ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 August 10; 8(15): 501-545

Published by Baishideng Publishing Group Inc

WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

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).

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 Kapetanos, *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*
Katsuhiro 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, *Kashihara*

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 Amornyotin, *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 Mentes, *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*

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Biweekly Volume 8 Number 15 August 10, 2016

World Journal of Gastrointestinal Endoscopy
Volume 8 Number 15 August 10, 2016

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

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

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i15.501

World J Gastrointest Endosc 2016 August 10; 8(15): 501-507
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

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, Batimore, 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.

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, Batimore, 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 (± 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 (± 39.3) cm proximal to the ileocecal valve and mean time to completion was 41.7 (± 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

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 technique of rSBE has been described previously and is widely recognized[6].

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)
Angioectasia	8 (11.6)
Erosion	3 (4.3)
Stricture	12 (17.4)
Polyp	14 (20.3)
Inflammation	9 (13.0)
Other	6 (8.7)

[1]As measured from the ileocecal valve. Values presented as mean (SD) for time and quantitative depth, and *n* (%) otherwise.

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

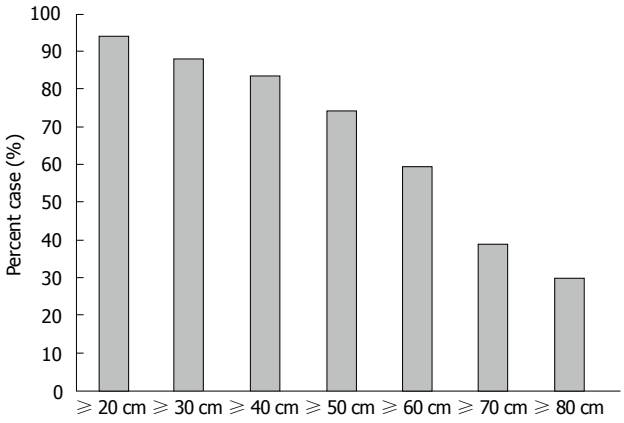


Figure 1 Insertion depth beyond the ileocecal valve.

(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%), hemoclipping 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%), hemoclipping 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 anterograde (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 and 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

1 **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]

2 **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]

3 **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]

4 **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]

5 **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]

6 **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]

7 **Peery AF**, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura 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**: 1179-187.e1-3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]

8 **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]

9 **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]

10 **Akyüz Ü**, Pata C, Kalayci M, Özdıl K, Altun H, Karıp 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]

11 **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]

12 **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]

13 **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.2 012.04.017]

14 **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]

15 **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]

16 **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]

17 **Prachayakul V**, Deesomsak M, Aswakul P, Leelakusolvong 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]

18 **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]

19 **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]

20 **Albert JG.** Interventional balloon-enteroscopy. *J Interv Gastroenterol* 2012; **2**: 42-50 [PMID: 22586550 DOI: 10.4161/jig.20134]

21 **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]

22 **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]

23 **Di Caro S**, May A, Heine DG, Fini L, Landi B, Petruzziello 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]

24 **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]

25 **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]

26 **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]

27 **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

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i15.508

World J Gastrointest Endosc 2016 August 10; 8(15): 508-516
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

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 clinicaltrial.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.

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

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		Not at all to very
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		Not at all to very
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

[1]Mineral water (low level), Rim, bottled at source by Rim Natural Spring Mineral Water SAL - Mount Sannine, Lebanon; [2]Mineral 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; [3]Orange juice (high level), Mr. Juicy, bottled by société moderne Libanaise pour le commerce SAL, Beirut, Lebanon; [4]Lemonade (high level), Balkis, Balkis SAL, Beirut, Lebanon; [5]Sweetener 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; [6]Cold 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; [7]Baking 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

[1]Bowel cleansing laxative solutions. $P > 0.05$ not significant (no superscript) *vs* [a]$P < 0.05$; [b]$P < 0.01$; [d]$P < 0.001$.

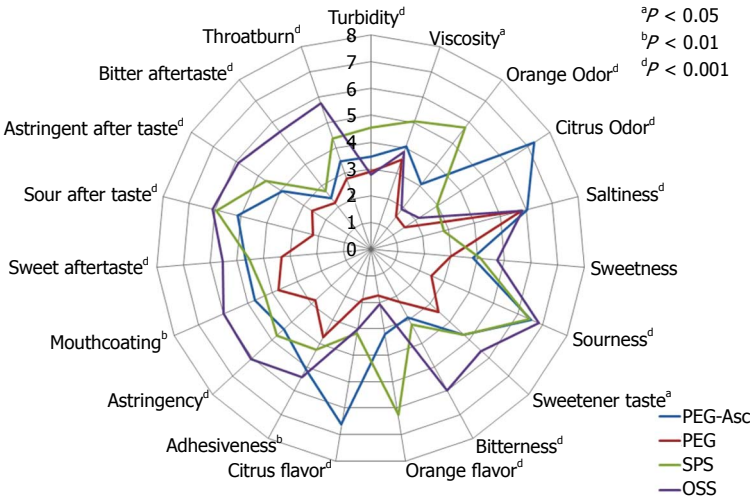


Figure 1 Sensory profiles for the 4 bowel cleansing laxative solutions. Individual attributes are positioned like the spokes of a wheel around a center (zero or not detected) point, with the spokes representing attribute intensity scales, with higher (more intense) values radiating outward. PEG: Polyethylene 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 ± SD)	PEG (mean ± SD)	SPS (mean ± SD)	OSS (mean ± SD)
Appearance				
Turbidity	3.5 ± 2.3[c]	2.9 ± 1.8[c]	4.5 ± 2.4[a]	2.8 ± 1.6[c]
Viscosity	4.1 ± 2.7[c]	3.5 ± 2.0[c]	5.0 ± 2.8[a]	3.8 ± 2.3[c]
Odor				
Orange	3.1 ± 3.1[c]	1.6 ± 0.4[e]	5.8 ± 3.4[a]	1.9 ± 1.4[e]
Citrus	7.3 ± 3.7[a]	1.5 ± 0.4[e]	3.0 ± 2.3[c]	2.2 ± 1.8[ce]
Flavor				
Saltiness	6.0 ± 3.1[a]	5.8 ± 3.2[a]	2.8 ± 1.9[c]	5.8 ± 3.4[a]
Sweetness	3.8 ± 2.4	3.0 ± 1.9	4.1 ± 2.6	4.7 ± 3.4
Sourness	6.6 ± 3.0[a]	2.5 ± 1.4[c]	6.5 ± 3.2[a]	6.9 ± 3.8[a]
Sweetener	4.7 ± 3.5[c]	3.5 ± 2.5[e]	4.7 ± 3.4[c]	5.6 ± 3.3[a]
Bitterness	2.9 ± 1.9[ce]	2.2 ± 1.7[e]	3.2 ± 2.1[c]	6.0 ± 4.2[a]
Orange	3.2 ± 3.3[c]	1.8 ± 0.9[e]	6.3 ± 4.1[a]	2.1 ± 2.0[e]
Citrus	6.6 ± 3.9[a]	1.9 ± 1.3[e]	3.2 ± 2.6[c]	3.0 ± 3.2[ce]
Mouthfeel				
Adhesiveness	5.1 ± 2.6[a]	3.7 ± 1.9[c]	4.3 ± 2.2[c]	5.4 ± 2.6[a]
Astringency	4.4 ± 2.6[c]	2.8 ± 2.0[e]	4.5 ± 2.2[c]	6.1 ± 3.4[a]
Mouthcoating	4.7 ± 2.8[c]	3.8 ± 2.3[c]	4.3 ± 2.5[c]	6.0 ± 3.2[a]
Aftertaste				
Sweet	4.7 ± 3.2[ac]	3.3 ± 2.3[e]	4.5 ± 3.3[c]	5.5 ± 3.3[a]
Sour	5.1 ± 2.6[a]	2.2 ± 1.4[c]	5.9 ± 3.1[a]	6.1 ± 3.9[a]
Astringent	4.0 ± 2.2[c]	2.6 ± 1.5[e]	4.6 ± 2.6[c]	5.9 ± 3.5[a]
Bitter	2.4 ± 1.4[c]	2.2 ± 1.7[c]	2.8 ± 1.6[c]	5.5 ± 3.7[a]
Throatburn	3.5 ± 2.5[ce]	2.8 ± 2.1[e]	4.4 ± 2.8[c]	5.7 ± 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]

[1]Bowel 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 ± SD)	PEG (mean ± SD)	SPS (mean ± SD)	OSS (mean ± SD)
Overall acceptability	3.8 ± 2.1[c]	3.1 ± 1.6[c]	5.5 ± 2.1[a]	3.8 ± 2.4[c]
Odor	5.5 ± 2.1[ac]	4.9 ± 0.9[c]	5.9 ± 1.8[a]	5.5 ± 2.5[ac]
Taste	3.5 ± 2.1[c]	2.9 ± 1.6[c]	5.1 ± 2.3[a]	3.1 ± 2.2[c]
Mouthfeel	4.2 ± 1.9[c]	3.8 ± 1.7[ce]	5.1 ± 2.0[a]	3.4 ± 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 consumed 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 + bicasodyl demonstrated higher taste acceptability and lower rates of difficulty swallowing when compared to PEG + bicasodyl 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

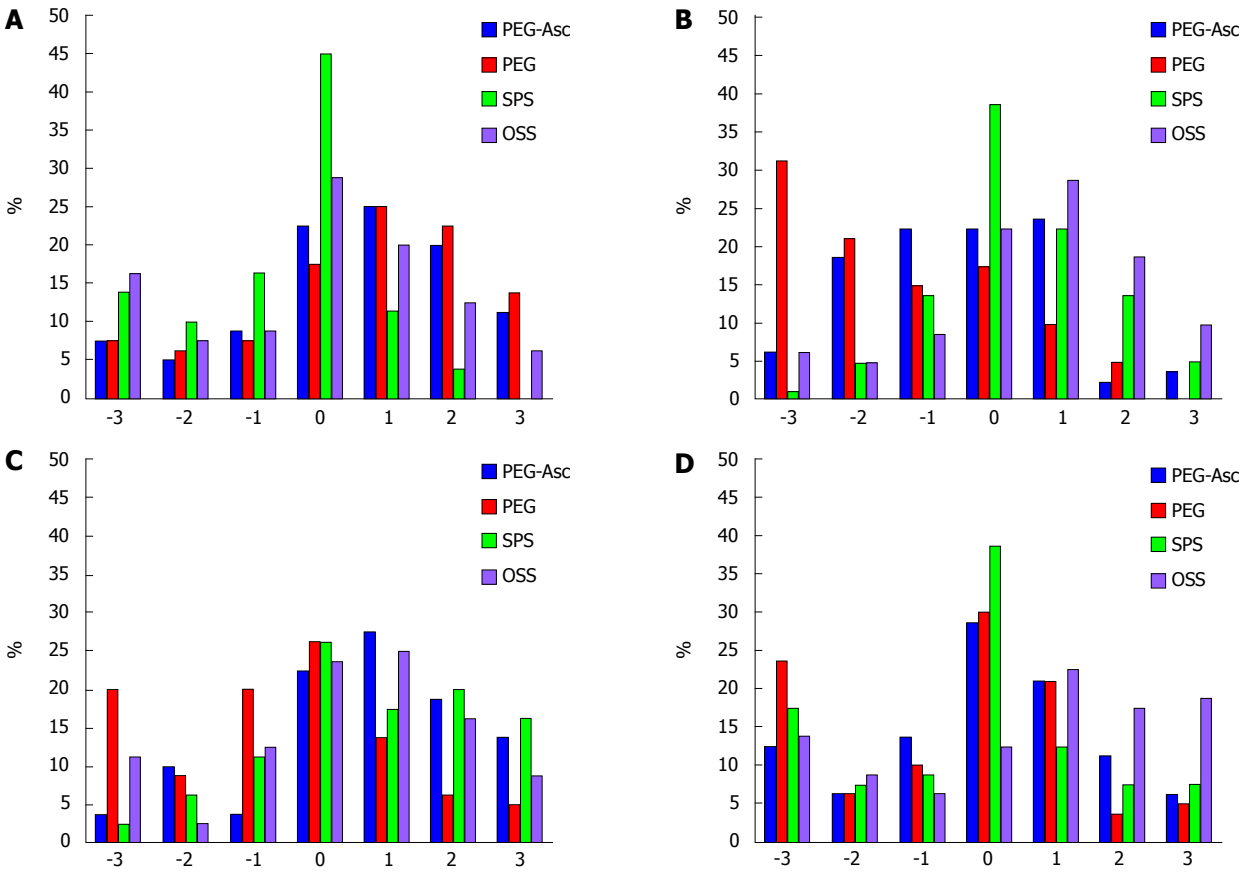


Figure 2 Just-About-Right ratings for saltiness (A), sweetness (B), sourness (C) and bitterness (D) for PEG-Asc (blue), PEG (red), SPS (green) and OSS (violet) samples. -3: Too little; 0: Just about right; 3: Too much; PEG: Polyethylene glycol; PEG-Asc: PEG + ascorbic acid; SPS: Sodium picosulfate; OSS: 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 **Srour 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

Tolerability Questionnaire. *Dig Liver Dis* 2014; **46**: 808-812 [PMID: 24953203 DOI: 10.1016/j.dld.2014.05.020]

P- Reviewer: Belsey J, Sakin YS **S- Editor**: Gong ZM **L- Editor**: A
E- Editor: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i15.517

World J Gastrointest Endosc 2016 August 10; 8(15): 517-532
ISSN 1948-5190 (online)

META-ANALYSIS

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.

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. dllevine@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

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.

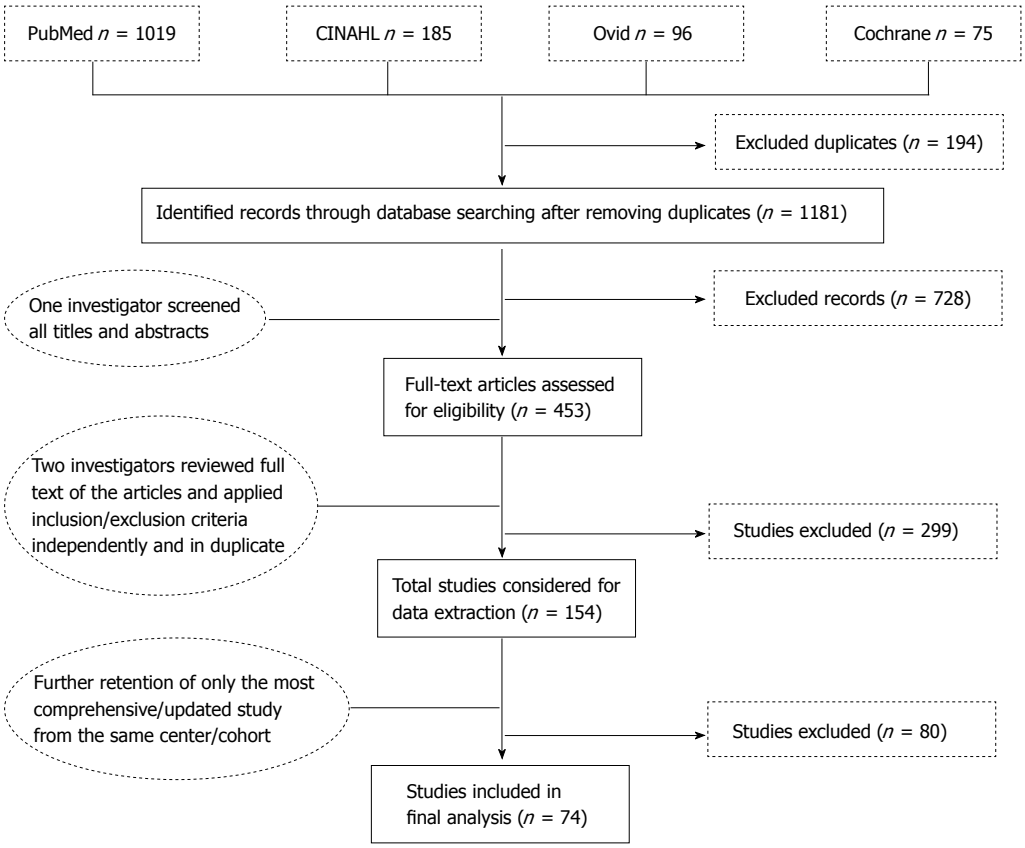


Figure 1 Screening and selection process.

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 μm 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),

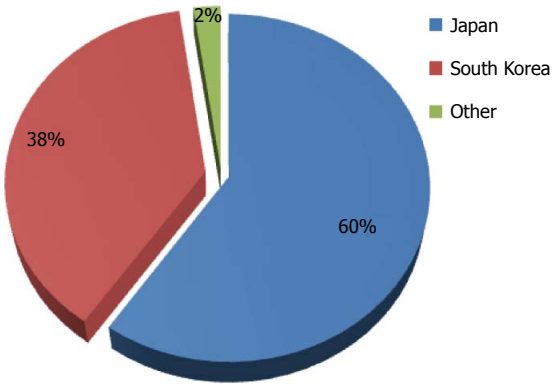


Figure 2 Percentage distribution of 27155 patients who underwent gastric endoscopic submucosal dissection between 1999 and 2014 in 11 countries. Others include China, Taiwan, Australia, Germany, Italy, Poland, Portugal, Brazil and Uruguay that contributed ⩽ 1% each.

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%), $P = 0.06$].

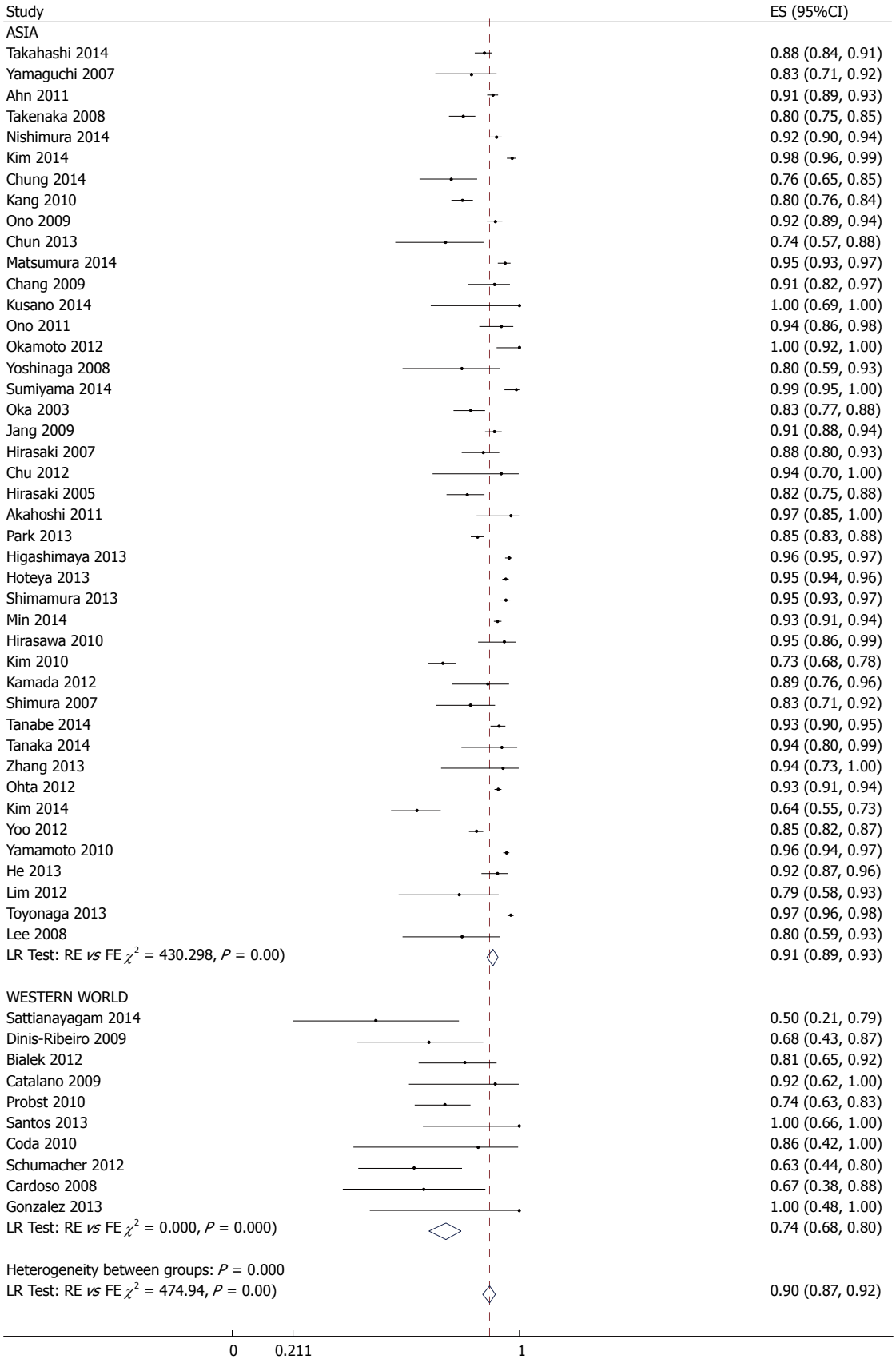


Figure 3 Meta-analysis of histologic *en bloc* resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection, stratified by region. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from 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 *et al*[21]	2008-2012	Australia	10	75 (43-86)	NA	12	35 (15-65)	NA
Cardoso *et al*[22]	2005-2007	Brazil	12	71.2 (27-91)	50	15	16.8 (8-20)	140
Chaves *et al*[23]	2007-2009	Brazil	15	67.1 (32-81)	20	16	16.2 (6-35)	85 (20-150)
Santos *et al*[24]	2010-2011	Brazil	9	65 (58-73)	0	9	28.6 (20-45)	103 (60-240)
Xu *et al*[25]	2006-2009	China	120	51.5 (26-75)	40	120	18.8 (8-30)	64.6 (30-120)
He *et al*[26]	2008-2012	China	144	55.8 (18-78)	72	145	15.14	63.4 (20-180)
Zhang *et al*[27]	2008-2011	China	18	65.3 (30-71)	61	18	26 (10-35)	90 (50-120)
Probst *et al*[28]	2003-2010	Germany	83	68.6 (41-87)	40	91	NA	142 (60-420)
Schumacher *et al*[29]	2008-2010	Germany	30	61 (35-93)	43	30	25 (20-70)	74 (15-402)
Catalano *et al*[30]	2005-2007	Italy	12	68 (38-83)	100	12	NA	111 (62-150)
Coda *et al*[31]	2007-2009	Italy	7	72 (61-83)	43	7	26 (15-50)	123 (50-360)
Hirasaki *et al*[32]	2000-2004	Japan	144	70 (45-91)	NA	144	13	73
Yokoi *et al*[33]	1999-2003	Japan	46	67 (45-89)	9	46	NA	NA
Ono *et al*[34]	2000-2007	Japan	408	67	NA	444	NA	NA
Hirasawa *et al*[35]	2000-2009	Japan	58	69.3	21	58	20.3 (3-50)	82 (22-275)
Yoshinaga *et al*[36]	2001-2006	Japan	24	61.7 (37-85)	8	25	16.5 (3-60)	NA
Takenaka *et al*[37]	2001-2005	Japan	275	NA	NA	306	NA	NA
Miyahara *et al*[38]	2001-2010	Japan	1082	71.7 (36-92)	29	1190	NA	99.8 (10-675)
Ohnita *et al*[39]	2001-2010	Japan	1209	72 (33-95)	27	1322	NA	NA
Oka *et al*[40]	2002-2004	Japan	185	NA	NA	195	19.4 (5-100)	84.4
Shimura *et al*[41]	2002-2005	Japan	55	71.4 (46-91)	22	59	15.5	58 (7-640)
Hirasaki *et al*[42]	2002-2006	Japan	112	70 (45-89)	NA	112	19	69
Ohta *et al*[43]	2002-2010	Japan	1500	NA	NA	1795	NA	NA
Kamada *et al*[44]	2002-2010	Japan	46	65.5 (29-90)	48	46	NA	NA
Toyonaga *et al*[45]	2002-2007	Japan	821	71 (31-93)	34	1136	13 (1-105)	NA
Kosaka *et al*[46]	2002-2007	Japan	438	69.4	26	438	14.6	47 (8-345)
Yamaguchi *et al*[47]	2003-2005	Japan	54	NA	NA	54	19.1 (30-70)	129 (29-440)
[1]Akasaka *et al*[48]	2003-2008	Japan	1188	71	27	1188	20 (2-105)	90 (6-750)
Ono *et al*[49]	2003-2011	Japan	80	69.6	20	80	NA	83.7
[1]Toyokawa *et al*[50]	2003-2010	Japan	967	NA	32	1123	18	98
Tanabe *et al*[51]	2003-2007	Japan	421	69 (41-91)	23	421	NA	67 (7-360)
Shimamura *et al*[52]	2004-2012	Japan	521	NA	NA	616	NA	NA
Takahashi *et al*[53]	2004-2013	Japan	459	71.4	25	459	17.2	NA
Yamamoto *et al*[54]	2005-2011	Japan	1430	69.6	28	1520	15.3	101
Higashimaya *et al*[55]	2005-2011	Japan	891	69.1	27	1027	18.3	NA
Hoteya *et al*[56]	2005-2010	Japan	1224	68	24	1463	21	89
Matsumura *et al*[57]	2005-2014	Japan	413	72.1	30	425	18.4	NA
Sohara *et al*[58]	2006-2011	Japan	681	70.9 (45-91)	40	850	20.8 (2-150)	42 (4-360)
[1]Nishimura *et al*[59]	2006-2012	Japan	669	71	27	750	NA	NA
Tsuji *et al*[60]	2007-2009	Japan	328	68	29	398	43	69
Akahoshi *et al*[61]	2007-2009	Japan	35	72 (52-85)	34	35	15.6	104 (33-264)
Mukai *et al*[62]	2007-2010	Japan	142	72.4	32	161	NA	81
Tanaka *et al*[63]	2008-2011	Japan	32	71 (56-84)	63	33	17 (4-67)	111 (23-399)
Okamoto *et al*[64]	2009-2010	Japan	45	69 (49-83)	29	45	14 (10-35)	80
Watari *et al*[65]	2010-2012	Japan	94	70.9 (48-87)	24	98	NA	NA
Sumiyama *et al*[66]	2010-2012	Japan	100	NA	18	105	18 (3-53)	34 (4-151)
Kusano *et al*[67]	2011-2012	Japan	10	69.2	20	10	16.3	130.5
Kawamura *et al*[68]	NA	Japan	4	NA	25	4	24 (14-36)	50.5 (28-72)
Lee *et al*[69]	2003-2008	South Korea	461	62	30	487	NA	NA
Kim *et al*[70]	2003-2006	South Korea	337	NA	23	337	16	49
[1]Shin *et al*[71]	2003-2010	South Korea	1105	65 (27-87)	32	1105	NA	NA
Jang *et al*[72]	2004-2007	South Korea	402	60 (34-84)	37	402	NA	NA
Kim *et al*[73]	2004-2007	South Korea	142	62	34	142	NA	NA
Kang *et al*[74]	2005-2008	South Korea	456	62.4	23	456	20.6	NA
Goh *et al*[75]	2005-2009	South Korea	210	NA	NA	210	NA	NA
Ahn *et al*[76]	2005-2008	South Korea	889	62.8	23	916	21.5	37.5
Yoo *et al*[77]	2005-2010	South Korea	729	64 (55-70)	26	823	18 (12-25)	52 (33-84)
Lim *et al*[78]	2005-2011	South Korea	24	63 (56-75)	21	24	16 (4-52)	42 (16-103)
Park *et al*[79]	2005-2011	South Korea	916	62	73	931	NA	NA
Chung *et al*[80]	2005-2010	South Korea	76	61.1	42	76	NA	NA
Kim *et al*[81]	2007-2012	South Korea	126	55 (28-85)	44	126	12 (1-50)	NA
Min *et al*[82]	2007-2011	South Korea	1527	63 (27-87)	21	1577	16 (1-110)	NA
Kim *et al*[83]	2008-2010	South Korea	440	64	29	450	19	48
Yoon *et al*[84]	2008-2010	South Korea	1319	63	34	1443	15.7	61.8
Choi *et al*[85]	2008-2012	South Korea	616	NA	26	616	12.9	27.7
Chun *et al*[86]	2009-2012	South Korea	35	54.15	NA	35	18	32.3 (7-84)

[1]Chung *et al*[87]	2010-2012	South Korea	76	64	36	76	NA	44
Kim *et al*[88]	2012-2013	South Korea	446	NA	34	446	NA	NA
Bialek *et al*[89]	2007-2010	Poland	37	63 (24-86)	62	37	25 (10-60)	NA
Dinis-Ribeiro *et al*[90]	2005-2008	Portugal	19	74	NA	19	NA	90 (40-300)
Lee *et al*[91]	2004-2006	Taiwan	25	69 (36-82)	44	25	19	NA
[1]Chang *et al*[92]	2004-2007	Taiwan	70	66.5 (35-84)	36	70	18.5 (8-40)	92.4 (25-210)
Chu *et al*[93]	2009-2011	Taiwan	16	51.9 (35-65)	63	16	26.1 (20-42)	52 (30-120)
González *et al*[94]	NA	Uruguay	5	NA	NA	5	25.2	85 (30-180)

[1]Multicenter studies. NA: Not available.

Table 3 Rates of adverse outcomes in patients undergoing gastric endoscopic submucosal dissection between 1998 and 2014

Adverse outcomes	Studies, *n*	Patients, *n*	Tumor, *n*	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)

[1]The rates are calculated as a percentage of the total number of tumors operated; [2]Immediate refers to adverse outcomes occurring within 24 h of the procedure; [3]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 declined by 0.29% (0.05%-0.54%) per year over the duration of study (P = 0.02); [4]The 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); [5]Delayed refers to adverse outcome occurring 24 h after the procedure; [6]The rate (95%CI) of delayed bleeding increases by 1.3% (0.07%-2.5%) for every 10 year increase in age; [7]Average follow-up was 26, 28 and 32 mo for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively; [8]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). R0: Histologically-confirmed *en bloc* resection.

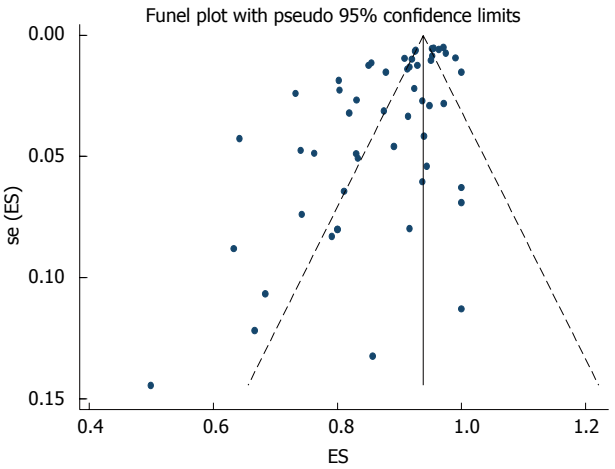


Figure 4 Funnel plot of histologically confirmed *en bloc* (R0) resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection. Each dot represents the R0 resection rate. Asymmetry in the distribution of study estimates around the center 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

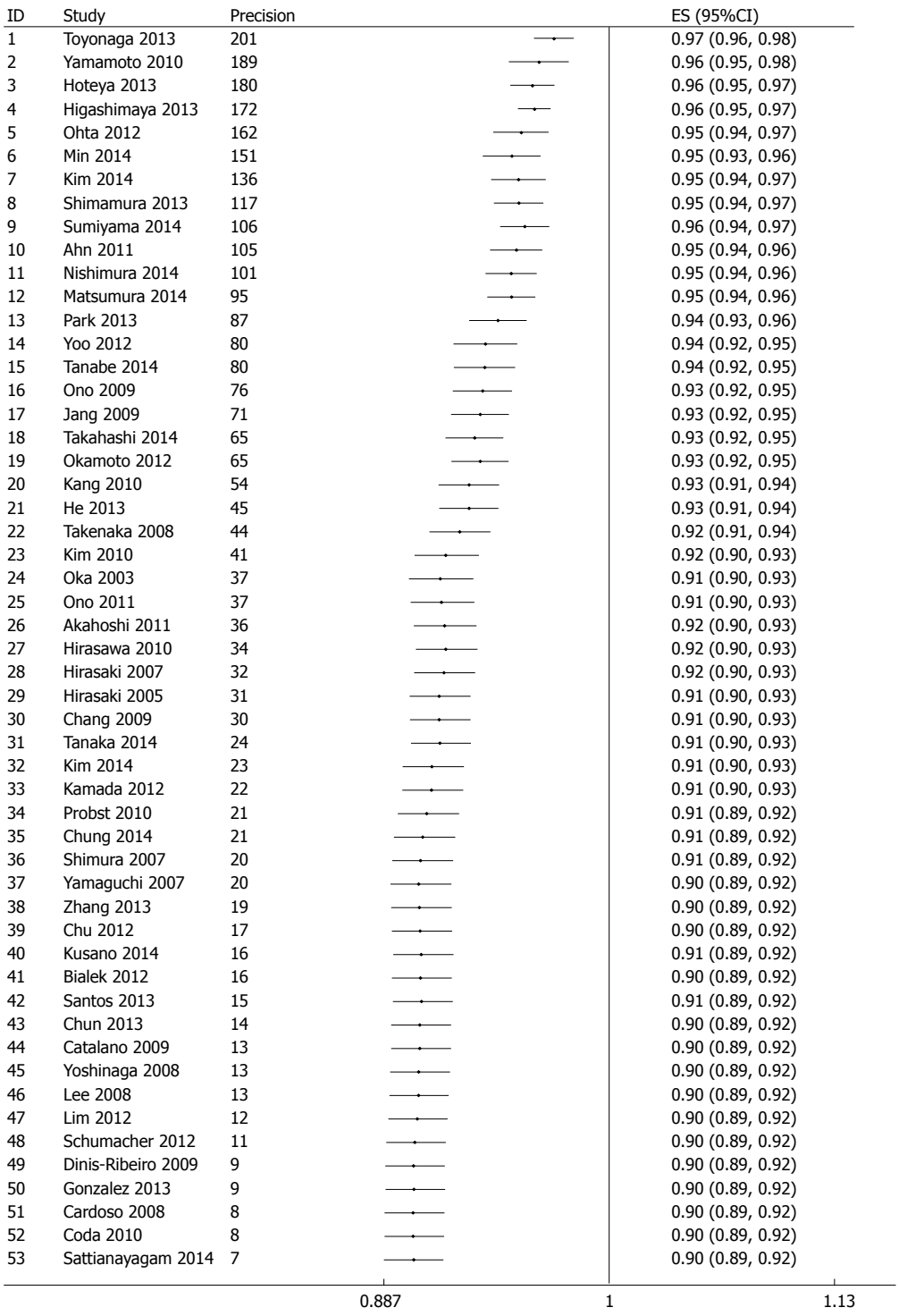
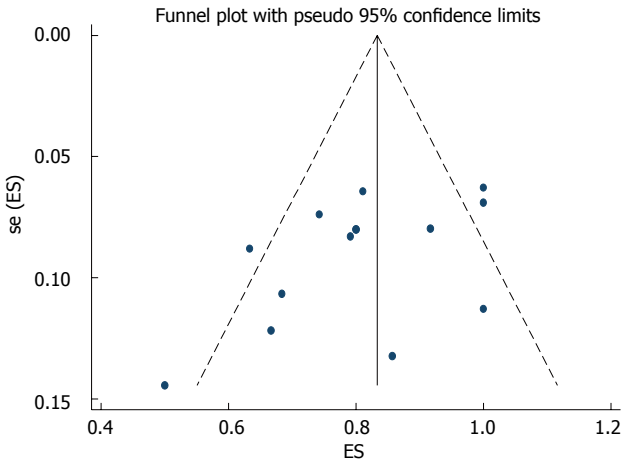


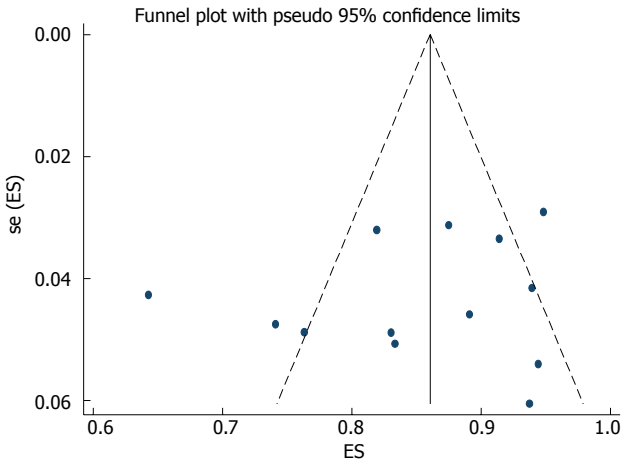
Figure 5 Evaluation of potential publication bias *via* a cumulative meta-analysis plotted as a function of study precision. The dots and the error bars correspond to the cumulative estimates and associated 95%CI respectively. After sorting by precision (calculated as inverse of standard error) from 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.

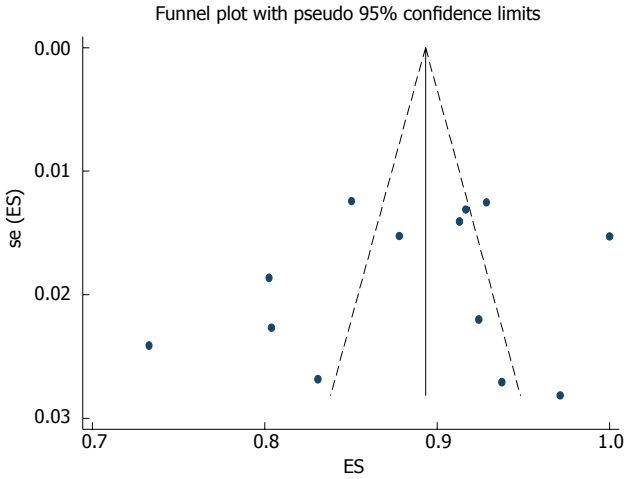
Perioperatively, major bleeding and perforation were the most common serious adverse events. However, most of these adverse events were successfully managed endoscopically with only very few ones requiring surgical



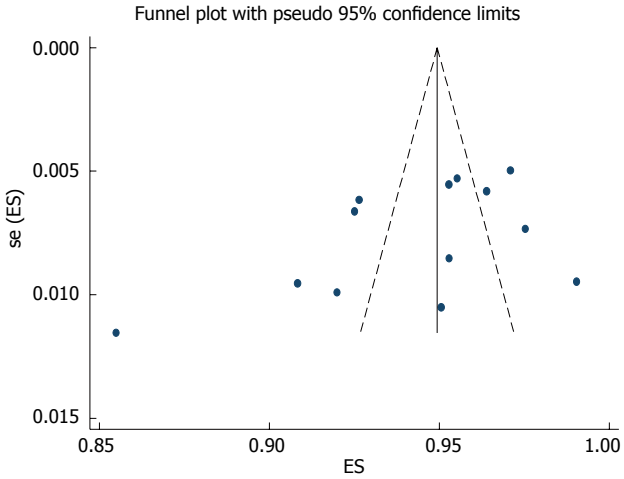
Funnel plot in the first quartile of sample size (n =14), P = 0.07



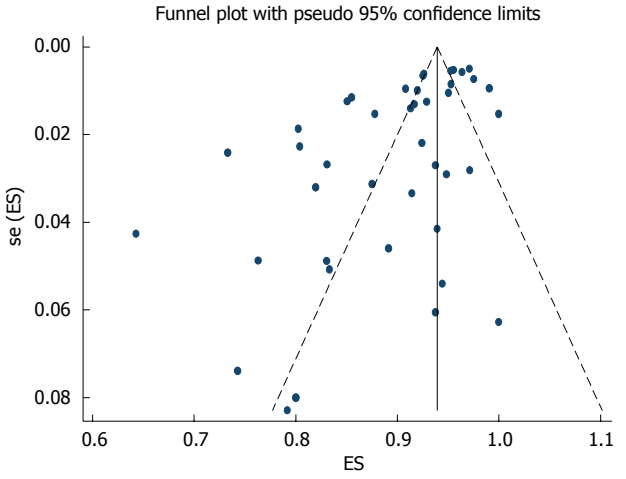
Funnel plot in the second quartile of sample size (n = 13), P = 0.40



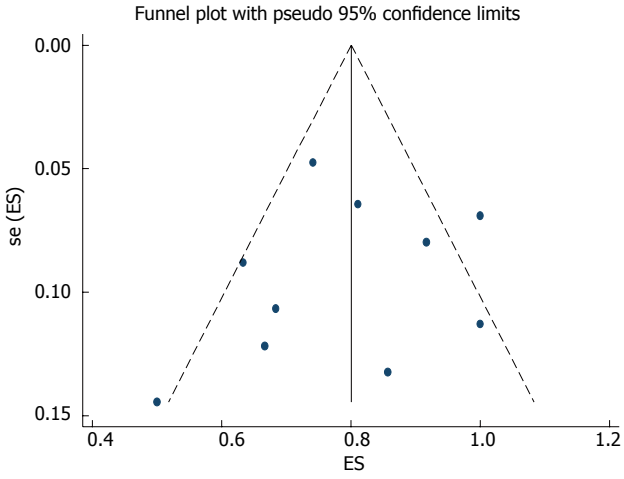
Funnel plot in the third quartile of sample size (n = 13), P = 0.40



Funnel plot in the fourth quartile of sample size (n = 13), P = 0.11



Funnel plot involving Asia studies (n = 43), P < 0.001



Funnel plot among studies from the western world (n = 10), P = 0.72

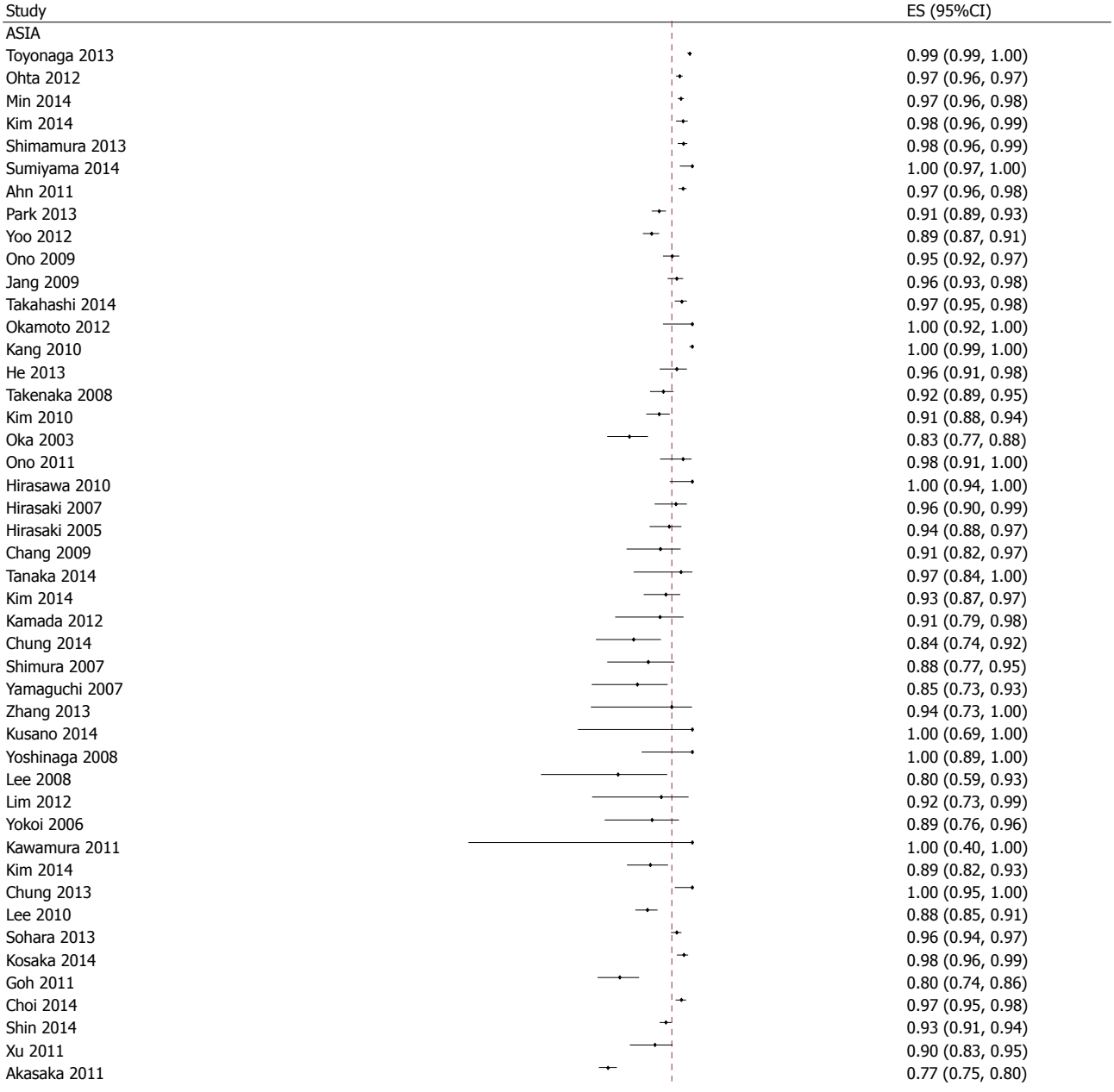
Figure 6 Funnel plot of histologically confirmed *en bloc* (R0) resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection, stratified based on sources of heterogeneity. Each dot represents the R0 resection rate. Lack of asymmetry in 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, *n*	Tumor, *n*	Rate (95%CI)[1]
Efficacy measures			
R0 resection	24	8520	87 (84-90)
Endoscopic *en bloc* 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)

[1]The rates are calculated as a percentage of the total number of tumors operated; [2]Immediate refers to adverse outcomes occurring within 24 h of the procedure; [3]Delayed refers to adverse outcome occurring 24 h after the procedure; [4]Average 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.



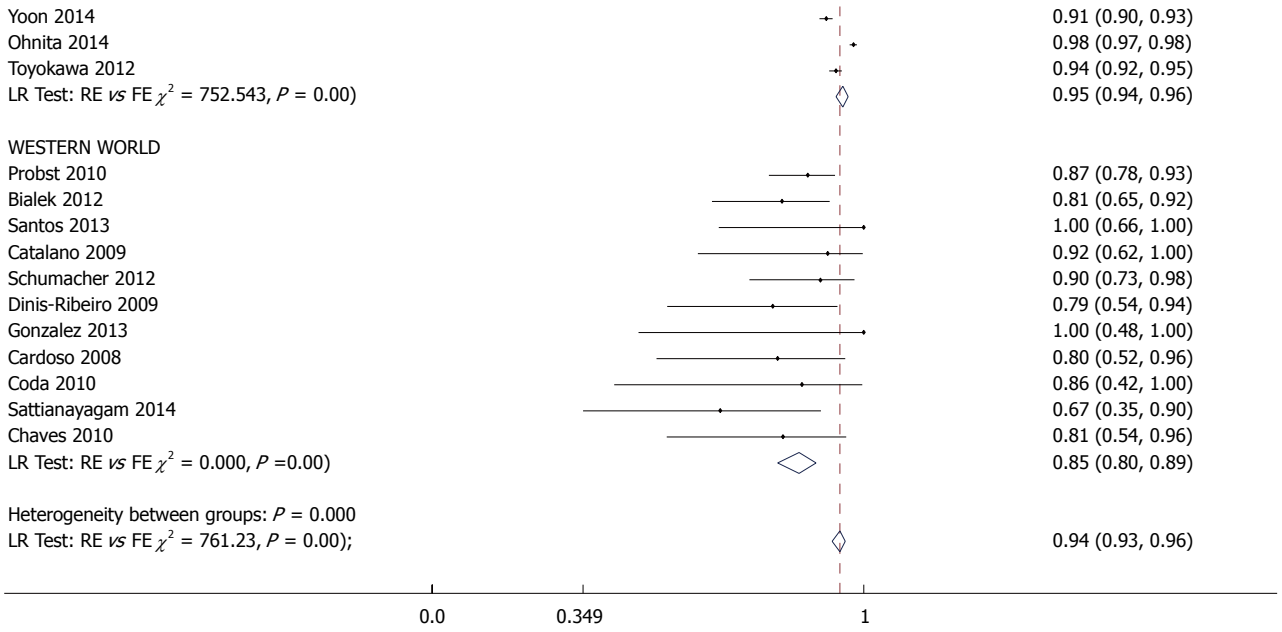


Figure 7 Meta-analysis of endoscopic *en bloc* resection rate in 60 studies involving 21511 tumors in 19935 patients that underwent gastric endoscopic submucosal dissection, stratified by region. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from 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.

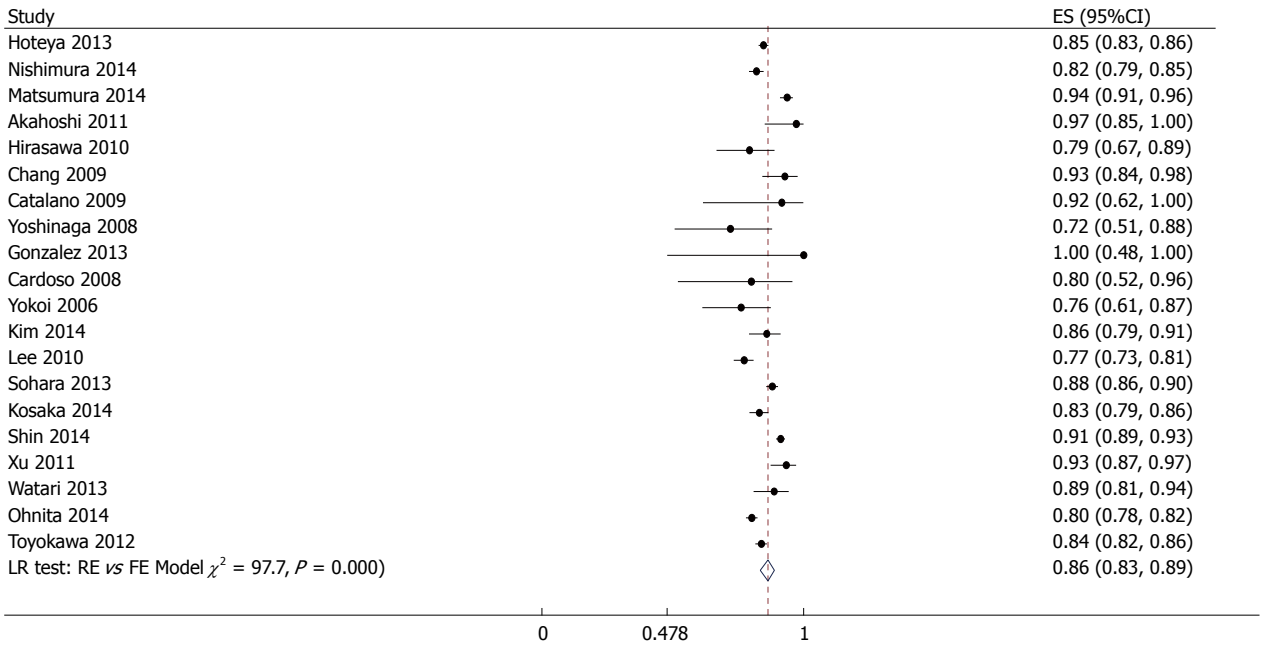


Figure 8 Meta-analysis of curative resection rate in 20 studies involving 8589 tumors in 7785 patients that underwent gastric endoscopic submucosal dissection. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the 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 guide-line-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.

COMMENTS

Background

Advances in endoscopic techniques have led to the development of endoscopic 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, Kajiwara 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,

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, Muscatiello 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, Leeflang 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 Júnior 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, Ayrizomo 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, Furuhata 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/s120 29-013-9544-0]
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:

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**, Toyoizumi 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: 10.3109/00365520903254304]
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 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]
89 **Białek 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]

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, Mentes O
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i15.533

World J Gastrointest Endosc 2016 August 10; 8(15): 533-540
ISSN 1948-5190 (online)

CASE REPORT

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.

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 periampullary 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

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-operatory 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

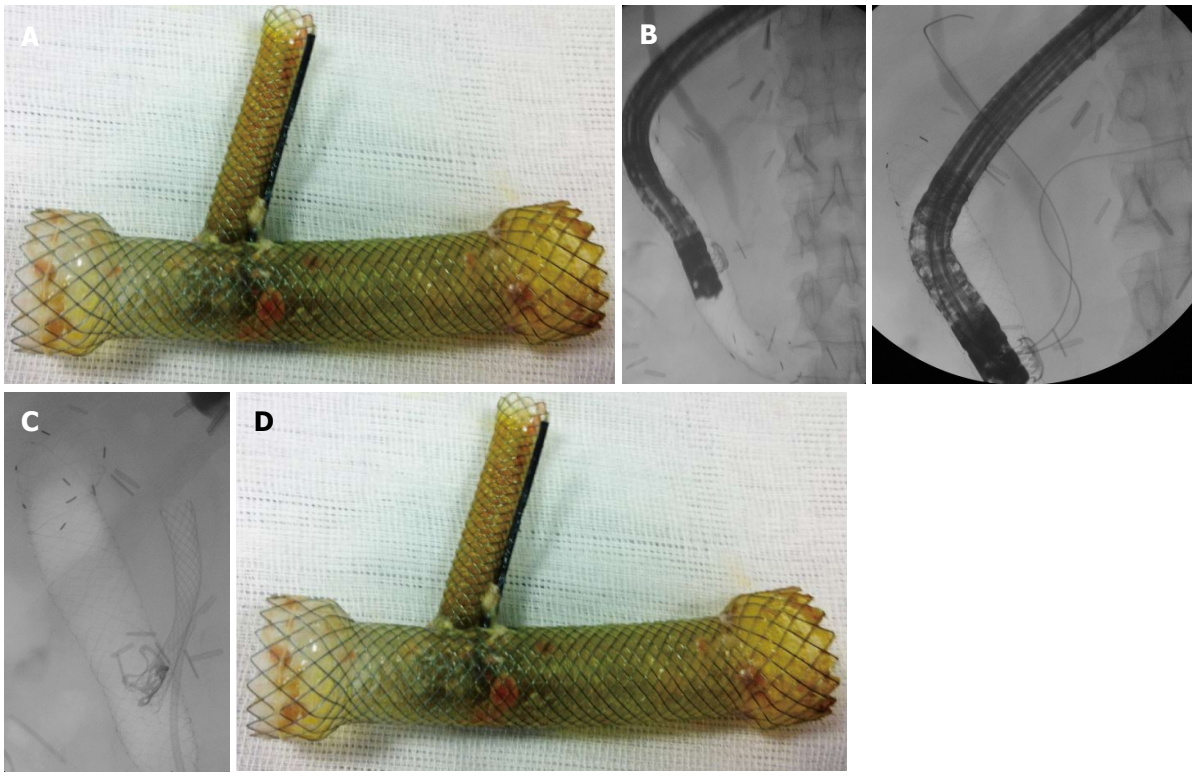


Figure 1 Fluoroscopy. A: Trans-stent duodenoscopy. Cholangiopancreatography already performed prior to enteral stenting; B: Two guidewires (biliary and pancreatic) inside the biliary and the pancreatic ducts; C: Final fluoroscopic image of a 6 cm × 10 mm biliary SEMS and a 7 Fr × 7 cm plastic pancreatic stent draining inside the enteral stent; D: After 4 wk, the multistent complex was removed endoscopically.

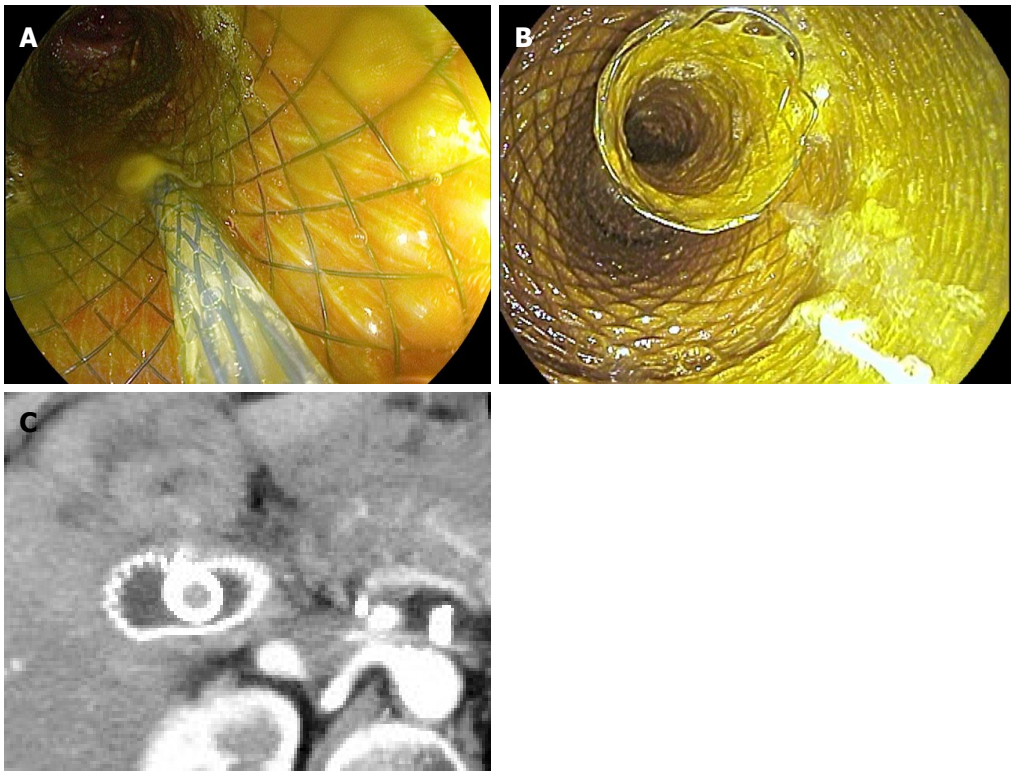


Figure 2 Bilio-enteric external fistula after pancreaticoduodenectomy. A: An 8 mm × 4 cm biliary SEMS was inserted into the common bile duct through the meshes of the enteral SEMS; B: Final stent complex at the end of the procedure; C: Detail of CT scan performed two days after the intervention showing 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 doth 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 nephrour-eterectomy, 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 periampullary duodenal wall. Thus, we decided to perform surgical necrosectomy of a retroperitoneal collection trough a lombotomy, 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 adeno Ca	Dehiscence of the bilio-enteric anastomosis	FCESEMS (8 cm × 20 mm) + FCBSEMS (4 cm × 10 mm)	Yes (3)	*En bloc* endoscopic removal 8 wk later	28
2 (57/M)	Whipple's procedure with pancreatic nelaton 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 nelaton tube into enteral stent + FCESEMS (8 cm × 20 mm)	Yes after second stenting (1)	First enteral stenting induced a jejunal perforation A 2nd 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, nasogastic 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 adeguate 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

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i15.541

World J Gastrointest Endosc 2016 August 10; 8(15): 541-545
ISSN 1948-5190 (online)

CASE REPORT

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.

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

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

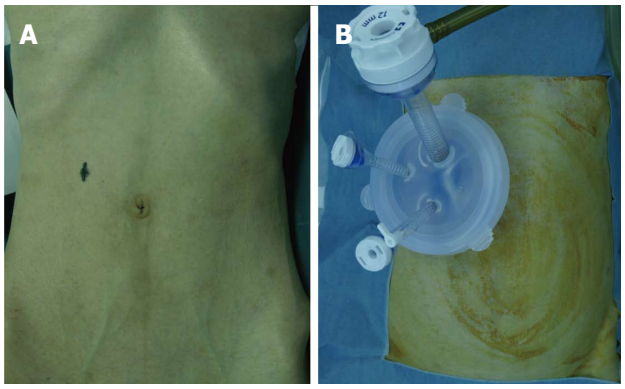


Figure 1 Image of the single-incision laparoscopic-assisted stoma creation technique. At the preoperatively-marked ideal stoma site (A), three trocars were placed in the EZ Access device (B).

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 recurrence and improve patient survival[1,10-12].

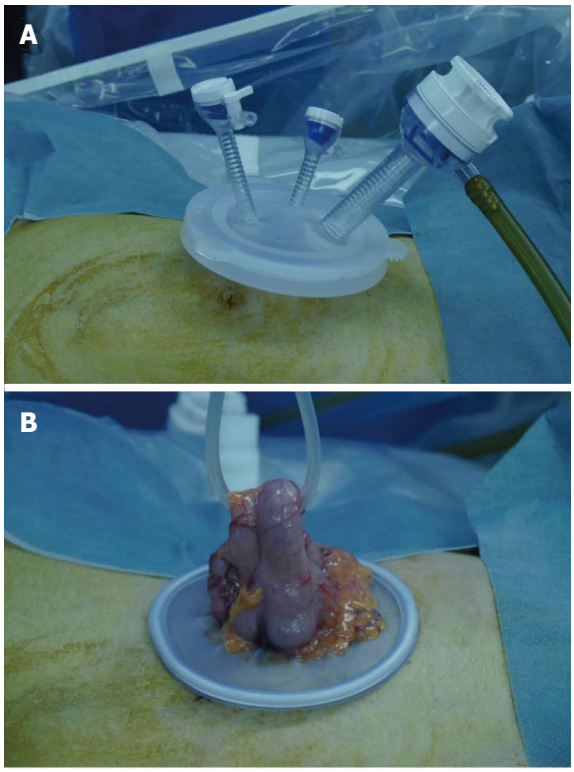


Figure 2 Image of single-incision laparoscopic-assisted stoma creation utilizing multi-trocar access *via* EZ Access at the stoma site. SILStoma was performed using a total of 3 trocars: 2 trocars for an operator and 1 trocar for a laparoscopist (A). After the mobilization to construct a loop colostomy the transverse colon was extracted through the Lap-Protector at the stoma site (B).

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 ≥ 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 ± 38.3
Blood loss (mL)	0.4 ± 1.4
Additional port (except single incision)	0 (0-2)
Conversion to open	0
Complications (Grade ≥ II[1])	0

[1]Postoperative complications ≥ 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-trocars 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

1 **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]

2 **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]

3 **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]

4 **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]

5 **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, Påhlman 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 colostomy. *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