrens A, Gossner L, Stolte M, Vieth M, Ell C. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. *Clin Gastroenterol Hepatol* 2013; **11**: 630-635; quiz e45 [PMID: 23357492 DOI: 10.1016/j.cgh.2012.12.040]
- 14 **Alvarez Herrero L**, Pouw RE, van Vilsteren FG, ten Kate FJ, Visser M, van Berge Henegouwen MI, Weusten BL, Bergman JJ. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. *Endoscopy* 2010; **42**: 1030-1036 [PMID: 20960392 DOI: 10.1055/s-0030-1255858]
- 15 **Tian J**, Prasad GA, Lutzke LS, Lewis JT, Wang KK. Outcomes of T1b esophageal adenocarcinoma patients. *Gastrointest Endosc* 2011; **74**: 1201-1206 [PMID: 22000793 DOI: 10.1016/j.gie.2011.08.006]
- 16 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: 1084-1091 [PMID: 21376940 DOI: 10.1053/j.gastro.2011.01.030]
- 17 **Schölvinc D**, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J, Weusten B. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. *Surg Endosc* 2016; **30**: 4102-4113 [PMID: 27357927 DOI: 10.1007/s00464-016-5071-y]
- 18 **Leggett CL**, Lewis JT, Wu TT, Schleck CD, Zinsmeister AR, Dunagan KT, Lutzke LS, Wang KK, Iyer PG. Clinical and histologic determinants of mortality for patients with Barrett's esophagus-related T1 esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 2015; **13**: 658-664.e1-e3 [PMID: 25151255 DOI: 10.1016/j.cgh.2014.08.016]
- 19 **Manner H**, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D, Fisseler-Eckhoff A, Stolte M, Vieth M, Ell C. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. *Surg Endosc* 2015; **29**: 1888-1896 [PMID: 25294553 DOI: 10.1007/s00464-014-3881-3]
- 20 **Thosani N**, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, Swisher SG, Hofstetter WL, Guha S, Bhutani MS. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. *Gastrointest Endosc* 2012; **75**: 242-253 [PMID: 22115605 DOI: 10.1016/j.gie.2011.09.016]

P- Reviewer: Bossen L, Dobrucali AM, Dinc T, Veitch AM

S- Editor: Qi Y **L- Editor:** A **E- Editor:** Wu HL



Retrospective Study

Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience

Alexandra Shingina, George Ou, Oliver Takach, Sigrid Svarta, Ricky Kwok, Jessica Tong, Kieran Donaldson, Eric Lam, Robert Enns

Alexandra Shingina, Department of Gastroenterology, Faculty of Medicine, University of Toronto, Toronto General Hospital, Ontario M5G 2C4, Canada

George Ou, Sigrid Svarta, Department of Gastroenterology, Faculty of Medicine, University of British Columbia, Vancouver V5Z 1M9, Canada

Oliver Takach, Ricky Kwok, Jessica Tong, Kieran Donaldson, Eric Lam, Robert Enns, Division of Gastroenterology, Saint Paul Hospital, Vancouver V6Z 2K5, Canada

Author contributions: Shingina A and Enns R designed the project; Shingina A and Svarta S designed ethics proposal; Shingina A, Ou G, Svarta S, Kwok R, Donaldson K collected the data; Takach O and Lam E analyzed the data; Shingina A, Ou G, Svarta S, Lam E and Enns R wrote the manuscript.

Institutional review board statement: This study was reviewed and approved by the University of British Columbia - Providence Health Care Research Institute.

Informed consent statement: The informed consent is not applicable since this study is a retrospective review. All clinical data collected was dissociated from patient identifiers using a combination of alphanumeric characters in accordance to ethics board's requirements.

Conflict-of-interest statement: All authors of this paper have no relevant conflicts of interest to declare.

Data sharing statement: No data were created so no data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Robert Enns, MD, Division of Gastroenterology, Saint Paul Hospital, 770-1190 Hornby Street, Vancouver V6Z 2K5, Canada. rob.enns@ubc.ca
Telephone: +1-604-6886332

Received: April 20, 2016

Peer-review started: April 20, 2016

First decision: June 12, 2016

Revised: July 25, 2016

Accepted: September 6, 2016

Article in press: September 8, 2016

Published online: December 16, 2016

Abstract

AIM

To develop a prediction model aimed at identifying patients that may require higher than usual sedation doses during colonoscopy.

METHODS

A retrospective chart review on 5000 patients who underwent an outpatient colonoscopy at St. Paul's Hospital from 2009 to 2010 was conducted in order to develop a model for identifying patients who will require increased doses of sedatives. Potential predictor variables including age, gender, endoscopy indication, high sedation requirements during previous endoscopies, difficulty of the procedure, bowel preparation quality, interventions, findings as well as current use of benzodiazepines, opioids and alcohol were analyzed. The outcome of study was the use of

high dose of sedation agents for the procedure. In particular, the high dose of sedation was defined as fentanyl greater than 50 mcg and midazolam greater than 3 mg.

RESULTS

Analysis of 5282 patients (mean age 57 ± 12 , 49% female) was performed. Most common indication for the procedure was screening colonoscopy (57%). Almost half of our patients received doses exceeding Fentanyl 50 mcg and Midazolam 3 mg. Logistic regression models identified the following variables associated with high sedation: Younger age (OR = 0.95 95%CI: 0.94-0.95; $P < 0.0001$); abdominal pain (OR = 1.45, 95%CI: 1.08-1.96; $P = 0.01$) and Inflammatory Bowel Disease (OR = 1.45, 95%CI: 1.04-2.03; $P = 0.02$) as indications for the procedure; difficult procedure as defined by gastroenterologist (OR = 1.73, 95%CI: 1.48-2.03; $P < 0.0001$); past history of abdominal surgery (OR = 1.33, 95%CI: 1.17-1.52; $P < 0.0001$) and previous colonoscopy (OR = 1.39, 95%CI: 1.21-1.60; $P = 0.0001$) and alcohol use (OR = 1.26, 95%CI: 1.03-1.54; $P = 0.02$). Age and gender adjusted analysis yielded inflammatory bowel disease as an indication (OR = 3.17, 95%CI: 1.58-6.37; $P = 0.002$); difficult procedure as defined by an endoscopist (OR = 5.13 95%CI: 2.97-8.85; $P = 0.0001$) and current use of opioids, benzodiazepines or antidepressants (OR = 2.88, 95%CI: 1.74-4.77; $P = 0.001$) having the highest predictive value of high sedation requirements. Our prediction model using the following pre-procedural variables including age, indication for the procedure, medication/substance use, previous surgeries yielded an area under the curve of 0.76 for Fentanyl ≥ 100 mcg and Midazolam ≥ 3 mg.

CONCLUSION

Pre-procedural planning is the key in conducting successful, efficient colonoscopy. Logistic regression analysis of 5000 patients who underwent out-patient colonoscopy revealed the following factors associated with increased sedation requirement: Younger age, female gender, difficult endoscopy, specific indications as well as cardiopulmonary complications and current use of opioids/benzodiazepines. Age and gender adjusted analysis yielded similar results. These patients are more likely to need a longer recovery periods post-endoscopy, which could result in additional time and personnel requirements. The final predictive model has good predictive ability for Fentanyl ≥ 100 mcg and Midazolam ≥ 3 mg and fair predictive ability for Fentanyl ≥ 50 mcg and Midazolam ≥ 2 mg. The external validity of this model is planned to be tested in another center.

Key words: Colonoscopy; Sedation; Sedation tolerance; Fentanyl; Midazolam; Predictive model

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This manuscript explores patient specific characteristics that are associated with increased

sedation tolerance based on retrospective review of 5000 patients that underwent outpatient colonoscopies. Using a logistic regression analysis, we developed a predictive model that can identify patients requiring higher than usual sedation doses using pre-procedurally available patient parameters. The final prediction model that includes age, indication for the procedure, medication/substance use, previous surgeries yielded an area under the curve of 0.76 for Fentanyl ≥ 100 mcg and Midazolam ≥ 3 mg. This modelling could help optimize periprocedural planning and potentially identify patients who would benefit from alternative sedation methods, *e.g.*, propofol.

Shingina A, Ou G, Takach O, Svarta S, Kwok R, Tong J, Donaldson K, Lam E, Enns R. Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience. *World J Gastrointest Endosc* 2016; 8(20): 770-776 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/770.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.770>

INTRODUCTION

Lower gastrointestinal endoscopy remains a key modality for colorectal cancer evaluation and polyp detection. Patient satisfaction with colonoscopies remains an important area for quality improvement and have been linked to the ability to achieve adequate sedation in the endoscopy suite^[1]. Several prospective studies evaluated patient characteristics that influence endoscopy satisfaction and identified younger age, female gender, high levels of pre-procedure anxiety and current use of benzodiazepines/opioids as risk factors for decreased procedure tolerance^[2-5]. Currently a combination of benzodiazepines (*e.g.*, Midazolam) with opioids (*e.g.*, Fentanyl) is recommended for sedation during colonoscopic procedures. However, few predictive tools have been developed to accurately identify patients who will require higher than routine doses of procedural sedation.

Recently, one model using a retrospective database was used to evaluate patient pain thresholds included such variables as younger age, procedure indication, gender, trainee participation, psychiatric history and benzodiazepine and opioid use^[5]. However, this model reached only moderate discriminative ability with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.648. The development of an accurate predictive model could simplify procedure planning, eliminate unnecessary patient discomfort thereby improving patient satisfaction. It can also decrease peri-procedural time associated with administration of additional doses of sedatives and ultimately lead to a potentially increased diagnostic yield of the procedure.

In an attempt to address the paucity of data on factors associated with increased sedation rates in

colonoscopy we reviewed our experience in a large tertiary care hospital and developed a predictive tool that could be used for this purpose.

MATERIALS AND METHODS

Patient population and data gathering

A retrospective chart review was conducted on 5282 consecutive patients who underwent a non-urgent, out-patient colonoscopy within a two-year period between January 2009 and December 2010. Patients undergoing upper endoscopy on the same day were excluded. The final analysis included 5064 patients after patients with missing information and duplicate entries were excluded. Charts were reviewed and the following patient related variables were recorded: (1) age at the time of procedure; (2) gender; (3) indication for the procedure; (4) use of sedatives as well as doses; (5) past surgical history; (6) previous endoscopy; (7) high sedation requirements during previous endoscopy; (8) current use of benzodiazepines/opioids/antidepressants; and (9) current alcohol use. Furthermore, peri-procedural factors including: (1) quality of preparation; (2) difficulty of procedure as commented by the endoscopist; (3) finding on endoscopy; (4) interventions; and (5) cardiopulmonary complications.

Definitions

Increased sedation rates were defined as Fentanyl doses > 50 mcg and Midazolam doses > 3 mg a priori at the discretion of the endoscopists at our center. Increased sedation rates during previous endoscopic procedures followed the same definition. However, variable dose cut offs were subsequently tested in predictive models. Mild alcohol use was defined as less than 4 drinks/wk with moderate/severe defined as over 4 drinks/wk. Alcohol use was subsequently excluded from final analysis due to large proportion of missing data. Indication for the procedure was classified into one of five categories: (1) screening/surveillance; (2) abdominal pain; (3) inflammatory bowel disease (IBD); (4) lower gastrointestinal bleeding; (5) change in bowel movements.

Statistical analysis

Summary statistics were used to describe the characteristics of the study cohort. In particular, the data were summarized as mean, standard deviation, for continuous variables and count and percentage for categorical variables. We used a logistic regression model in an attempt to identify variables associated with higher than expected doses for midazolam and fentanyl. These variables were then included in the multivariate regression model.

In order to create a clinical prediction model of increased doses of sedation, multivariable logistic regression model with backward elimination based

Table 1 Study population characteristics

Variable	No. (%)
Age (mean \pm standard deviation)	56.94 \pm 13.06
Female gender	2306 (50.1%)
Indication of the procedure	Screening/surveillance 2892 (57.15%)
	Bleeding 1036 (20.4%)
	Abdominal pain 240 (4.72%)
	Change in bowel movements 690 (13.64%)
	Inflammatory bowel disease 210 (3.99%)
Previous history of surgery	No 2343 (50.7%)
	Yes 2363 (49.26%)
Previous history of colonoscopy and of increased dose of sedation for colonoscopy	Colonoscopy with high dose (Fent > 50 mcg, Midazolam > 3 mg) 3300 (64.1%)
	Colonoscopy with standard dose 470 (9.1%)
	Colonoscopy with unknown sedation dose 305 (5.9%)
	No previous colonoscopy 1076 (20.9%)
Current use of opioids	243 (4.8%)
Current use benzodiazepines	254 (5%)
Current use antidepressants	589 (11.6%)
Current use of opioids or benzodiazepines or antidepressants	826 (16.96%)
Difficult procedure	1038 (19%)
Cardiopulmonary complications	23 (0.4%)
Findings	Any 4139 (78%)
	Polyps 3439 (83%)
	Haemorrhoids 1970 (48%)
	Diverticuli 1050 (35%)
	Colitis 72 (1.7%)
	Stricture 71 (1.7%)
Intervention	Any 3231 (61%)
	Biopsy 2139 (66%)
	Polypectomy 1621 (50%)
Current use alcohol	1930 (46.9%)
Fentanyl dose > 50 mcg	2244 (46%)
Midazolam dose > 3 mg	3000 (62%)
Fentanyl dose > 50 mcg and midazolam > 3 mg	1959 (40%)

on Akaike Information Criterion was applied^[7]. The performance of the final model was evaluated from two aspects, discrimination (the ability to discriminate patients who need high doses and those that do not) and calibration (the agreement between observed outcomes and model predictions). The discrimination of the model was measured with the use of the area under ROC curves. Discrimination is assumed to be useful if $AUC \geq 0.75$ ^[6]. Furthermore, we applied bootstrapping technique to account for model over-fitting as internal model validation. Three hundred bootstrapping samples were created. A biased corrected AUC and calibration plot were generated. All statistical analysis was performed using SAS software. The statistical methods of this study were reviewed by Oliver Takach, Dr. Eric Lam, Terry Lee and Hong Qian.

Table 2 Multivariate logistic regression analysis for Fentanyl dose > 50 mcg

Variable for fentanyl > 50 mcg	Coefficient	P value	OR (95%CI)
Age	-0.04	0.0001	0.957 (0.952-0.963)
Indication for endoscopy			
Bleeding	-0.04	0.62	0.96 (0.82-1.12)
Abdominal pain	0.29	0.06	1.34 (0.99-1.81)
Change in BM	0.07	0.44	1.08 (0.88-1.31)
IBD	0.46	0.009	1.59 (1.22-2.49)
Intraprocedural characteristics			
Difficult procedure	0.45	0.0001	1.57 (1.34-1.81)
Intervention	0.15	0.013	1.17 (1.033-1.32)
Bad preparation	0.16	0.14	1.17 (0.94-1.45)
Past history			
Abdominal surgery	0.33	0.0001	1.40 (1.23-1.59)
Colonoscopy	0.26	0.0002	1.30 (1.13-1.49)
Current medications/substance use			
Opioids	0.34	0.028	1.40 (1.03-1.91)
Benzodiazepines	0.37	0.017	1.45 (1.06-1.98)
Antidepressants	0.26	0.009	1.30 (1.06-1.60)
Alcohol	0.23	0.022	1.26 (1.03-1.54)
(any <i>vs</i> none)			

IBD: Inflammatory bowel disease; BM: Bowel movements.

RESULTS

Characteristics of study population

The study population consisted of 50.1% females, mean age of 56 years (Table 1). The most common indication for colonoscopy was malignancy screening/surveillance that accounted for 57% of procedures. Approximately half of the population had some history of abdominal surgery (49%) and colonoscopy (79%). The use of opioids, benzodiazepines and antidepressants was identified in 4.8%, 5% and 11.6% of patients respectively or 17% of all patients on any of the three drugs. There was a significant proportion of alcohol use data missing (30%); of patients on whom the data was available 46% used alcohol on a regular basis.

The procedure was identified as difficult in 19% by a gastroenterologist. The most common cause for difficult procedure was identified as "tortuous colon" accounting for almost 50%, followed by looping of the colonoscope in 20% of patients. Poor preparation and patient discomfort was identified as a reason in 2% and 3% respectively. Cardiopulmonary complications were recorded in 0.4% of procedures. Presences of any findings were seen in 78% of procedures with polyps being the most common one (83%). Interventions were carried out in 61% of all colonoscopies, most common of those being a biopsy (66%).

Logistic regression analyses to identify variables predicting high sedation doses

Univariate logistic regression analysis revealed that younger age, indication for colonoscopy, intraprocedural characteristics such as difficult procedure, interventional procedure, poor preparation, past history of abdominal

Table 3 Multivariate logistic regression analysis for midazolam dose > 3 mg

Variable for midazolam > 3 mg	Coefficient	P value	OR (95%CI)
Age	-0.05	0.0001	0.94 (0.939-0.95)
Female gender	-0.06	0.0004	0.78 (0.68-0.89)
Indication for endoscopy (reference - screening)			
Bleeding	-0.41	0.0001	0.65 (0.56-0.77)
Abdominal pain	0.38	0.032	1.46 (1.03-2.08)
Change in BM	0.02	0.849	1.02 (0.82-1.25)
IBD	0.19	0.346	1.21 (0.81-1.80)
Intraprocedural characteristics			
Difficult procedure	0.50	0.0001	1.64 (1.38-1.96)
Past history			
Abdominal surgery	0.31	0.0001	1.37 (1.20-1.57)
Medication/substance use			
Opioids	0.38	0.025	1.47 (1.04-2.07)
Antidepressants	0.33	0.018	1.39 (1.11-1.73)

IBD: Inflammatory bowel disease; BM: Bowel movements.

surgery as well as substance use were independently predictive of increased Fentanyl doses defined as more than 50 mcg (data not shown). Including these variables in the multivariate regression model showed that younger age (OR = 0.95, 95%CI: 0.95-0.96), presence of IBD (OR = 1.59, 95%CI: 1.22-2.49), difficult procedure (OR = 1.57, 95%CI: 1.34-1.81), presence of intervention (OR = 1.17, 95%CI: 1.03-1.32), past history of surgery (OR = 1.4, 95%CI: 1.23-1.59) and colonoscopy (OR = 1.3, 95%CI: 1.13-1.49) were predictors of Fentanyl doses over 50 mcg (Table 2).

Similar multivariate analysis of Midazolam dosages over 3 mg revealed female gender (OR = 0.78, 95%CI: 0.68-0.89) in addition to younger age (OR = 0.94, 95%CI: 0.93-0.95), presence of bleeding (OR = 0.65, 95%CI: 0.56-0.77) and abdominal pain (OR = 1.46, 95%CI: 1.03-2.08) as indications for the procedure, difficulty of the procedure (OR = 1.64, 95%CI: 1.38-1.96), history of abdominal surgery (OR = 1.37, 95%CI: 1.20-1.57) as well as opioid (OR = 1.47, 95%CI: 1.04-2.07) and antidepressant use (OR = 1.39, 95%CI: 1.11-1.73) (Table 3).

Multivariate regression analysis of patients requiring both Fentanyl dose of over 50 mcg and midazolam dose over 3 mg revealed the following significant variables: Younger age (OR = 0.95, 95%CI: 0.94-0.95), abdominal pain (OR = 1.45, 95%CI: 1.08-1.96) and IBD (OR = 1.45, 95%CI: 1.04-2.03) as indications for the procedure, difficult procedure (OR = 1.73, 95%CI: 1.48-2.03), past history of abdominal surgery (OR = 1.33, 95%CI: 1.17-1.52) and colonoscopy (OR = 1.39, 95%CI: 1.21-1.60) as well as alcohol use (OR = 1.26, 95%CI: 1.03-1.53) (Table 4).

Age and gender adjusted analysis

Since previously published literature identified younger age and female gender as predictors of high sedation requirements, we also carried out age and gender

Table 4 Multivariate regression analysis of both Fentanyl > 50 mcg and Midazolam > 3 mg

Variable for Fentanyl > 50 mcg and midazolam > 3 mg	Coefficient	P value	OR (95%CI)
Age	-0.04	< 0.0001	0.95 (0.94-0.95)
Indication for endoscopy (reference - screening)			
Bleeding	-0.11	0.18	0.89 (0.76-1.05)
Abdominal pain	0.37	0.01	1.45 (1.08-1.96)
Change in BM	0.13	0.18	1.14 (0.93-1.40)
IBD	0.37	0.02	1.45 (1.04-2.032)
Intraprocedural characteristics			
Difficult procedure	0.55	< 0.0001	1.73 (1.48-2.03)
Interventions	0.1	0.12	1.10 (0.97-1.25)
Past history			
Abdominal surgery	0.30	< 0.0001	1.33 (1.17-1.52)
Colonoscopy	0.33	0.0001	1.39 (1.21-1.60)
Medication/substance use			
Opioids	0.41	0.46	0.49 (0.07-3.36)
Benzodiazepines	0.36	0.36	3.76 (0.21-64)
Antidepressants	0.22	0.6	0.48 (0.03-7.76)
Alcohol	0.23	0.02	1.26 (1.03-1.54)

BM: Bowel movements; IBD: Inflammatory bowel disease.

adjusted analyses (Supplemental Table 1). Significance of only one variable changed: Abdominal pain as an indicator for the procedure was no longer statistically impacting the higher dose of sedation medications ($P = 0.03$ in unadjusted vs $P = 0.06$ in age/gender adjusted analysis).

Development of predictive model

To predict patients who will require higher than routine doses of procedural sedation before the procedure, a prediction model was created using patient characteristics recorded at admission. Age, gender, previous history of surgery, previous history of colonoscopy with high dose, indication of the procedure and current use of opioids, benzodiazepines, antidepressants or alcohol were included in the final model for predicting the use of fentanyl > 50 mcg plus midazolam > 3 mg (Table 5).

In our model the probability of high dose correlated negatively with younger age, with proportional decrease for every 10 years of life, female gender, previous colonoscopies, and history of surgical procedures, composite of current use of opioids/benzodiazepines/antidepressants as well indications for the procedure. The bootstrapping bias corrected ROC AUC of the final prediction model was 0.66 for Midazolam > 3 mg and Fentanyl > 50 mcg doses indicating moderate discriminative ability (supplemental material).

We analysed the predictive ability of our model in variable higher Fentanyl and Midazolam doses (Table 6). The model using Fentanyl > 100 mcg and Midazolam > 3 and 4 mg reached the acceptable level of discrimination ability of 0.7 and remained under 0.8 indicating its moderate discrimination ability.

Table 5 Multivariable prediction model for high Fentanyl and Midazolam doses

Pre-procedural variables	Measurement units	Odds ratio, 95%CI; P value
Age	10-yr	0.62, 0.52-0.73; $P < 0.0001$
Gender	Female vs male	2.31, 1.32-4.05; $P = 0.01$
Previous colonoscopy	Yes vs no	1.98, 1.15-3.42; $P = 0.02$
Previous surgery	Yes vs no	1.33, 0.78-2.25; $P = 0.25$
Current use of opioids, benzodiazepines or antidepressants	Yes vs no	2.50, 1.47-4.27; $P = 0.004$
Indications (reference - screening)	Bleeding	1.90, 1.03-3.51; $P = 0.04$
	Abdominal pain	3.07, 1.29-7.31; $P = 0.01$
	Change in BM	1.45, 0.71-2.97; $P = 0.30$
	IBD	3.01, 1.43-6.35; $P = 0.01$

BM: Bowel movements; IBD: Inflammatory bowel disease.

DISCUSSION

Pre-procedural planning is key for successful and efficient colonoscopy. Identifying patients requiring higher sedation rates could optimize sedation methods and use of scheduling with improved efficiency in addition to better tolerated procedures.

Our analysis of over 5000 patients yielded several prediction variables of high sedation rates. These included: Younger age, indication for the procedure, difficulty of the procedure, previous history of high endoscopy sedation requirements and substance use. A predictive model including patients' age, indication for procedure, medication/substance use, previous surgeries as well as previously high sedation requirements yielded a good predictive model. These factors can help physicians in planning endoscopy slots and ensure appropriate time can be booked for procedure completion.

To our knowledge, this is the first and the largest study using Canadian data that describes sedation tolerance in outpatient colonoscopies. Another predictive model was recently described by Braunstein *et al*^[5] after reviewing data on 13711 EGDs and 21763 colonoscopies using a retrospective database in the United States. In contrast to our study, the stratifying clinical outcomes prior to endoscopy (SCOPE) scoring system included inpatient colonoscopies as well as used a composite endpoint of sedation doses in top quintile stratified per endoscopist plus endoscopist report of patient discomfort or agitation during the procedure. The SCOPE model did not evaluate previous surgical or endoscopic history of the patients, however it did include the use of tobacco and lower BMI. Despite these differences, the final model for colonoscopy prediction tool was similar to ours perhaps validating our findings despite a smaller sample size. The predictive value of the SCOPE class model remained only moderate with areas under the ROC curves of 0.648 and comparable to ours at 0.7. It is possible that the moderate predictive ability of both models is attributed to variables that

Table 6 Performance of prediction model using variable sedation doses cut-offs

Fentanyl (mcg)	Midazolam (mg)	AUC	Prevalence rate
> 50	> 3	0.67	43%
> 50	> 4	0.70	22%
> 75	> 3	0.68	23%
> 75	> 4	0.70	18%
> 100	> 3	0.76	2%
> 100	> 4	0.77	2%

AUC: Area under the curve.

could not be extracted from retrospective data, such as the patient's pre-procedural anxiety as well as the subjective discretion of the endoscopist. Nevertheless, these models may help in pre-identifying patients that may benefit from deeper sedation (e.g., propofol) and may serve as a starting point in pre-endoscopic assessment.

This study has several limitations. First, our experience is limited to one tertiary care center with eight endoscopists. As such, it may have limited generalizability to other centers and perhaps could reflect the specific sedation preferences of individual endoscopists. Second, a large proportion of substance and alcohol use data was missing which could otherwise improve the discriminatory ability of our predictive model. Third, this was a retrospective review study and the model needs to be prospectively evaluated. Finally, propofol was not assessed in this study as it is not commonly used in a Canadian population and as such this study may not be applicable to this patient population.

Further prospective studies are needed to test the model in order to increase its generalizability and also potentially incorporating subjective variables such as patient anxiety and endoscopist subjective judgement.

ACKNOWLEDGMENTS

We would like to thank Terry Lee and Hong Qian for providing statistical support for the analysis; Joseph Frenette for assistance with data collection/sorting; the Department of Gastroenterology of the Saint Paul Hospital for the support with this project.

COMMENTS

Background

Patient satisfactions with colonoscopies remain an important area for quality improvement and have been linked to the ability to achieve adequate sedation in the endoscopy suite. Predicting which patients may require high doses of opioid/benzodiazepine combination may help with peri-procedural planning (e.g., accounting for longer recovery times, using alternative sedation methods such as propofol) and improve overall patient experience.

Research frontiers

Recently, one model using a retrospective database was used to evaluate patient pain thresholds included such variables younger age, procedure indication, gender, trainee participation, psychiatric history and benzodiazepine and opioid

use. However, this model reached only moderate discriminative ability with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.648.

Innovations and breakthroughs

This is the first and the largest study using Canadian data that describes sedation tolerance in outpatient colonoscopies to our knowledge. In this model the probability of high dose correlated negatively with younger age, with proportional decrease for every 10 years of life, female gender, previous colonoscopies, and history of surgical procedures, composite of current use of opioids/benzodiazepines/antidepressants as well indications for the procedure. The model for predicting patients requiring Fentanyl > 100 mcg and Midazolam > 3-4 mg reached the acceptable level of discrimination ability of 0.7 and remained under 0.8 indicating its moderate discrimination ability.

Applications

The analysis of over 5000 patients yielded a moderately predictive model for identifying patients requiring high opioid/benzodiazepine doses. This is in concordance with previously reported models in SCOPE study. It is possible that the moderate predictive ability of both models is attributed to variables that could not be extracted from retrospective data, such as the patient's pre-procedural anxiety as well as the subjective discretion of the endoscopist. Nevertheless, these models may help in pre-identifying patients that may benefit from deeper sedation (e.g., propofol) and may serve as a starting point in pre-endoscopic assessment.

Terminology

To assess the ability of the prediction model to discriminate patients who need high doses with those don't, the concordant statistics (C-index) was calculated. The C-index is equivalent to the area under ROC curve and ranges from 0 to 1. A value of 0.5 is considered as no discrimination ability. As a general rule, a value between 0.7 and 0.8 is considered the threshold for acceptable discriminatory performance and a value of > 0.8 is considered to be the threshold for excellent discriminatory performance.

Peer-review

This paper presents the results of retrospective analysis of sedation dose requirement of benzodiazepine with opiates used for colonoscopy. The basic objective of the study was to provide the data as to the optimization of sedation conditions for patients undergoing colonoscopy. The data obtained with 5000 patients support the notion that the predictive model can help to identify patients requiring higher than usual sedation doses. Statistical analyses were conducted in detail and authors have led a conclusion based on the findings. That was helpful for us to identify patients that may require higher sedation doses for successful and efficient colonoscopy.

REFERENCES

- 1 **Kilgert B**, Rybizki L, Grottke M, Neurath MF, Neumann H. Prospective long-term assessment of sedation-related adverse events and patient satisfaction for upper endoscopy and colonoscopy. *Digestion* 2014; **90**: 42-48 [PMID: 25139268 DOI: 10.1159/000363567]
- 2 **Yacavone RF**, Locke GR, Gostout CJ, Rockwood TH, Thieling S, Zinsmeister AR. Factors influencing patient satisfaction with GI endoscopy. *Gastrointest Endosc* 2001; **53**: 703-710 [PMID: 11375575 DOI: 10.1067/mge.2001.115337]
- 3 **Bal BS**, Crowell MD, Kohli DR, Menendez J, Rashti F, Kumar AS, Olden KW. What factors are associated with the difficult-to-sedate endoscopy patient? *Dig Dis Sci* 2012; **57**: 2527-2534 [PMID: 22565338 DOI: 10.1007/s10620-012-2188-2]
- 4 **Peña LR**, Mardini HE, Nickl NJ. Development of an instrument to assess and predict satisfaction and poor tolerance among patients undergoing endoscopic procedures. *Dig Dis Sci* 2005; **50**: 1860-1871 [PMID: 16187188 DOI: 10.1007/s10620-005-2952-7]
- 5 **Braunstein ED**, Rosenberg R, Gress F, Green PH, Lebwohl B. Development and validation of a clinical prediction score (the SCOPE score) to predict sedation outcomes in patients undergoing endoscopic procedures. *Aliment Pharmacol Ther* 2014; **40**: 72-82

- [PMID: 24815064 DOI: 10.1111/apt.12786]
- 6 **Fan J**, Upadhye S, Worster A. Understanding receiver operating characteristic (ROC) curves. *CJEM* 2006; **8**: 19-20 [PMID: 17175625]
- 7 **Harrell FE**. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression and Survival Analysis. Verlag: Springer, 2001

P-Reviewer: Muguruma N, Slomiany B, Yu B
S-Editor: Qiu S **L-Editor:** A **E-Editor:** Wu HL



Retrospective Study

Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis

Shiro Hayashi, Tsutomu Nishida, Hiromi Shimakoshi, Akiyoshi Shimoda, Takahiro Amano, Aya Sugimoto, Kei Takahashi, Kaori Mukai, Tokuhiko Matsubara, Masashi Yamamoto, Sachiko Nakajima, Koji Fukui, Masami Inada

Shiro Hayashi, Tsutomu Nishida, Hiromi Shimakoshi, Akiyoshi Shimoda, Takahiro Amano, Aya Sugimoto, Kei Takahashi, Kaori Mukai, Tokuhiko Matsubara, Masashi Yamamoto, Sachiko Nakajima, Koji Fukui, Masami Inada, Department of Gastroenterology and Hepatology, Toyonaka Municipal Hospital, Osaka 560-8565, Japan

Author contributions: All authors contributed to this manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Toyonaka Municipal Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis retrospectively used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. However, this study was announced on the website at our hospital for a certain period and subjects who did not want to be used their data in this study were guaranteed the right to refuse.

Conflict-of-interest statement: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Data sharing statement: Dataset is available from the corresponding author at hayashishiro1976@yahoo.co.jp, when data sharing was anonymized and the project was approved by the Institutional Review Board of Toyonaka Municipal Hospital.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Shiro Hayashi, MD, Department of Gastroenterology and Hepatology, Toyonaka Municipal Hospital, 4-14-1 Shibahara, Toyonaka, Osaka 560-8565, Japan. hayashishiro1976@yahoo.co.jp
Telephone: +81-6-68430101
Fax: +81-6-68583531

Received: June 29, 2016

Peer-review started: July 1, 2016

First decision: August 5, 2016

Revised: August 30, 2016

Accepted: September 21, 2016

Article in press: September 22, 2016

Published online: December 16, 2016

Abstract

AIM

To estimate the efficacy of 2 h post-endoscopic retrograde cholangiopancreatography (ERCP) serum amylase levels and other factors for predicting post-ERCP pancreatitis.

METHODS

This was a retrospective, single-center cohort study of consecutive patients who underwent ERCP from January 2010 to December 2013. Serum amylase levels were measured 2 h post-procedure, and patient- and procedure-related pancreatitis (PEP) risk factors were

analyzed using a logistic model.

RESULTS

A total of 1520 cases (average age 72 ± 12 years, 60% male) were initially enrolled in this study, and 1403 cases (725 patients) were ultimately analyzed after the exclusion of 117 cases. Fifty-five of these cases developed PEP. We established a 2 h serum amylase cutoff level of two times the upper limit of normal for predicting PEP. Multivariate analysis revealed that a cannulation time of more than 13 min [odds ratio (OR) 2.28, 95%CI: 1.132-4.651, $P = 0.0210$] and 2 h amylase levels greater than the cutoff level (OR = 24.1, 95%CI: 11.56-57.13, $P < 0.0001$) were significant predictive factors for PEP. Forty-seven of the 55 patients who developed PEP exhibited 2 h amylase levels greater than the cutoff level (85%), and six of the remaining eight patients who developed PEP (75%) required longer cannulation times. Only 2 of the 1403 patients (0.14%) who developed PEP did not exhibit concerning 2 h amylase levels or require longer cannulation times.

CONCLUSION

These findings indicate that the combination of 2 h post-ERCP serum amylase levels and cannulation times represents a valuable marker for identifying patients at high risk for PEP.

Key words: Serum amylase levels; Cannulation time; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Predictor

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Serum amylase levels have a high negative predictive value (NPV; 95%-100%) and have therefore previously been used to predict post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) to facilitate patient discharges. However, the positive predictive value (PPV) of serum amylase is highly variable (4%-62%); therefore, a more useful PEP predictor is needed. In this retrospective study, we identified useful predictive factors *via* multivariate analysis and the combination 2 h amylase levels and cannulation times. The 2 h amylase levels exhibited a good NPV (99%) and a poor PPV (22%) similar to those of previous reports but exhibited a sensitivity of only 86% with respect to PEP detection. However, the combined use of the above two variables increased the sensitivity to 96%; thus, this combination may enable clinicians to detect patients at high risk for PEP during the early phase of treatment.

Hayashi S, Nishida T, Shimakoshi H, Shimoda A, Amano T, Sugimoto A, Takahashi K, Mukai K, Matsubara T, Yamamoto M, Nakajima S, Fukui K, Inada M. Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastrointest Endosc* 2016; 8(20): 777-784 Available from: URL:

<http://www.wjgnet.com/1948-5190/full/v8/i20/777.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.777>

INTRODUCTION

Acute pancreatitis is a common post-endoscopic retrograde cholangiopancreatography (ERCP) complication and is therefore known as post-ERCP pancreatitis (PEP). PEP may result in procedure-related death and is often unpreventable. Moreover, no medications appear to be effective with respect to acute pancreatitis treatment^[1,2]. Andriulli *et al*^[3] conducted a systematic review of 21 selected surveys involving 16855 patients exhibiting a 3.5% incidence of PEP and observed that 0.11% of those patients died. Although many PEP prophylactic treatments have been reported^[4-6], only prompt aggressive intravenous hydration is reportedly effective at reducing morbidity and mortality^[7-10]. Therefore, early PEP identification is important, as it facilitates early intervention and may prevent disease progression and death.

Many studies have investigated the factors that increase the risk of PEP^[7-10]. Those risk factors can generally be divided into the following two types: Patient-related factors and procedure-related factors. The patient-related risk factors for PEP reportedly include previous PEP, female gender, younger age, normal serum bilirubin levels, and the absence of chronic pancreatitis, whereas the procedure-related risk factors for PEP reportedly include cannulation attempt duration, pancreatic guidewire passage, pancreatic injection, precut sphincterotomy, biliary balloon sphincter dilatation, and failed bile duct stone clearance. No evidence exists indicating that hospital ERCP volume influences PEP occurrence^[11,12]. The aforementioned risk factors synergistically increase PEP risk. Serum amylase levels less than 1.5 times the upper limit of normal (ULN) at 2-4 h post-ERCP have a very negative predictive value (NPV) for PEP. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend testing serum amylase or lipase levels 2-6 h after ERCP in patients presenting with pain. Patients exhibiting amylase or lipase values less than 1.5 and 4 times the ULN, respectively, may be discharged on the day of ERCP without concern regarding PEP risk^[5]. However, very few tests with good positive predictive values (PPVs) for PEP exist. This study aimed to estimate the efficacy of 2 h post-ERCP serum amylase levels and other risk factors for predicting PEP.

MATERIALS AND METHODS

This study was a retrospective single-center cohort study of consecutive hospitalized patients who underwent ERCP or ERCP-related procedures at Toyonaka Municipal Hospital, certified as a teaching hospital by the Japan Gastroenterological Endoscopy Society (JGES)

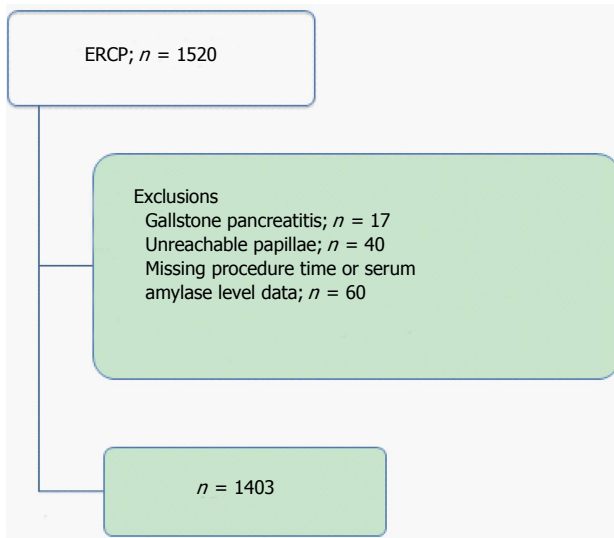


Figure 1 Study flow chart. ERCP: Endoscopic retrograde cholangiopancreatography.

(No. 1239), from January 2010 to December 2013. A total of 1520 procedures were enrolled in this study. Of these cases, 117 procedures with the following conditions were excluded: (1) gallstone pancreatitis, $n = 17$; (2) unreachable papillae, $n = 40$; and (3) missing procedure time or serum amylase level data, $n = 60$ (including cases with pancreatitis before ERCP). A total of 1403 procedures were ultimately analyzed in the present study (Figure 1).

The following demographic and clinical data were collected: Age and sex, ERCP indications, ERCP history, and 2 h post-ERCP serum amylase levels (after scope removal from the patient). The following procedural data were retrospectively collected from patient medical records: Biliary and pancreatic sphincterotomy with and without stent placement, procedure time, cannulation time, and complications. This study was approved by the Institutional Review Board of Toyonaka Municipal Hospital.

ERCP and pharmacological prophylaxis

Trainees or experts performed ERCP because our hospital is a JGES-certified teaching hospital, and trainees were assisted by experts as needed to avoid complications and ensure procedural quality when performing ERCP. We did not use a strict cannulation protocol. Cannulation was attempted *via* the wire-loaded cannulation method, which entails the use of contrast and wire-guided cannulation using a side-viewing duodenoscope (JF260 V; Olympus Optical Co. Tokyo, Japan). Procedure times were measured using a stopwatch, and images were recorded at key points and subsequently reviewed. Patients underwent routine blood tests 2 h after the procedure and the following day and received routine protease inhibitor (200 mg gabexate mesilate \times 2/d) treatments until the day after the procedure. No patients received rectal diclofenac or indomethacin for PEP prophylaxis during this period.

Complications

PEP was diagnosed based on consensus criteria^[13]. Briefly, PEP was defined as the combination of abdominal pain persisting for at least 24 h after the procedure and a high serum amylase level equivalent to 3 times the ULN at 24 h after the procedure. Bleeding was defined as blood loss requiring emergency endoscopic hemostasis or a transfusion or a hemoglobin level decrease greater than 2 g/dL following ERCP. Perforation was diagnosed endoscopically during ERCP or based on the observation of free air on post-ERCP plain radiography or computed tomography. Procedure-related mortality was defined as any death within 30 d of ERCP.

Analysis of PEP predictive factors

Patient- and procedure-related PEP risk factors were analyzed *via* logistic regression using the following factors: Sex, native papilla, cannulation time, total procedure time, endoscopic nasobiliary drainage, endoscopic biliary stent (EBS) placement, precut sphincterotomy, endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), pancreatic duct brush cytology, and 2 h amylase levels. Cannulation time was defined as the time from papilla identification until successful biliary cannulation, and procedure time was defined as the time from papilla identification until the scope was removed from the patient. PEP development was analyzed in relation to the following factors *via* univariate logistic regression: Patient-related factors (sex, age, and native papilla), procedure-related factors (cannulation time, total procedure time, endoscopic nasal pancreatic drainage, EBS, endoscopic metallic stent, endoscopic pancreatic stent, precut sphincterotomy, EST, EPBD, and pancreatic duct brush cytology), and 2 h post-ERCP amylase levels.

Statistical analysis

All continuous variables are expressed as the mean \pm SD, except for the nonparametric variables, which are expressed as the median and range. Categorical variables are expressed as the number in each category or the frequency. Continuous variables were compared using student's *t* test, whereas categorical variables were compared using a χ^2 test or Fisher's exact test when appropriate. Receiver operating characteristic (ROC) curve analysis was used to determine the 2 h amylase level cutoff, the cannulation times, and the procedure times for predicting PEP. Univariate and multivariate logistic regression analyses were performed to identify complication-related factors. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP software (ver. 11.1.1, SAS Institute Inc., Cary, NC, United States).

RESULTS

Patients and ERCP procedures

Patient characteristics are summarized in Table 1. A total

Table 1 Patient characteristics

Patients	<i>n</i>
Male, %	846, 60%
Age, median (range)	73 (12-99)
Native papilla	668, 47.6%
Indication	
Malignancy	522
Choledocholithiasis	771
Others	110
Cannulation time, median (range)	5 min (1-185)
Procedure time, median	37 min (3-185)
2 h amylase median (range)	97 IU/mL (10-3502)
ERCP and related procedures	
Total ERCP	1403
ENBD	362
EBS	380
EMS	42
EPS	124
Precut	35
EST	505
EPBD	20
EPLBD	38
Pancreatic duct brush	15

ERCP: Endoscopic retrograde cholangiopancreatography; EBS: Endoscopic biliary stent; EMS: Endoscopic metallic stent; EPS: Endoscopic pancreatic stent; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ENBD: Endoscopic nasobiliary drainage.

of 1403 procedures (725 patients) were analyzed in the present study. The median age of the study population was 73 years, and 846 patients were male (60%). A total of 688 patients (59%) exhibited naïve papillae. ERCP was performed for choledocholithiasis ($n = 771$); biliary malignancies from pancreatic cancer ($n = 203$); biliary malignancies from common bile duct cancer ($n = 161$); other biliary malignancies, including gallbladder cancer, intrahepatic bile duct cancer and other metastatic cancers ($n = 158$); and other conditions ($n = 110$). The median cannulation time was 5 min (range 1-185), and the median procedure time was 37 min (range 3-185 min). Primary cannulation was successful in 97.7% of cases. The median 2 h post-ERCP amylase level was 97 IU/L.

Complications

The overall complication rate was 4.8%. PEP developed in 55 patients (4.5%, 95%CI: 3.02-5.07), and perforation and bleeding occurred in 5 (0.35%, 95%CI: 0.15-0.83) and 8 patients (0.57%, 95%CI: 0.28-1.12), respectively (Table 2). All the patients who developed PEP improved with conservative therapy. The 2 h amylase cutoff value for predicting PEP was 264 IU/L (AUC: 0.93) (Figure 2) and remained 264 IU/L when limited to naïve papilla cases ($n = 688$). This cutoff level was 2.2 times the ULN at our hospital; thus, we established a serum amylase cutoff level of 2 times the ULN (240 U/L) for predicting PEP. Patients with an amylase level greater than 2 times the ULN (47/238, 19.8%) exhibited a significantly higher PEP rate than

Table 2 Complications

Complications	<i>n</i> , % (95%CI)
Bleeding	8, 0.57 (0.28-1.12)
Perforation	5, 0.35 (0.15-0.83)
Pancreatitis	55, 3.9 (3.02-5.07)
(severe pancreatitis)	[3, 0.2 (0.073-0.64)]
Procedure-related death	0, 0

patients with a lower amylase level (8/1165, 0.7%) ($P < 0.0001$). Two-hour post-ERCP amylase levels greater than 2 times the ULN exhibited an NPV and a PPV for PEP of 99.3% and 19.8%, respectively.

The cannulation and procedure time cutoff values for predicting PEP were 13 (AUC: 0.93) and 54 min (AUC: 0.72), respectively (Figure 2), and similar results (13 and 55 min) were observed in naïve cases. Patients with cannulation times ≥ 13 min exhibited a significantly higher PEP rate (34/327, 10.4%) than patients with shorter cannulation times (21/1075, 2.0%) ($P < 0.0001$), and patients with procedure times ≥ 54 min exhibited a significantly higher PEP rate (33/359, 9.2%) than patients with shorter procedure times (22/1044, 2.1%) ($P < 0.0001$).

Logistic regression analysis of PEP predictors

We analyzed the ability of patient- and procedure-related risk factors to predict PEP. Univariate analysis identified 10 significant predictive factors for PEP: Female sex, native papillae, cannulation time, total procedure time, EBSs, precut sphincterotomy, EST, EPBD, pancreatic duct brush cytology, and 2 h amylase levels (Table 3).

Multivariate analysis adjusted for age revealed that cannulation times longer than 13 min (OR = 2.28, 95%CI: 1.132-4.651, $P = 0.0210$) and 2 h amylase levels 2 times the ULN (OR = 24.1, 95%CI: 11.56-57.13, $P < 0.0001$) were significant predictive factors for PEP (Table 4).

DISCUSSION

The consensus PEP definition and severity grading system developed by Cotton *et al.*^[13] has been used for more than 20 years, but PEP remains a primary concern for endoscopists performing ERCP, as it is the most frequent post-ERCP complication, with an incidence of 3.5% in unselected patients^[3,5]. Approximately 90% of cases are of mild-to-moderate in severity; however, PEP results procedure-related death in 3% of PEP cases^[3]. Many prophylactic treatments have been reported, and the most recent ESGE guidelines recommend rectal NSAID administration for PEP prophylaxis^[5]. However, PEP is difficult to prevent, and few medications are effective at treating PEP once it develops. Only prompt aggressive intravenous hydration is reportedly effective with respect to decreasing morbidity and mortality^[2,7,8,10]. Appropriate and early fluid therapy can mitigate PEP severity^[14]; therefore, PEP must be diagnosed, and

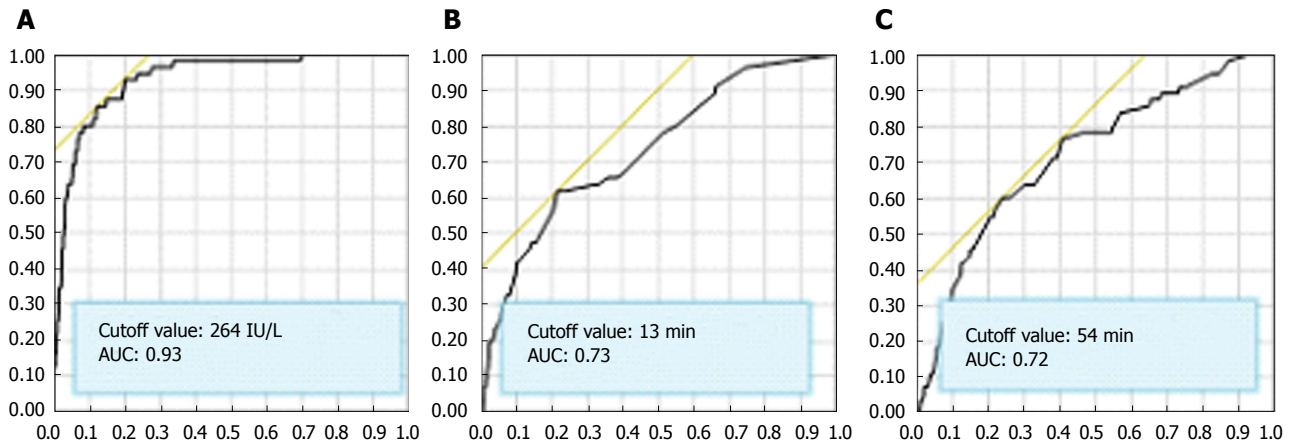


Figure 2 Receiver operating characteristic curve of 2 h amylase levels (A), cannulation times (B), and procedure times (C). AUC: Area under the curve.

Table 3 Univariate analysis of pancreatitis predictors

Predictors	Odds ratio	95%CI	P value
Sex (female)	0.53	0.31-0.92	0.0245
Native papilla	5.62	2.73-11.6	< 0.0001
ENBD	0.77	0.43-1.38	0.4313
EBS ¹	2.62	1.18-5.85	0.0129
EMS	0.37	0.13-1.08	0.0784
EPS	0.47	0.22-1.00	0.0528
Precut	0.23	0.08-0.61	0.0102
EST	0.49	0.28-0.84	0.0099
EPBD	0.22	0.06-0.78	0.0405
EPLBD	-	-	0.3983
Pancreatic duct brush	6.42	1.75-23.5	0.0186
2 h amylase \geq 2 times ULN	36.6	17.6-76.3	< 0.0001
Cannulation time \geq 13 min	5.82	3.33-10.2	< 0.0001
Procedure time \geq 54 min	4.70	2.70-8.18	< 0.0001

¹EBS: Including with and without EST. EBS: Endoscopic biliary stent; EMS: Endoscopic metallic stent; EPS: Endoscopic pancreatic stent; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; ULN: Upper limit of normal; EPLBD: Endoscopic papillary large balloon dilation; ENBD: Endoscopic nasobiliary drainage.

treatment must be initiated during the early phase of the disease to prevent severe acute pancreatitis development and progression.

Numerous studies have identified factors that increase PEP risk. Among these factors, the measured amylase levels after ERCP have been evaluated for the prediction of PEP^[15-17]. Many reports have shown the effectiveness of the 2-8 h amylase measurement. Generally, the NPVs are 95%-100%, the PPVs are 4%-62%, the sensitivity values are 23%-100% and the specificities are 63%-98%, although some differences in the definition of PEP and amylase cutoff levels exist across studies (Table 5).

Consequently, the ESGE guidelines indicate that 2-4 h amylase levels have very high NPVs but do not demonstrate sufficient PPVs (evidence level 2+)^[4] and therefore recommend measuring serum amylase or lipase levels 2-6 h after ERCP in patients presenting with pain who are to be discharged on the day of their ERCP procedure (recommendation grade B). In this study, 2

Table 4 Age-adjusted multivariate analysis of pancreatitis predictors

Predictors	Odds ratio	95%CI	P value
Sex (female)	1.46	0.77-2.75	0.2431
Native papilla	1.78	0.75-4.48	0.1908
Endoscopic biliary stent	0.61	0.23-1.45	0.2810
Precut	1.71	0.43-6.00	0.4288
EST	1.18	0.60-2.35	0.6278
EPBD	1.94	0.34-8.91	0.4296
Pancreatic duct brush	3.15	0.54-15.5	0.1870
2 h amylase \geq 2 times ULN	25.4	12.2-59.9	< 0.0001
Cannulation time \geq 13 min	2.63	1.34-5.23	0.0051
Procedure time \geq 54 min	1.23	0.389-3.67	0.7183

EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; ULN: Upper limit of normal.

h amylase levels exhibited a good NPV of 99% and a poor PPV of 20%, findings consistent with the above results, as well as a good sensitivity (84%) for the diagnosis of PEP. Previous studies have reported values of 70%-90%, particularly studies using the Consensus Criteria PEP definition. A PPV of 20% is not sufficient to identify PEP but may be suitable for identifying patients at high risk for developing PEP. Moreover, 2 h amylase levels may enable clinicians to identify high-risk patients requiring early acute PEP treatments, such as infusion therapy.

Previous studies have demonstrated that difficult cannulation is a risk factor for PEP^[12,18,19]. Tian *et al.*^[20] reported that cannulation time is a more accurate measure of cannulation difficulty in ERCP than other parameters. Moreover, Halttunen *et al.*^[21] reported that cannulation attempts lasting > 5 min may increase the incidence of PEP and that procedures lasting less than 5 min had a lower PEP rate (2.6%) than longer procedures (11.8%). The most recent ESGE guidelines state that PEP risk factor analyses have demonstrated that cannulation attempts lasting > 10 min had an odds ratio (OR) of 1.76 (1.13-2.74) with respect to PEP development and that the pooled incidences of PEP in patients with and without this risk factor were

Table 5 Previous reports of hourly variations in post-endoscopic retrograde cholangiopancreatography amylase levels

Ref.	Year	n	Time ¹ (h)	Amylase cut off	Sensitivity	Specificity	PPV	NPV	Definition of PEP
LaFerla <i>et al</i> ^[23]	1986	20	2	800	n.d.	n.d.	n.d.	Unlikely	Amy > 1200
Gottlieb <i>et al</i> ^[24]	1996	231	2	276	82	76	15	98	Consensus criteria
Testoni <i>et al</i> ^[25]	1999	409	2	5 ×	23.1	98.2	46.2	94.9	Amy > 5 × ULN
			4	5 ×	53.8	95	42.4	96.8	
			8	5 ×	76.9	96.9	62.5	98.4	
Testoni <i>et al</i> ^[26]	2001	1185	6-8	3 ×	n.d.	n.d.	n.d.	100	Pancreatic type pain
Thomas <i>et al</i> ^[27]	2001	263	4	2 ×	90	92.9	24.3	99.6	Consensus criteria
			4	3 ×	70	95.3	36.8	98.8	
Kapetanios <i>et al</i> ^[28]	2007	97	2	3 ×	72	79	32	95	Consensus criteria
			6	3 ×	82	75	30	97	
Ito <i>et al</i> ^[16]	2007	1291	3	3 ×	77	n.d.	29	n.d.	Amy > 1 × ULN, with pain at 24 h
			6	3 ×	85	n.d.	24	n.d.	
Nishino <i>et al</i> ^[29]	2009	1631	4	3 ×	89.8	72.9	12.7	99.4	Consensus criteria
			4	4 ×	84.7	80.4	16	99.2	
Artifon <i>et al</i> ^[30]	2010	300	4	1.5 ×	77	63	26	94	Consensus criteria
Sutton <i>et al</i> ^[15]	2011	959	4	2.5 × ²	80	80.4	11.1	99.2	Consensus criteria (mod/severe only)
			4	2.5 × ³	100	91.8	4.3	100	
Our study	2015	1403	2	2 ×	85.5	85.8	19.8	99.3	Consensus criteria
			2	2 × ⁴	96.4	68.8	11.2	99.8	

¹Hourly variations in serum amylase measurements after the procedure; ²With pancreatogram; ³Without pancreatogram; ⁴Longer cannulation time. Consensus criteria: Amy > 3 × ULN with pain at 24 h. n.d.: Not described; ULN: Upper limit of normal.

10.8% and 3.8%, respectively. ROC curve analysis was performed in the present study and demonstrated that the cannulation and the procedure time cutoff values for predicting PEP were 13 (AUC: 0.93) and 54 min (AUC: 0.72), respectively. The incidences of PEP in patients with and without cannulation attempts lasting > 13 min were 10.4% and 2.0%, respectively, and the incidences of PEP in patients with and without cannulation times lasting > 10 min were 9.6% and 2.1%, respectively (data not shown), findings similar to those reported by Halttunen *et al*^[21]. Multivariate analysis indicated that cannulation time is another significant PEP risk factor; therefore, we propose that cannulation time is a reliable marker for predicting PEP, in addition to 2 h post-ERCP amylase levels.

Based on above findings, we used the following markers to predict PEP development: 2 h post-ERCP amylase levels greater than 2 times the ULN and cannulation times greater than 13 min. Figure 3 includes a flowchart depicting these markers. A total of 238 patients (17%) in the present study exhibited 2 h post-ERCP amylase levels greater than 2 times the ULN, 47 of whom (20%) developed PEP, whereas a total of 1165 patients (83%) exhibited 2 h post-ERCP amylase levels less than 2 times the ULN. Eight patients (0.7%) in the latter group developed PEP; however, six of these patients required more than 13 min for cannulation. Thus, only 2 of the 1403 patients (0.14%) who developed PEP did not exhibit concerning 2 h post-ERCP amylase levels or require longer cannulation times. This study demonstrated that cannulation time inclusion may rescue 75% (6/8) of patients with non-concerning 2 h amylase levels and that the combination of 2 h post-ERCP levels and cannulation times exhibited a 96%

sensitivity and an 11.2% PPV for the identification of PEP. The latter percentage is not sufficient to identify PEP but may be useful for identifying high-risk patients in whom early treatments, such as aggressive infusions, are necessary.

The present study had several limitations because of its retrospective design. Routine protease inhibitor administration without rectal diclofenac or indomethacin administration may have influenced the frequency of PEP. However, nonsteroidal anti-inflammatory drugs (NSAIDs) were reportedly used infrequently for PEP prevention in clinical practice in Japan until the publication of the 2015 Japanese Guideline^[22], which recommends prophylactic NSAID administration to prevent PEP. In addition, we did not strictly evaluate certain PEP risk factors, such as the number of cannulation attempts, pancreatic guidewire, and pancreatic injection, because of the retrospective design of this study. The number of cannulation attempts represents the degree of cannulation difficulty; the most recent ESGE guidelines recommend keeping this number as low as possible^[21]. The degree of cannulation difficulty during ERCP is positively correlated with PEP^[18]. The degree of cannulation difficulty during ERCP procedures may differ when different methods are used (total cannulation time vs number of attempts); thus, grading scales used to evaluate the difficulty of performing ERCP *via* different methods should not be used interchangeably. Tian *et al*^[20] reported that cannulation time is a more objective and accurate means of grading cannulation difficulty than the number of papilla cannulation attempts. The ESGE guidelines categorize pancreatic guidewire use and pancreatic injection as definite PEP risk factors. However, it is sometimes difficult to establish if either

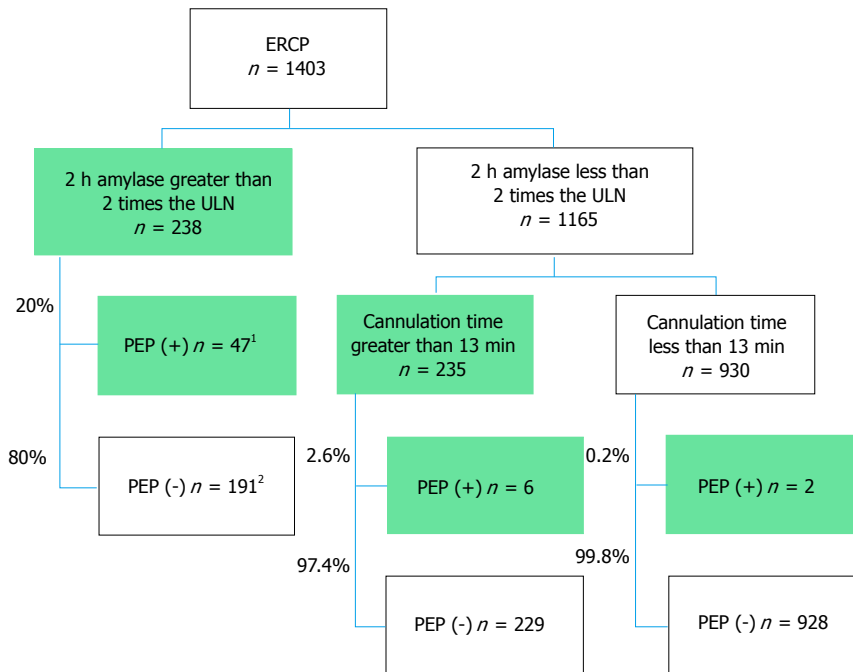


Figure 3 Flow chart using two-hour amylase levels and cannulation times for predicting pancreatitis. ¹Includes cannulation times greater than 13 min, $n = 28$; ²Includes cannulation times greater than 13 min, $n = 64$. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post ERCP Pancreatitis; ULN: Upper limit of normal.

procedure has been performed, particularly cannulation, which is performed *via* contrast and wire-guided methods at our institution. In addition, the ESGE guidelines recommend that prophylactic pancreatic stent placement should be strongly considered in patients at high risk for PEP. Prophylactic pancreatic stents were placed in 124 patients in the present study, 9 of whom (7.3%) developed PEP. However, multivariate analysis demonstrated that stent placement did not significantly prevent PEP, perhaps because pancreatic stents tend to be used in patients at high risk for PEP, in accordance with the above guidelines. Therefore, we must target patients at high risk for PEP to evaluate the efficacy of prophylactic pancreatic stent placement. Because of the above limitations, in the present study, we evaluated cannulation time and procedure time as surrogate markers of procedure-related risk factors in the present study. Despite these limitations, we believe that this study has effectively demonstrated that Two-hour post-ERCP amylase levels and cannulation times are useful PEP predictors.

In conclusion, 2 h post-ERCP serum amylase levels and cannulation times may be useful markers for predicting PEP development. We plan to conduct prophylactic interventions to reduce the incidence of PEP in high-risk patients exhibiting 2 h post-ERCP amylase levels greater than 2 times the ULN or requiring cannulation times greater than 13 min.

COMMENTS

Background

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) may result in procedure-related death and is often unpreventable. So it is

important to predict and treat in early phase.

Research frontiers

Post-ERCP serum amylase levels are known as a predictor of PEP, which have good negative predictive value (NPV) and poor positive predictive value (PPV). The aim of this study was to estimate the efficacy of post-ERCP 2 h serum amylase levels and other factors for predicting PEP.

Innovations and breakthroughs

The 2-h amylase levels exhibited a good NPV (99%) and a poor PPV (22%) similar to previous reports but exhibited a sensitivity of 86%, and the combined use with cannulation time increased the sensitivity to 96%.

Applications

Combination of Two-hour post-ERCP amylase levels and cannulation times may be simple useful markers for predicting PEP development in early phase.

Terminology

PEP is one of the major adverse events of ERCP. It is most frequent and sometimes results in death, so that it has been the most concern still now.

Peer-review

This retrospective study was performed to identify the risk factors for PEP, and the authors revealed that two factors of serum amylase levels 2 h after ERCP and cannulation time were significant independent factor. This is well designed study which revealed interesting results.

REFERENCES

- 1 Steinberg W, Tenner S. Acute pancreatitis. *N Engl J Med* 1994; **330**: 1198-1210 [PMID: 7811319 DOI: 10.1056/NEJM199404283301706]
- 2 Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379-2400 [PMID: 17032204 DOI: 10.1111/j.1572-0241.2006.00856.x]
- 3 Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/

- j.1572-0241.2007.01279.x]
- 4 **Dumonceau JM**, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, Testoni PA. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy* 2010; **42**: 503-515 [PMID: 20506068 DOI: 10.1055/s-0029-1244208]
- 5 **Dumonceau JM**, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, Marek T, Baron TH, Hassan C, Testoni PA, Kapral C. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. *Endoscopy* 2014; **46**: 799-815 [PMID: 25148137 DOI: 10.1055/s-0034-1377875]
- 6 **Wong LL**, Tsai HH. Prevention of post-ERCP pancreatitis. *World J Gastrointest Pathophysiol* 2014; **5**: 1-10 [PMID: 24891970 DOI: 10.4291/wjgp.v5.i1.1]
- 7 **Sagi SV**, Schmidt S, Fogel E, Lehman GA, McHenry L, Sherman S, Watkins J, Coté GA. Association of greater intravenous volume infusion with shorter hospitalization for patients with post-ERCP pancreatitis. *J Gastroenterol Hepatol* 2014; **29**: 1316-1320 [PMID: 24372871 DOI: 10.1111/jgh.12511]
- 8 **Gardner TB**, Vege SS, Chari ST, Petersen BT, Topazian MD, Clain JE, Pearson RK, Levy MJ, Sarr MG. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatol* 2009; **9**: 770-776 [PMID: 20110744 DOI: 10.1159/000210022]
- 9 **Tenner S**, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400-1415; 1416 [PMID: 23896955 DOI: 10.1038/ajg.2013.218]
- 10 **Warndorf MG**, Kurtzman JT, Bartel MJ, Cox M, Mackenzie T, Robinson S, Burchard PR, Gordon SR, Gardner TB. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 2011; **9**: 705-709 [PMID: 21554987 DOI: 10.1016/j.cgh.2011.03.032]
- 11 **Loperfido S**, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Frattin A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; **48**: 1-10 [PMID: 9684657 DOI: 10.1016/S0016-5107(98)70121-X]
- 12 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M. Risk factors for complication following ERCP: results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801 [PMID: 17703388 DOI: 10.1055/s-2007-966723]
- 13 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]
- 14 **DiMagno MJ**, Wamsteker EJ, Maratt J, Rivera MA, Spaete JP, Ballard DD, Elmunzer J, Saini SD. Do larger periprocedural fluid volumes reduce the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis? *Pancreas* 2014; **43**: 642-647 [PMID: 24713841 DOI: 10.1097/MPA.0000000000000101]
- 15 **Sutton VR**, Hong MK, Thomas PR. Using the 4-hour Post-ERCP amylase level to predict post-ERCP pancreatitis. *JOP* 2011; **12**: 372-376 [PMID: 21737899 DOI: 10.6092/1590-8577/3223]
- 16 **Ito K**, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Takasawa O, Obana T. Relationship between post-ERCP pancreatitis and the change of serum amylase level after the procedure. *World J Gastroenterol* 2007; **13**: 3855-3860 [PMID: 17657841 DOI: 10.3748/wjg.v13.i28.3855]
- 17 **Sultan S**, Baillie J. What are the predictors of post-ERCP pancreatitis, and how useful are they? *JOP* 2002; **3**: 188-194 [PMID: 12432185]
- 18 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]
- 19 **Wang P**, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol* 2009; **104**: 31-40 [PMID: 19098846 DOI: 10.1038/ajg.2008.5]
- 20 **Tian C**, Gamboa A, Chaudhury B, Willingham FF, Keilin S, Cai Q. Cannulation time is a more accurate measure of cannulation difficulty in endoscopic retrograde cholangiopancreatography than the number of attempts. *Gastroenterol Rep (Oxf)* 2013; **1**: 193-197 [PMID: 24759965 DOI: 10.1093/gastro/got024]
- 21 **Halttunen J**, Meisner S, Aabakken L, Arnelo U, Grönroos J, Hauge T, Kleiveland PM, Nordblad Schmidt P, Saarela A, Swahn F, Toth E, Mustonen H, Löhr JM. Difficult cannulation as defined by a prospective study of the Scandinavian Association for Digestive Endoscopy (SADE) in 907 ERCPs. *Scand J Gastroenterol* 2014; **49**: 752-758 [PMID: 24628493 DOI: 10.3109/00365521.2014.894120]
- 22 **Yokoe M**, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, Itoi T, Sata N, Gabata T, Igarashi H, Kataoka K, Hirota M, Kadoya M, Kitamura N, Kimura Y, Kiriya S, Shirai K, Hattori T, Takeda K, Takeyama Y, Hirota M, Sekimoto M, Shikata S, Arata S, Hirata K. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepatobiliary Pancreat Sci* 2015; **22**: 405-432 [PMID: 25973947 DOI: 10.1002/jhbp.259]
- 23 **LaFerla G**, Gordon S, Archibald M, Murray WR. Hyperamylasaemia and acute pancreatitis following endoscopic retrograde cholangiopancreatography. *Pancreas* 1986; **1**: 160-163 [PMID: 2437564]
- 24 **Gottlieb K**, Sherman S, Pezzi J, Esber E, Lehman GA. Early recognition of post-ERCP pancreatitis by clinical assessment and serum pancreatic enzymes. *Am J Gastroenterol* 1996; **91**: 1553-1557 [PMID: 8759660]
- 25 **Testoni PA**, Caporuscio S, Bagnolo F, Lella F. Twenty-four-hour serum amylase predicting pancreatic reaction after endoscopic sphincterotomy. *Endoscopy* 1999; **31**: 131-136 [PMID: 10223361 DOI: 10.1055/s-1999-13660]
- 26 **Testoni PA**, Bagnolo F. Pain at 24 hours associated with amylase levels greater than 5 times the upper normal limit as the most reliable indicator of post-ERCP pancreatitis. *Gastrointest Endosc* 2001; **53**: 33-39 [PMID: 11154486 DOI: 10.1067/mge.2001.111390]
- 27 **Thomas PR**, Sengupta S. Prediction of pancreatitis following endoscopic retrograde cholangiopancreatography by the 4-h post procedure amylase level. *J Gastroenterol Hepatol* 2001; **16**: 923-926 [PMID: 11555108 DOI: 10.1046/j.1440-1746.2001.02547.x]
- 28 **Kapetanios D**, Kokozidis G, Kinigopoulou P, Xiarchos P, Antonopoulos Z, Progia E, Kitis G. The value of serum amylase and elastase measurements in the prediction of post-ERCP acute pancreatitis. *Hepatogastroenterology* 2007; **54**: 556-560 [PMID: 17523321]
- 29 **Nishino T**, Toki F, Oyama H, Shiratori K. More accurate prediction of post-ERCP pancreatitis by 4-h serum lipase levels than amylase levels. *Digest Endosc* 2008; **20**: 169-177 [DOI: 10.1111/j.1443-1661.2008.00802.x]
- 30 **Artifon EL**, Chu A, Freeman M, Sakai P, Usmani A, Kumar A. A comparison of the consensus and clinical definitions of pancreatitis with a proposal to redefine post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreas* 2010; **39**: 530-535 [PMID: 20093992 DOI: 10.1097/MPA.0b013e3181c306c0]

P-Reviewer: Altonbary AY, Ikeuchi N, Isaji S, Kitamura K, Kikuyama M, Paduani GF **S-Editor:** Ji FF **L-Editor:** A **E-Editor:** Wu HL



Observational Study

Current state of practice for colonic diverticular bleeding in 37 hospitals in Japan: A multicenter questionnaire study

Ryota Niikura, Naoyoshi Nagata, Hisashi Doyama, Ryosuke Ota, Naoki Ishii, Katsuhiro Mabe, Tsutomu Nishida, Takuto Hikichi, Kazuki Sumiyama, Jun Nishikawa, Toshio Uraoka, Shu Kiyotoki, Mitsuhiro Fujishiro, Kazuhiko Koike

Ryota Niikura, Mitsuhiro Fujishiro, Kazuhiko Koike, Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan

Naoyoshi Nagata, Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo 162-8655, Japan

Hisashi Doyama, Ryosuke Ota, Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa-shi, Ishikawa 920-8201, Japan

Naoki Ishii, Department of Gastroenterology, St. Luke's International Hospital, Chuo-ku, Tokyo 104-8560, Japan

Katsuhiro Mabe, Division of Endoscopy, Hokkaido University Hospital, Kita-ku, Sapporo 060-0808, Hokkaido, Japan

Katsuhiro Mabe, Department of Gastroenterology, National Hospital Organization Hakodate Hospital, Kawaharachou, Hakodate-shi 041-0844, Hokkaido, Japan

Tsutomu Nishida, Department of Gastroenterology, Toyonaka Municipal Hospital, Toyonaka-shi, Osaka 560-0055, Japan

Takuto Hikichi, Department of Endoscopy, Fukushima Medical University Hospital, Fukushima-shi, Fukushima 960-1295, Japan

Kazuki Sumiyama, Department of Endoscopy, the Jikei University School of Medicine, Minato-ku, Tokyo 105-8471, Japan

Jun Nishikawa, Department of Clinical Laboratory Science, Yamaguchi University Graduate School of Medicine, Ube-shi, Yamaguchi 755-0046, Japan

Toshio Uraoka, Department of Gastroenterology, National Hospital Organization Tokyo Medical Center, Meguro-ku, Tokyo 150-0021, Japan

Shu Kiyotoki, Department of Gastroenterology, Shuto General

Hospital, Yanai-shi, Yamaguchi 742-0032, Japan

Mitsuhiro Fujishiro, Endoscopy and Endoscopic Surgery, the University of Tokyo Hospital, Bunkyo-ku, Tokyo 113-8655, Japan

Author contributions: Nagata N and Doyama H conceived and designed the experiments; Niikura R and Ota R analyzed the data; Niikura R and Nagata N wrote the paper; Nagata N, Doyama H, Ishii N, Mabe K, Nishida T, Hikichi T, Sumiyama K, Nishikawa J, Uraoka T, Kiyotoki S, Fujishiro M and Koike K contributed to editing the manuscript.

Institutional review board statement: Owing to the anonymous nature of the data in this retrospective questionnaire survey of endoscopists, institutional review board approval was waived.

Informed consent statement: Informed consent was waived because this study included no personal information about patients.

Conflict-of-interest statement: Dr. Mitsuhiro Fujishiro has received grant support from Hoya and Pentax.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Ryota Niikura, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655,

Japan. rniikura@triton.ocn.ne.jp
Telephone: +81-3-38155411
Fax: +81-3-38155411

Received: May 14, 2016
Peer-review started: May 17, 2016
First decision: August 10, 2016
Revised: August 20, 2016
Accepted: November 1, 2016
Article in press: November 2, 2016
Published online: December 16, 2016

Abstract

AIM

To clarify the current state of practice for colonic diverticular bleeding (CDB) in Japan.

METHODS

We conducted multicenter questionnaire surveys of the practice for CDB including clinical settings (8 questions), diagnoses (8 questions), treatments (7 questions), and outcomes (4 questions) in 37 hospitals across Japan. The answers were compared between hospitals with high and low number of inpatient beds to investigate which factor influenced the answers.

RESULTS

Endoscopists at all 37 hospitals answered the questions, and the mean number of endoscopists at these hospitals was 12.7. Of all the hospitals, computed tomography was performed before colonoscopy in 67% of the hospitals. The rate of bowel preparation was 46.0%. Early colonoscopy was performed within 24 h in 43.2% of the hospitals. Of the hospitals, 83.8% performed clipping as first-line endoscopic therapy. More than half of the hospitals experienced less than 20% rebleeding events after endoscopic hemostasis. No significant difference was observed in the annual number of patients hospitalized for CDB between high- (≥ 700 beds) and low-volume hospitals. More emergency visits ($P = 0.012$) and endoscopists ($P = 0.015$), and less frequent participation of nursing staff in early colonoscopy ($P = 0.045$) were observed in the high-volume hospitals.

CONCLUSION

Some practices unique to Japan were found, such as performing computed tomography before colonoscopy, no bowel preparation, and clipping as first-line therapy. Although, the number of staff differed, the practices for CDB were common irrespective of hospital size.

Key words: Colonic diverticular hemorrhage; Lower gastrointestinal bleeding; Computed tomography; Endoscopy; Bowel preparation

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Colonic diverticular bleeding (CDB) is increasing in Asia. There are no practice guidelines for CDB, and it is important to determine which recommendation is acceptable to a majority of hospitals. We conducted multicenter questionnaire surveys of 37 hospitals in Japan regarding management of CDB including clinical settings, diagnosis, treatment, and clinical outcomes, and made comparisons between hospitals with different patient volumes and between hospitals in different regions. Thus, practice styles unique to Japan such as performing computed tomography before colonoscopy, no bowel preparation, and clipping as first-line therapy were identified. However, management of CDB was common among hospitals irrespective of hospital size and region.

Niikura R, Nagata N, Doyama H, Ota R, Ishii N, Mabe K, Nishida T, Hikichi T, Sumiyama K, Nishikawa J, Uraoka T, Kiyotoki S, Fujishiro M, Koike K. Current state of practice for colonic diverticular bleeding in 37 hospitals in Japan: A multicenter questionnaire study. *World J Gastrointest Endosc* 2016; 8(20): 785-794 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/785.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.785>

INTRODUCTION

Colonic diverticular bleeding (CDB) is a major cause of lower gastrointestinal bleeding, and is estimated to cause 25% to 40% of all cases of lower gastrointestinal bleeding^[1-3]. In Japan, CDB was found in 427 (1.5%) of 28192 patients who underwent colonoscopy at an emergency hospital^[4]. Its occurrence has increased in Japan as well as in Western countries^[4-7]. CDB results in hemorrhagic shock requiring blood transfusion^[8,9], and has a high recurrence rate of 20% within 1 year^[10,11]. As a result, patients are often burdened by the frequent examinations, hospitalization, repeated blood transfusions, and a consequent decrease in their quality of life. Furthermore, these practices for CDB may be different between Western countries and Japan. For example, Western countries perform purged colonoscopy using polyethylene glycol as the first diagnostic procedure, and perform endoscopic hemostasis using clipping^[12]. In contrast, Japanese hospitals have good access to computed tomography (CT)^[13] and may select CT as the first diagnostic procedure. In addition, diagnostic tools, endoscopic environment, and treatment strategy may potentially differ among hospitals in Japan. Moreover, the practice for CDB may differ according to hospital patient volume and region, as is seen in the practice for other lower gastrointestinal disease^[14,15]. Some studies have reported significant associations between hospital volume and clinical outcome, and between hospital region and diagnosis methods^[14,15]. Today, there are no practice guidelines for CDB, and it is

important to determine what recommendations would be acceptable to a large number of hospitals.

Therefore, we conducted a multicenter questionnaire survey of the practice for CDB in 37 hospitals across Japan to elucidate the current state of the clinical settings, diagnosis, treatment, and clinical outcomes of patients with CDB, and to compare these findings according to hospital volumes and regions.

MATERIALS AND METHODS

Contents of the questionnaire

First, 1 endoscopist (Doyama H) developed the questionnaire on practice for CDB. Then, 3 endoscopists (Ota R, Niikura R and Nagata N) reviewed and edited the questionnaire regarding the length, clarity, and contents. Finally, 27 survey questions on practice for CDB were developed. The questionnaire consisted of 4 parts (clinical settings, diagnosis, treatment, clinical outcomes) as follows. In part (I), there were 9 questions for clinical settings on: (1) the clinical database for CDB such as gastrointestinal bleeding database, inpatient database, or endoscopy database; (2) institution-specific strategy for CDB; (3) number of CDB admissions; (4) number of emergency ambulance visits; (5) number of endoscopists performing early colonoscopy within 24 h of patient arrival; (6) number of expert endoscopists with hemostatic technical skills; (7) nursing staff who monitored vital signs during bowel preparation; (8) nursing staff assisting early colonoscopy; and (9) use of a water-jet colonoscope. For part (II), there were 8 questions for diagnoses of CDB on (10) the first choice diagnostic examination; (11) early contrast-enhanced CT within 3 h of patient arrival; (12) early colonoscopy; (13) bowel preparation; (14) cap-assisted colonoscopy; (15) how to improve the identification of stigmata of recent hemorrhage (SRH); (16) availability of small bowel examinations in case of negative colonoscopy; and (17) modality for small bowel examinations. For part (III), there were 6 questions for treatment of CDB on (18) first-line endoscopic therapy; (19) selection of non-endoscopic therapy; (20) first-line therapy among non-endoscopic therapies; (21) how to prevent rebleeding; (22) discontinuation of antithrombotic drugs on admission; and (23) strategy for restarting antithrombotic drugs. In part (IV), there were 4 questions for clinical outcomes of CDB on (24) identification rate of SRH; (25) rebleeding rate after endoscopic hemostasis; (26) rebleeding rate after interventional radiology; and (27) rebleeding rate after barium impaction therapy.

Questionnaire survey

The questionnaire survey was conducted by e-mail that was sent to 1 or 2 endoscopists at each of the 37 hospitals with different numbers of inpatient beds and in different regions in Japan between May 2015 and June 2015. Selection of the hospitals was made by Fujishiro M, who knew that the representative

endoscopists would be interested in this topic from his personal communications. To assess the reproducibility of questionnaire, we conducted a blinded secondary questionnaire survey 2 mo after using the same 16 questionnaire items. Selection of these questionnaire items was made by Niikura R and Nagata N. because these items were found to be related to the practice for CDB. These 37 hospitals were located in East or West Japan and have 100 to 1000 inpatient beds (Appendix).

Statistical analysis

The data from the first questionnaire survey were analyzed, and the intra-observer agreement between the first and second questionnaires was analyzed using kappa statistics. Kappa values were evaluated as follows: > 0.80, excellent agreement; > 0.60 to 0.80, good agreement; > 0.40 to 0.60, moderate; > 0.20 to 0.40, fair; and ≤ 0.20 , poor^[16].

A high-volume hospital was defined as one with over 700 beds, because the median number of beds in our data was 700 beds per hospital. Expert endoscopists were defined as those who were able to perform endoscopic hemostatic treatment by themselves. We evaluated the clinical settings, diagnosis methods, treatment, and outcomes between the groups of hospital separated by hospital volume and region (East Japan, West Japan) using a χ^2 test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann-Whitney *U* test. We also evaluated the associations of the rates of SRH identification and rebleeding with type of procedure from questionnaire answers using a nonparametric trend test. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using the STATA version 13 software (StataCorp, College Station, TX, United States).

RESULTS

The number of beds per hospital in each region of Japan is shown in Figure 1. There were 18 high-volume hospitals (≥ 700 beds) and 19 low-volume hospitals. Twenty-one of the 37 (56.8%) hospitals were located in East Japan, and 16 hospitals (43.2%) were located in West Japan (Figure 1). All 37 hospitals completed the first questionnaires, and 35 of the hospitals completed the second questionnaires. Intra-observer agreement for each question between the first and second surveys was excellent (mean κ , 0.83, 95% confidence interval 0.78-0.87) (Supplementary Table 1).

Questionnaire items for clinical settings

Questions and answers regarding clinical settings are shown in Table 1. Of all the hospitals, 86.5% answered the questionnaire based on the clinical database of each hospital. Only 13.5% of hospitals had an institution-specific strategy for CDB. The number of CDB patients who received therapy, and the number of emergency ambulance visits, differed among hospitals. The mean

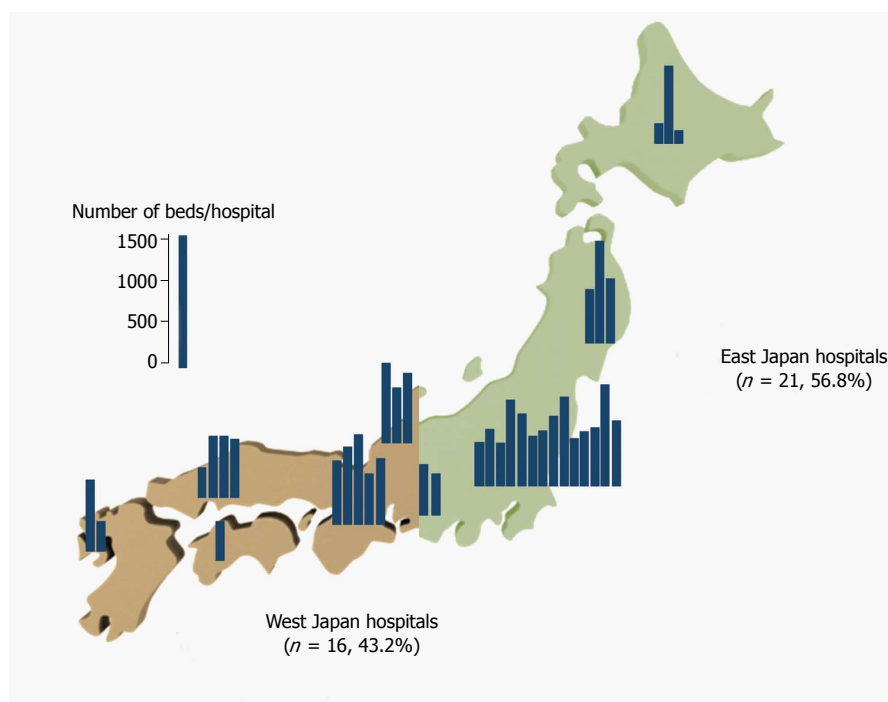


Figure 1 Number of beds per hospital in East and West Japan.

Table 1 Questions and answers regarding clinical settings in 37 hospitals *n* (%)

No.	Question	Answer (<i>n</i> = 37)	High volume (<i>n</i> = 18)	Low volume (<i>n</i> = 19)	<i>P</i> value	East Japan (<i>n</i> = 21)	West Japan (<i>n</i> = 16)	<i>P</i> value
1	Did you answer the questions based on a clinical database?							
	Yes	31 (83.8)	16 (51.6)	15 (48.4)		18 (58.1)	13 (41.9)	
	No	6 (16.2)	2 (33.3)	4 (66.7)	0.660	3 (50.0)	3 (50.0)	1.000
2	Do you have a specific institutional strategy for CDB?							
	Yes	5 (13.5)	0	5 (100)		2 (40.0)	3 (60.0)	
	No	32 (86.5)	18 (56.3)	14 (43.7)	0.046	19 (59.4)	13 (40.6)	0.634
3	How many patients are hospitalized for CDB annually?							
	1-10	12 (32.5)	7 (58.3)	5 (41.7)		7 (58.3)	5 (41.7)	
	11-20	10 (27.0)	4 (40.0)	6 (60.0)		4 (40.0)	6 (60.0)	
	21-30	5 (13.5)	2 (40.0)	3 (60.0)		1 (20.0)	4 (80.0)	
	≥ 31	10 (27.0)	2 (50.0)	5 (50.0)	0.824	9 (90)	1 (10)	0.035
4	How many emergency ambulance visits do you receive annually? ¹							
	< 2000	15 (44.1)	5 (33.3)	10 (66.7)		8 (53.3)	7 (46.7)	
	2000-6000	11 (32.3)	4 (36.4)	7 (63.6)		5 (45.5)	6 (54.5)	
	6000-10000	6 (17.7)	6 (100)	0		3 (50.0)	3 (50.0)	
	≥ 10000	2 (5.9)	0	2 (100)	0.012	2 (100)	0	0.724
5	How many endoscopists perform early colonoscopy within 24 h after patient arrival at your hospital?	12.7 ± 9.4	17.0 ± 11.6	8.8 ± 4.4	0.015	10.4 ± 5.7	15.8 ± 12.5	0.296
6	How many are expert endoscopists with endoscopic hemostasis technical skills are there at your hospital?	10.1 ± 7.5	13.1 ± 9.5	7.3 ± 3.3	0.019	7.9 ± 3.3	13.0 ± 10.2	0.143
7	Do you have nursing staff who monitor the patients' vital signs during bowel preparation?							
	Yes	33 (89.2)	17 (51.5)	16 (48.5)		19 (57.6)	14 (42.4)	
	No	4 (10.8)	1 (25.0)	3 (75.0)	0.604	2 (50.0)	2 (50.0)	1.000
8	Do you have nursing staff for early colonoscopy examinations within 24 h after patient arrival at the hospital?							
	Yes	23 (62.2)	8 (34.8)	15 (65.2)		13 (56.5)	10 (43.5)	
	No	14 (37.8)	10 (71.4)	4 (28.6)	0.045	8 (57.1)	6 (42.9)	1.000
9	Do you have a water-jet colonoscope?							
	Yes	34 (91.9)	17 (50.0)	17 (50.0)		20 (58.9)	14 (41.1)	
	No	3 (8.1)	1 (33.3)	2 (66.7)	1.000	1 (33.3)	2 (66.7)	0.568

¹Missing data included. The values in parentheses are percentages, and continuous data are shown as mean ± standard deviation. CDB: Colonic diverticular bleeding.

number of endoscopists and expert endoscopists were 12.7 and 10.1, respectively. Of all the hospitals, 89.2% and 62.2% had nursing staff for monitoring vital signs during bowel preparation and early colonoscopy examination, respectively. Ninety-one percent of hospitals had a water-jet colonoscope.

Comparing hospital with high and low patient volumes, more emergency visits ($P = 0.012$), endoscopists ($P = 0.015$), and expert endoscopists ($P = 0.019$), and less institution-specific management for CDB ($P = 0.046$) and frequent participation of nursing staff in early colonoscopy ($P = 0.045$) were observed

Table 2 Questions and answers regarding diagnosis of colonic diverticular bleeding in 37 hospitals *n* (%)

No.	Question	Answer (<i>n</i> = 37)	High volume (<i>n</i> = 18)	Low volume (<i>n</i> = 19)	<i>P</i> value	East Japan (<i>n</i> = 21)	West Japan (<i>n</i> = 16)	<i>P</i> value
10	What do you use as the first-line diagnostic method for hematochezia and suspected CDB?							
	Non-contrast-enhanced CT	3 (8.1)	0	3 (100)		0	3 (100)	
	Contrast-enhanced CT	22 (59.5)	11 (50.0)	11 (50.0)		12 (54.6)	10 (45.4)	
	Colonoscopy	10 (27.0)	6 (60.0)	4 (40.0)		7 (70.0)	3 (30.0)	
	Contrast-enhanced CT and colonoscopy	2 (5.4)	1 (50.0)	1 (50.0)	0.359	2 (100)	0	0.101
11	Can you perform urgent contrast-enhanced CT within 3 h after patient arrival at hospital? ²							
	Yes	22 (61.1)	12 (54.6)	10 (45.4)		13 (59.1)	9 (40.9)	
	No	14 (38.9)	6 (42.9)	8 (57.1)	0.494	7 (50.0)	7 (50.0)	0.593
12	Can you perform early colonoscopy within 24 h after patient arrival at hospital?							
	Yes	16 (43.2)	9 (56.3)	7 (43.7)		10 (62.5)	6 (37.5)	
	No	21 (56.8)	9 (42.9)	12 (57.1)	0.419	11 (52.4)	10 (47.6)	0.538
13	Do you request bowel preparation?							
	Yes	17 (46.0)	6 (35.3)	11 (64.7)		13 (76.5)	4 (23.5)	
	No	3 (8.1)	3 (100)	0		2 (66.7)	1 (33.3)	
	Case by case	17 (45.9)	9 (52.9)	8 (47.1)	0.105	6 (35.3)	11 (64.7)	0.046
14	Do you use a cap-assisted colonoscopy for early colonoscopy?							
	Yes	24 (64.9)	11 (45.8)	13 (54.2)		15 (62.5)	9 (37.5)	
	No	13 (35.1)	7 (53.9)	6 (46.1)	0.642	6 (46.2)	7 (53.8)	0.338
15	How do you perform colonoscopy to improve identification of SRH? ¹							
	Cap-assisted colonoscopy	17 (46.0)	10 (58.8)	7 (41.2)	0.254	10 (58.8)	7 (41.2)	0.815
	Long cap-assisted colonoscopy	13 (35.1)	6 (46.2)	7 (53.8)	0.823	7 (53.9)	6 (46.1)	0.793
	Inverting diverticulum <i>via</i> suction of colonoscopy	18 (48.7)	11 (61.1)	7 (38.9)	0.140	11 (61.1)	7 (38.9)	0.603
	Wash out with water	36 (97.3)	18 (50.0)	18 (50.0)	1.000	21 (58.3)	15 (41.7)	0.432
	Colonoscopy by multiple doctors	3 (8.1)	1 (33.3)	2 (66.7)	1.000	2 (66.7)	1 (33.3)	1.000
	Colonoscopy under X-ray	3 (8.1)	1 (33.3)	2 (66.7)	1.000	1 (33.3)	2 (66.7)	0.568
16	Do you examine the small bowel when you are unable to diagnose definite CDB by colonoscopy?							
	Yes	18 (48.7)	11 (61.1)	7 (38.9)		10 (55.6)	8 (44.4)	
	No	7 (18.9)	1 (14.3)	6 (85.7)		4 (57.1)	3 (42.9)	
	Case by case	12 (32.4)	6 (50.0)	6 (50.0)	0.145	7 (58.3)	5 (41.7)	1.000
17	Which modality do you select for the small bowel examination? ²							
	Capsule endoscopy	29 (85.3)	17 (58.6)	12 (41.4)		18 (62.1)	11 (37.9)	
	Balloon-endoscopy	2 (5.9)	0	2 (100)		1 (50.0)	1 (50.0)	
	Case by case	3 (8.8)	1 (33.3)	2 (66.7)	0.301	1 (33.3)	2 (66.7)	0.776

¹Duplicated data allowed; ²Missing data included. Parenthesis shows percentage. CT: Computed tomography; CDB: Colonic diverticular bleeding; SRH: Stigmata of recent hemorrhage.

in high-volume hospitals (Table 1). No significant differences were observed in other questionnaire items such as number of patients hospitalized for CDB between the two groups (Table 1). Comparing hospitals in East and West Japan, a higher number of patients hospitalized for CDB was observed in East Japan hospitals ($P = 0.035$) (Table 1). No significant difference was observed in other questionnaire items between the two groups (Table 1).

Questionnaire items for diagnoses

Questions and answers regarding diagnosis are shown in Table 2. Of all the hospitals, 59.5% selected contrast-enhanced CT as first examination of choice. The rates of urgent CT, early colonoscopy, bowel preparation, cap-assisted colonoscopy were 61.1%, 43.2%, 46.0%, and 64.9%, respectively. Ninety-one percent of hospitals washed out with water to improve identification of SRH. There was a wide variation among hospitals in small bowel intestinal examination, but 85.3% of hospitals selected capsule endoscopy as the tool of choice when it was unable to diagnose definite CDB.

No significant differences between hospitals with high and low patient volumes were observed in all questionnaire items (Table 2). Comparing hospitals in East and West Japan, East Japan hospitals performed more frequent bowel preparation compared with West Japan hospitals ($P = 0.046$) (Table 2). No significant differences were observed in other questionnaire items between the two groups (Table 2).

Questionnaire items for treatments

Questions and answers regarding treatment are shown in Table 3. In endoscopic treatment, clipping, band ligation, and epinephrine injection were performed as first-line therapy in 83.8%, 13.5%, and 2.7% of hospitals. Seventy-three percent and 67% of hospitals selected non-endoscopic therapy for patients with rebleeding and hemorrhagic shock, and 77.4% of hospitals performed interventional radiology as first-line non-endoscopic therapy. Fifty-nine percent of hospitals discontinued antithrombotic drugs on admission and only 15% of hospitals had a strategy for restarting these drugs.

Table 3 Questions and answers regarding treatments of colonic diverticular bleeding in 37 hospitals *n* (%)

No.	Question	Answer (<i>n</i> = 37)	High volume (<i>n</i> = 18)	Low volume (<i>n</i> = 19)	<i>P</i> value	East Japan (<i>n</i> = 21)	West Japan (<i>n</i> = 16)	<i>P</i> value
18	What kind of endoscopic treatment do you perform as first-line therapy?							
	Clipping	31 (83.8)	15 (48.4)	16 (51.6)	1.000	17 (54.8)	14 (45.2)	
	Endoscopic band ligation	5 (13.5)	3 (60.0)	2 (40.0)		3 (60.0)	2 (40.0)	
	Epinephrine injection	1 (2.7)	0	1 (100)		1 (100)	0	1.000
19	What kinds of patient undergo non-endoscopic therapy? ¹							
	Patients with an unidentified bleeding source	18 (48.7)	10 (55.6)	8 (44.4)	0.413	8 (44.4)	10 (55.6)	0.141
	Patients with rebleeding	27 (73.0)	15 (55.6)	12 (44.4)	0.269	17 (63.0)	10 (37.0)	0.274
	Patients with hemorrhagic shock	25 (67.6)	15 (60.0)	10 (40.0)	0.079	13 (52.0)	12 (48.0)	0.491
20	What kind of non-endoscopic therapy do you perform as first-line therapy or when you are unable to identify SRH at endoscopy?							
	IVR	24 (77.4)	2 (50.0)	2 (50.0)	0.253	10 (41.7)	14 (58.3)	
	Surgery	3 (9.7)	14 (58.3)	10 (41.7)		3 (100)	0	
	Barium impaction therapy	4 (12.9)	0	3 (100)		3 (75.0)	1 (25.0)	0.145
21	What kind of treatment do you perform to prevent rebleeding? ¹							
	Treatment of diabetes mellitus	0	0	0	NA	0	0	NA
	Treatment of hypertension	6 (17.1)	2 (33.3)	4 (66.7)	0.658	3 (50.0)	3 (50.0)	1.000
	Discontinuation NSAIDs	14 (40.0)	7 (50.0)	7 (50.0)	0.890	10 (71.4)	4 (28.6)	0.296
	Discontinuation antithrombotic drugs	22 (62.9)	11 (50.0)	11 (50.0)	0.826	15 (68.2)	7 (31.8)	0.086
	Administering vitamin D	0	0	0	NA	0	0	NA
	Treatment of constipation	14 (40.0)	9 (64.3)	5 (35.7)	0.129	6 (42.9)	8 (57.1)	0.163
	Administering a low fiber diet	5 (14.3)	2 (40.0)	3 (60.0)	1.000	3 (60.0)	2 (40.0)	1.000
22	Do you discontinue antithrombotic drugs on admission?							
	Yes	22 (59.5)	10 (45.5)	12 (54.5)		12 (54.6)	10 (46.4)	
	No	12 (32.4)	7 (58.3)	5 (41.7)		6 (50.0)	6 (50.0)	
	Case by case	3 (8.1)	1 (33.3)	2 (66.7)	0.693	3 (100)	0	0.398
23	Do you have a strategy for restarting antithrombotic drugs? ²							
	Yes	4 (15.4)	4 (100)	0		0	4 (100)	
	No	22 (84.6)	6 (27.3)	16 (72.7)	0.014	15 (68.2)	7 (31.8)	0.022

¹Duplicated data allowed; ²Missing data included. Values in parentheses are percentages. IVR: Interventional radiology; NSAIDs: Non-steroidal anti-inflammatory drugs; SRH: Stigmata of recent bleeding.

Comparing hospitals with high and low patient volume, low-volume hospitals had more strategies for restarting antithrombotic drugs ($P = 0.014$) than low-volume hospitals (Table 3). No significant differences were observed in other questionnaire items between the two groups (Table 3). Comparing hospitals in East and West Japan, East Japan hospitals had less strategies for restarting antithrombotic drugs than West Japan hospitals ($P = 0.022$) (Table 3). No significant differences were observed in other questionnaire items between the two groups (Table 3).

Questionnaire items for clinical outcomes

Questions and answers regarding clinical outcomes are shown in Table 4. The rate of identification of SRH varied widely among hospitals. No significant association between SRH identification rate and type of procedure was observed from questionnaire answers (Table 5). Forty-one percent of hospitals experienced less than 20% rebleeding events after endoscopic hemostasis, interventional radiology, and barium impaction therapy. No significant association was observed between rebleeding rate and endoscopic treatments from questionnaire answers (Table 5). No significant differences between hospitals with high and low patient volumes were observed in all questionnaire items (Table 4). Comparing hospitals in East and West Japan, East

Japan hospitals experienced less rebleeding events after barium impaction therapy than West Japan hospitals ($P = 0.005$). No significant differences were observed in other questionnaire items between the two groups (Table 4).

DISCUSSION

Our questionnaire-based study was the first investigation to evaluate the current practice for CDB such as clinical settings, diagnoses, treatments, and clinical outcomes in 37 hospitals nationwide in Japan. Although the clinical setting such as the number of endoscopists and nursing staff were different between hospitals with high and low patient volumes, the practice for CDB was almost the same throughout Japan, such as performing CT before colonoscopy, various procedures to improve SRH identification rate, and clipping as first-line endoscopic therapy, irrespective of hospital size.

In regard to clinical settings, a high number of emergency visits, endoscopists, and expert endoscopists were observed in high-volume hospitals compared with low-volume hospitals. CDB is a major cause of acute lower gastrointestinal bleeding, and CDB patients experience severe bleeding and require transfusion and intensive care because of their advanced age or comorbidities^[8,17-19]. Therefore, the management of CDB

Table 4 Questions and answers regarding clinical outcomes of colonic diverticular bleeding in 37 hospitals *n* (%)

No.	Question	Answer (<i>n</i> = 37)	High volume (<i>n</i> = 18)	Low volume (<i>n</i> = 19)	<i>P</i> value	East Japan (<i>n</i> = 21)	West Japan (<i>n</i> = 16)	<i>P</i> value
24	How often do you identify SRH in patients who undergo colonoscopy? ¹							
	0%-20%	15 (41.7)	6 (40.0)	9 (60.0)		7 (46.7)	8 (53.3)	
	21%-40%	16 (44.4)	7 (43.8)	9 (56.2)		10 (62.5)	6 (37.5)	
	41%-60%	4 (11.1)	4 (100)	0		3 (75.0)	1 (25.0)	
	61%-80%	1 (2.8)	0	1 (100)		0	1 (100)	
	81%-100%	0	0	0	0.122	0	0	0.658
25	How often do you experience rebleeding events after endoscopic hemostasis? ¹							
	0%-20%	22 (61.1)	10 (45.5)	12 (54.6)		13 (59.1)	9 (40.9)	
	21%-40%	10 (27.8)	4 (40.0)	6 (60.0)		7 (70.0)	3 (30.0)	
	41%-60%	3 (8.3)	2 (66.7)	1 (33.3)		1 (33.3)	2 (66.7)	
	61%-80%	1 (2.8)	1 (100)	0		0	1 (100)	
	81%-100%	0	0	0	0.721	0	0	0.458
26	How often do you experience rebleeding events after IVR? ¹							
	0%-20%	27 (90.1)	15 (55.6)	12 (44.4)		16 (59.3)	11 (40.7)	
	21%-40%	0	0	0		0	0	
	41%-60%	1 (3.3)	0	1 (100)		0	1 (100)	
	61%-80%	1 (3.3)	1	1 (100)		0	1 (100)	
	81%-100%	1 (3.3)	1 (100)	0	0.448	0	1 (100)	0.090
27	How often do you experience rebleeding events after barium impaction therapy? ¹							
	0%-20%	10 (71.6)	6 (60.0)	4 (40.0)		9 (90.0)	1 (10.0)	
	21%-40%	1 (7.1)	0	1 (100)		0	1 (100)	
	41%-60%	1 (7.1)	0	1 (100)		0	1 (100)	
	61%-80%	1 (7.1)	1 (100)	0		0	1 (100)	
	81%-100%	1 (7.1)	0	1 (100)	0.559	0	1 (100)	0.005

¹Missing data included. Values in parentheses are percentages. SRH: Stigmata of recent hemorrhage; IVR: Interventional radiology.

Table 5 Association between procedures and outcomes *n* (%)

Procedure ¹ (Question No. 15)	Answer (<i>n</i> = 37)	SRH identification rate ²					<i>P</i> for trend
		0%-20% (<i>n</i> = 15)	21%-40% (<i>n</i> = 16)	41%-60% (<i>n</i> = 4)	61%-80% (<i>n</i> = 1)	81%-100% (<i>n</i> = 0)	
Cap-assisted colonoscopy	17 (46.0)	4 (25.0)	9 (56.3)	2 (12.5)	1 (6.2)	0	0.081
Long cap-assisted colonoscopy	13 (35.1)	6 (46.2)	5 (38.5)	2 (15.3)	0	0	0.735
Inverting diverticulum <i>via</i> suction of colonoscopy	18 (48.7)	5 (29.4)	10 (58.8)	2 (11.8)	0	0	0.588
Wash out with water	36 (97.3)	14 (40.0)	16 (45.7)	4 (11.4)	1 (2.9)	0	0.323
Colonoscopy by multiple doctors	3 (8.1)	2 (66.7)	1 (33.3)	0	0	0	0.328
Colonoscopy under X-ray	3 (8.1)	2 (66.7)	1 (33.3)	0	0	0	0.328
Answer				Rebleeding rate ²			
Endoscopic treatment (Question No. 18)	(<i>n</i> = 37)	0%-20% (<i>n</i> = 22)	21%-40% (<i>n</i> = 10)	41%-60% (<i>n</i> = 3)	61%-80% (<i>n</i> = 1)	81%-100% (<i>n</i> = 0)	<i>P</i> for trend
Clipping	31 (83.8)	19 (63.3)	8 (26.7)	3 (10.0)	0	0	0.290
Endoscopic band ligation	5 (13.5)	2 (40.0)	2 (40.0)	0	1 (20.0)	0	0.142
Epinephrine injection	1 (2.7)	1 (100)	0	0	0	0	0.489

¹Duplicated data allowed; ²Missing data included. Values in parentheses are percentages. SRH: Stigmata of recent bleeding.

patients requires an adequate number of medical staff and expert endoscopists, and a careful nursing system during the nighttime and weekend. However, there was no significant difference in the number of CDB patients who received treatment between high- and low-volume hospitals, which indicated that low-volume hospitals also need to treat CDB patients as well as high-volume hospitals regardless of the small number of endoscopists. Therefore, action is needed to handle an increasing number of CDB patients, such as transfer of CDB patients to core hospitals in each region.

In regard to diagnostic methods, most Japanese

hospitals performed CT before colonoscopy for CDB diagnosis, and there were no significant differences between the groups separated by hospital volume and region. In contrast, Western countries may perform colonoscopy or scintigraphy, not CT^[20]. This is probably because there were some studies from Japan that showed the usefulness of CT for the diagnosis of CDB, which had a sensitivity of 20.0%-42.9% and specificity of 78.6%-87.5%^[13,21]. Only 46% of hospitals performed bowel preparation, and there was a significant difference between East and West Japan in this respect. This is probably because some physicians are concerned

that bowel preparation potentially increases the risk of aspiration pneumonia, volume overload, and a change in vital signs with blood loss^[22]. However, the presence of colonic diverticula with poor visualization was a risk factor for perforation in screening colonoscopy^[23]. Recent studies have shown that bowel preparation during acute lower gastrointestinal bleeding did not increase adverse events compared with non-gastrointestinal bleeding^[24], and bowel preparation for early colonoscopy was safe as well as for elective colonoscopy^[25]. In addition, bowel preparation contributes to excellent SRH identification rates^[24,26]. Therefore, we may need to expand awareness of the safety of full bowel preparation in CDB diagnosis in Japan. Moreover, the rate of early colonoscopy was 43.2%. Now, we are conducting a randomized control study to resolve these unclarified issues in the diagnostic methods (UMIN 000021129).

In endoscopic treatment, clipping, band ligation, and epinephrine injection were performed as first-line therapy in 83.8%, 13.5%, and 2.7% of cases, which might be different from Western countries^[27]. Some reports have indicated that Western countries usually performed thermal contact therapy^[18,26,28,29]; however, this therapy is not approved in Japan^[30]. Several reports from Western countries showed that clipping was a useful hemostasis treatment^[12,31,32], and clipping may be performed as a common endoscopic treatment for CDB patients. On the other hand, in Japan, endoscopic band ligation was reported as useful for hemostasis in CDB, and therapeutic options for CDB have been expanding in Japan^[33].

There was very limited data on the strategy for antithrombotic drugs in patients with acute gastrointestinal bleeding. The American Society for Gastrointestinal Endoscopy guidelines reported^[34] that endoscopic hemostasis was considered as a procedure with a high risk of bleeding, and recommended that: (1) patients requiring endoscopic hemostasis taking non-steroidal anti-inflammatory drugs or low-dose aspirin continue these medications; (2) those taking thienopyridine should have the medication discontinued; and (3) those taking anticoagulants should consider bridging therapy. In contrast, Japan and European countries have no guidelines on the management of antithrombotic drugs in patients with gastrointestinal bleeding. Only 15% of hospitals have a strategy for antithrombotic drugs, and the timing of discontinuation and restart of antithrombotic drugs were individualized. Physicians considered discontinuation of antithrombotic therapy in patients following a hospitalization for gastrointestinal bleeding^[35,36]. Discontinued use of antithrombotic drugs may decrease the risk of gastrointestinal bleeding, but discontinuation of these drugs was associated with an increased risk of thrombosis and mortality^[37,38]. Although there is no consensus, we believed that patients with antithrombotic drugs need to have these medications continued, or restarted as soon as possible if patients discontinued antithrombotic drugs.

Our study has several strengths. First, our data

were obtained from a large number of hospitals, so the generalizability of the results is high. Second, we evaluated intra-observer agreement, and our data showed a high level of reproducibility. However, our study has limitations. Our study was based on data from a questionnaire, and not based on patient data, so caution should be exercised in the interpretation of our results. In addition, our study has the potential of selection bias.

In conclusion, compared with Western countries, some practice styles unique to Japan such as performing CT before colonoscopy, no bowel preparation, and clipping as first-line endoscopic therapy were found. Although the number of endoscopists and nursing staff were different, the practices for CDB were almost the same, irrespective of the size of the hospital in Japan.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Kazuya Matsumoto, Atsushi Imagawa, Kenichiro Nakachi, Mikitaka Iguchi, Kyoko Katakura, Teruhito Kishihara, Yorimasa Yamamoto, Takamitsu Sato, Tomoyuki Yada, Tomoki Fujita, Waku Hatta, Katsuya Endo, Tomoo Nakagawa, Koichi Nonaka, Kazuya Kitamura, Tetsuya Sumiyoshi, Taku Sakamoto, Kazuo Hara, Tsukasa Furuhashi, Syu Hoteya, Shiro Oka, Tatsuya Mikami, Manabu Sawaya, Yoshito Hayashi, Takashi Otsuka, Yoshinori Morita, Naomi Kakushima, Kenji Ishido, Takuya Inoue, Tetsuro Honda, Maiko Tabuchi, Hitomi Minami, Tomoki Michida, Shinichi Hashimoto, and Kenkei Hasatani for their help with answering the questionnaire.

COMMENTS

Background

Colonic diverticular bleeding (CDB) is increasing in Asia however there are no practice guidelines for CDB. It is important to determine which recommendation is acceptable to a majority of hospitals.

Research frontiers

To clarify the current state of the clinical settings, diagnosis, treatment, and clinical outcomes of patients with CDB.

Innovations and breakthroughs

The authors conducted multicenter questionnaire surveys of 37 hospitals in Japan regarding management of CDB such as the clinical settings, diagnosis, treatment, and clinical outcomes, comparing them between hospitals with different patient volumes and between hospitals in different regions. As a result, some practice styles unique to Japan such as performing computed tomography before colonoscopy, no bowel preparation, and clipping as first-line therapy were found. However, the management of CDB was common among hospitals irrespective of hospital size and region.

Applications

These data were obtained from a large number of hospitals, so the generalizability of the results is high.

Peer-review

This multicenter trial by questionnaire is very useful for assessment of current state of diagnosis and treatment of CDB.

REFERENCES

- 1 **Steinmuller DR**, Graneto D, Swift C, Novick AC, Strem SB, Cunningham RJ, Hodge E, Bretan P. Use of intravenous immunoglobulin prophylaxis for primary cytomegalovirus infection post living-related-donor renal transplantation. *Transplant Proc* 1989; **21**: 2069-2071 [PMID: 2540554]
- 2 **Nagata N**, Niikura R, Aoki T, Shimbo T, Kishida Y, Sekine K, Tanaka S, Okubo H, Watanabe K, Sakurai T, Yokoi C, Akiyama J, Yanase M, Mizokami M, Uemura N. Lower GI bleeding risk of nonsteroidal anti-inflammatory drugs and antiplatelet drug use alone and the effect of combined therapy. *Gastrointest Endosc* 2014; **80**: 1124-1131 [PMID: 25088922 DOI: 10.1016/j.gie.2014.06.039]
- 3 **Tsuruoka N**, Iwakiri R, Hara M, Shirahama N, Sakata Y, Miyahara K, Eguchi Y, Shimoda R, Ogata S, Tsunada S, Sakata H, Fujimoto K. NSAIDs are a significant risk factor for colonic diverticular hemorrhage in elder patients: evaluation by a case-control study. *J Gastroenterol Hepatol* 2011; **26**: 1047-1052 [PMID: 21198829 DOI: 10.1111/j.1440-1746.2010.06610.x]
- 4 **Nagata N**, Niikura R, Aoki T, Shimbo T, Itoh T, Goda Y, Suda R, Yano H, Akiyama J, Yanase M, Mizokami M, Uemura N. Increase in colonic diverticulosis and diverticular hemorrhage in an aging society: lessons from a 9-year colonoscopic study of 28,192 patients in Japan. *Int J Colorectal Dis* 2014; **29**: 379-385 [PMID: 24317937 DOI: 10.1007/s00384-013-1808-4]
- 5 **Song JH**, Kim YS, Lee JH, Ok KS, Ryu SH, Lee JH, Moon JS. Clinical characteristics of colonic diverticulosis in Korea: a prospective study. *Korean J Intern Med* 2010; **25**: 140-146 [PMID: 20526386 DOI: 10.3904/kjim.2010.25.2.140]
- 6 **Sharara AI**, El-Halabi MM, Mansour NM, Malli A, Ghaith OA, Hashash JG, Maasri K, Sowaid A, Barada K, Mourad FH, El Zahabi L. Alcohol consumption is a risk factor for colonic diverticulosis. *J Clin Gastroenterol* 2013; **47**: 420-425 [PMID: 23164685 DOI: 10.1097/MCG.0b013e31826be847]
- 7 **Peery AF**, Barrett PR, Park D, Rogers AJ, Galanko JA, Martin CF, Sandler RS. A high-fiber diet does not protect against asymptomatic diverticulosis. *Gastroenterology* 2012; **142**: 266-72.e1 [PMID: 22062360 DOI: 10.1053/j.gastro.2011.10.035]
- 8 **McGuire HH**. Bleeding colonic diverticula. A reappraisal of natural history and management. *Ann Surg* 1994; **220**: 653-656 [PMID: 7979613 DOI: 10.1097/00000658-199411000-00008]
- 9 **Niikura R**, Yasunaga H, Yamaji Y, Horiguchi H, Fushimi K, Yamada A, Hirata Y, Koike K. Factors affecting in-hospital mortality in patients with lower gastrointestinal tract bleeding: a retrospective study using a national database in Japan. *J Gastroenterol* 2015; **50**: 533-540 [PMID: 25181990 DOI: 10.1007/s00535-014-0994-3]
- 10 **Niikura R**, Nagata N, Yamada A, Akiyama J, Shimbo T, Uemura N. Recurrence of colonic diverticular bleeding and associated risk factors. *Colorectal Dis* 2012; **14**: 302-305 [PMID: 21692963 DOI: 10.1111/j.1463-1318.2011.02611.x]
- 11 **Okamoto T**, Watabe H, Yamada A, Hirata Y, Yoshida H, Koike K. The association between arteriosclerosis related diseases and diverticular bleeding. *Int J Colorectal Dis* 2012; **27**: 1161-1166 [PMID: 22584295 DOI: 10.1007/s00384-012-1491-x]
- 12 **Kaltenbach T**, Watson R, Shah J, Friedland S, Sato T, Shergill A, McQuaid K, Soetikno R. Colonoscopy with clipping is useful in the diagnosis and treatment of diverticular bleeding. *Clin Gastroenterol Hepatol* 2012; **10**: 131-137 [PMID: 22056302 DOI: 10.1016/j.cgh.2011.10.029]
- 13 **Nagata N**, Niikura R, Aoki T, Moriyasu S, Sakurai T, Shimbo T, Shinozaki M, Sekine K, Okubo H, Watanabe K, Yokoi C, Yanase M, Akiyama J, Uemura N. Role of urgent contrast-enhanced multidetector computed tomography for acute lower gastrointestinal bleeding in patients undergoing early colonoscopy. *J Gastroenterol* 2015; **50**: 1162-1172 [PMID: 25812518 DOI: 10.1007/s00535-015-1069-9]
- 14 **Finlayson EV**, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. *Arch Surg* 2003; **138**: 721-725; discussion 726 [PMID: 12860752 DOI: 10.1001/archsurg.138.7.721]
- 15 **Schreuders EH**, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, Kuipers EJ. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015; **64**: 1637-1649 [PMID: 26041752 DOI: 10.1136/gutjnl-2014-309086]
- 16 **Sim J**, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther* 2005; **85**: 257-268 [PMID: 15733050]
- 17 **Nagata N**, Niikura R, Aoki T, Shimbo T, Sekine K, Okubo H, Watanabe K, Sakurai T, Yokoi C, Akiyama J, Yanase M, Mizokami M, Uemura N. Impact of discontinuing non-steroidal antiinflammatory drugs on long-term recurrence in colonic diverticular bleeding. *World J Gastroenterol* 2015; **21**: 1292-1298 [PMID: 25632204 DOI: 10.3748/wjg.v21.i4.1292]
- 18 **Fouch PG**. Diverticular bleeding: are nonsteroidal anti-inflammatory drugs risk factors for hemorrhage and can colonoscopy predict outcome for patients? *Am J Gastroenterol* 1995; **90**: 1779-1784 [PMID: 7572894]
- 19 **Strate LL**, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. *Arch Intern Med* 2003; **163**: 838-843 [PMID: 12695275 DOI: 10.1001/archinte.163.7.838]
- 20 **Pasha SF**, Shergill A, Acosta RD, Chandrasekhara V, Chathadi KV, Early D, Evans JA, Fisher D, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Saltzman JR, Cash BD. The role of endoscopy in the patient with lower GI bleeding. *Gastrointest Endosc* 2014; **79**: 875-885 [PMID: 24703084 DOI: 10.1016/j.gie.2013.10.039]
- 21 **Obana T**, Fujita N, Sugita R, Hirasawa D, Sugawara T, Harada Y, Oohira T, Maeda Y, Koike Y, Suzuki K, Yamagata T, Kusaka J, Masu K. Prospective evaluation of contrast-enhanced computed tomography for the detection of colonic diverticular bleeding. *Dig Dis Sci* 2013; **58**: 1985-1990 [PMID: 23504354 DOI: 10.1007/s10620-013-2629-6]
- 22 **Lhewa DY**, Strate LL. Pros and cons of colonoscopy in management of acute lower gastrointestinal bleeding. *World J Gastroenterol* 2012; **18**: 1185-1190 [PMID: 22468081 DOI: 10.3748/wjg.v18.i11.1185]
- 23 **Loffeld RJ**, Engel A, Dekkers PE. Incidence and causes of colonoscopic perforations: a single-center case series. *Endoscopy* 2011; **43**: 240-242 [PMID: 21165826 DOI: 10.1055/s-0030-1255939]
- 24 **Niikura R**, Nagata N, Aoki T, Shimbo T, Tanaka S, Sekine K, Kishida Y, Watanabe K, Sakurai T, Yokoi C, Yanase M, Akiyama J, Mizokami M, Uemura N. Predictors for identification of stigmata of recent hemorrhage on colonic diverticula in lower gastrointestinal bleeding. *J Clin Gastroenterol* 2015; **49**: e24-e30 [PMID: 24859714 DOI: 10.1097/MCG.0000000000000140]
- 25 **Nagata N**, Niikura R, Sakurai T, Shimbo T, Aoki T, Moriyasu S, Sekine K, Okubo H, Imbe K, Watanabe K, Yokoi C, Yanase M, Akiyama J, Uemura N. Safety and Effectiveness of Early Colonoscopy in Management of Acute Lower Gastrointestinal Bleeding on the Basis of Propensity Score Matching Analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 558-564 [PMID: 26492844 DOI: 10.1016/j.cgh.2015.10.011]
- 26 **Jensen DM**, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. *N Engl J Med* 2000; **342**: 78-82 [PMID: 10631275 DOI: 10.1056/NEJM200001133420202]
- 27 **Strate LL**, Naumann CR. The role of colonoscopy and radiological procedures in the management of acute lower intestinal bleeding. *Clin Gastroenterol Hepatol* 2010; **8**: 333-343; quiz e44 [PMID: 20036757 DOI: 10.1016/j.cgh.2009.12.017]
- 28 **Bloomfield RS**, Rockey DC, Shetzline MA. Endoscopic therapy of acute diverticular hemorrhage. *Am J Gastroenterol* 2001; **96**: 2367-2372 [PMID: 11513176 DOI: 10.1111/j.1572-0241.2001.04048.x]
- 29 **Green BT**, Rockey DC, Portwood G, Tarnasky PR, Guarisco S, Branch MS, Leung J, Jowell P. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. *Am J Gastroenterol* 2005; **100**: 2395-2402 [PMID: 16279891 DOI: 10.1111/j.1572-0241.2005.00306.x]
- 30 **Yamada A**, Niikura R, Yoshida S, Hirata Y, Koike K. Endoscopic management of colonic diverticular bleeding. *Dig Endosc* 2015; **27**: 720-725 [PMID: 26258405 DOI: 10.1111/den.12534]
- 31 **Yen EF**, Ladabaum U, Muthusamy VR, Cello JP, McQuaid KR,

- Shah JN. Colonoscopic treatment of acute diverticular hemorrhage using endoclips. *Dig Dis Sci* 2008; **53**: 2480-2485 [PMID: 18157637 DOI: 10.1007/s10620-007-0151-4]
- 32 **Simpson PW**, Nguyen MH, Lim JK, Soetikno RM. Use of endoclips in the treatment of massive colonic diverticular bleeding. *Gastrointest Endosc* 2004; **59**: 433-437 [PMID: 14997150 DOI: 10.1016/S0016-5107(03)02711-1]
- 33 **Ishii N**, Setoyama T, Deshpande GA, Omata F, Matsuda M, Suzuki S, Uemura M, Iizuka Y, Fukuda K, Suzuki K, Fujita Y. Endoscopic band ligation for colonic diverticular hemorrhage. *Gastrointest Endosc* 2012; **75**: 382-387 [PMID: 21944311 DOI: 10.1016/j.gie.2011.07.030]
- 34 **Anderson MA**, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukami N, Ikenberry SO, Jain R, Khan K, Krinsky ML, Lichtenstein DR, Maple JT, Shen B, Strohmeyer L, Baron T, Dominitz JA. Management of antithrombotic agents for endoscopic procedures. *Gastrointest Endosc* 2009; **70**: 1060-1070 [PMID: 19889407 DOI: 10.1016/j.gie.2009.09.040]
- 35 **White RH**, McKittrick T, Takakuwa J, Callahan C, McDonnell M, Fihn S. Management and prognosis of life-threatening bleeding during warfarin therapy. National Consortium of Anticoagulation Clinics. *Arch Intern Med* 1996; **156**: 1197-1201 [PMID: 8639014 DOI: 10.1001/archinte.1996.00440100095011]
- 36 **Guerrouij M**, Uppal CS, Alklabi A, Douketis JD. The clinical impact of bleeding during oral anticoagulant therapy: assessment of morbidity, mortality and post-bleed anticoagulant management. *J Thromb Thrombolysis* 2011; **31**: 419-423 [PMID: 21181236 DOI: 10.1007/s11239-010-0536-7]
- 37 **Witt DM**, Delate T, Garcia DA, Clark NP, Hylek EM, Ageno W, Dentali F, Crowther MA. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012; **172**: 1484-1491 [PMID: 22987143 DOI: 10.1001/archinternmed.2012.4261]
- 38 **Rodríguez LA**, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011; **343**: d4094 [PMID: 21771831 DOI: 10.1136/bmj.d4094]

P- Reviewer: Narasaka T **S- Editor:** Gong ZM
L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

