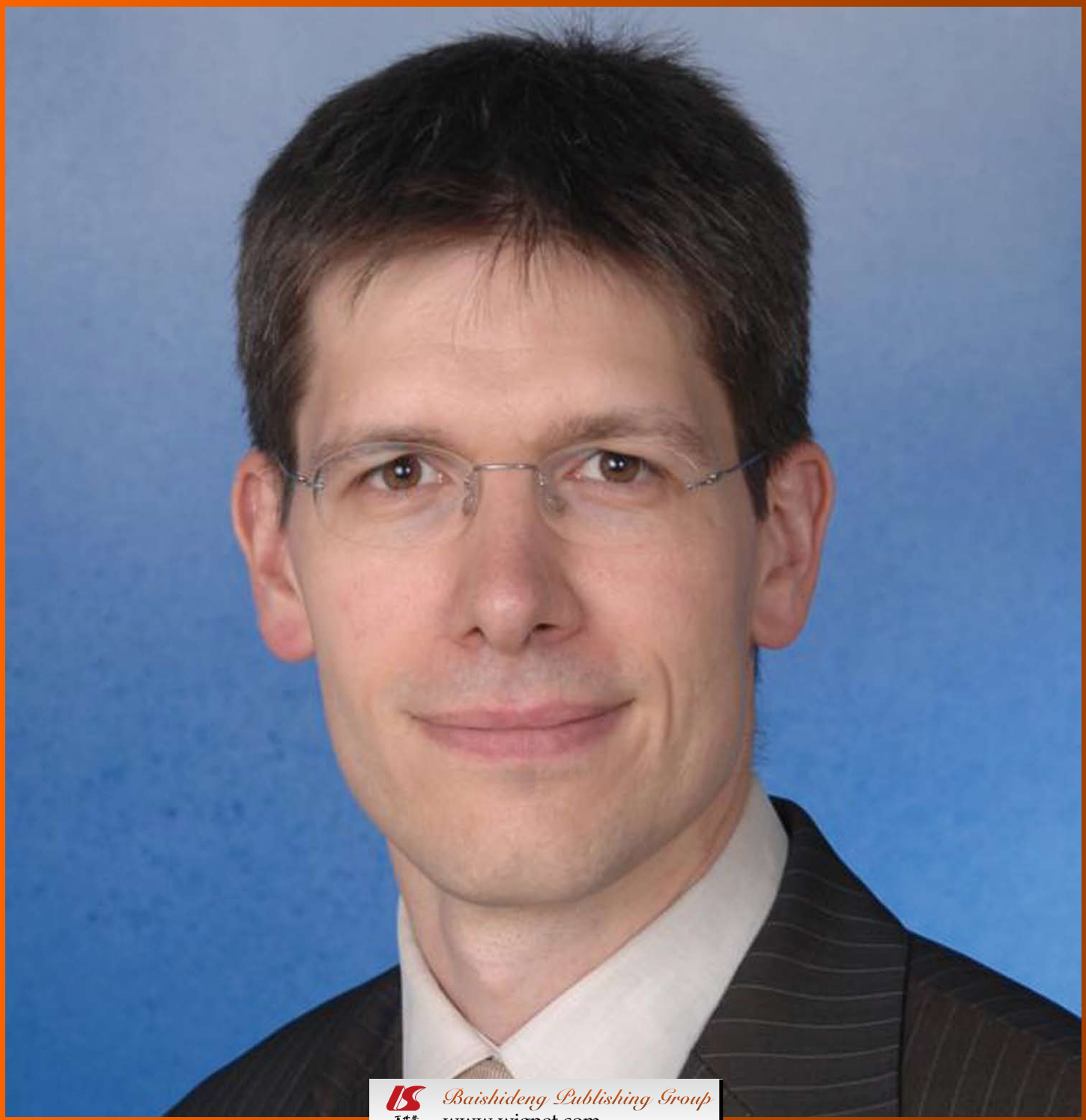
ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2012 November 16; 4(11): 479-517



Baishideng Publishing Group
www.wjgnet.com

WJGE World Journal of Gastrointestinal Endoscopy

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

Editorial Board

2009-2013

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 400 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 45 countries, including Australia (7), Austria (1), Belgium (6), Brazil (7), Canada (5), Chile (2), China (26), Croatia (2), Cuba (1), Czech Republic (3), Denmark (1), Ecuador (1), Egypt (1), Finland (2), France (10), Germany (27), Greece (11), Hungary (4), India (15), Iran (2), Ireland (2), Israel (6), Italy (37), Japan (62), Lebanon (1), Lithuania (1), Malaysia (2), Mexico (1), Netherlands (6), New Zealand (1), Norway (2), Pakistan (2), Poland (2), Portugal (5), Romania (2), Singapore (2), South Africa (1), South Korea (13), Spain (17), Sweden (3), Thailand (5), Turkey (8), United Arab Emirates (1), United Kingdom (15), and United States (69).

Czech Republic

Marcela Kopacova, *Hradec Kralove*
Michal Procke, *Prague*
Miroslav Zavoral, *Prague*

Denmark

Peter Bytzer, *Koege*

Ecuador

Carlos Robles-Medranda, *Portoviejo*

Egypt

Nabil Ali Gad El-Hak, *Mansoura*

Finland

Paulina Salminen, *Turku*
Lars Mikael Victorzon, *Vaasa*

France

Romain Coriat, *Paris*
Bernard G Dallemagne, *Strasbourg*
Gerard Jean Gay, *Vandoeuvre les Nancy*
Lesur Gilles, *Boulogne*
René Lambert, *Lyon*
Sylvain Manfredi, *Rennes*
Barthet Marc, *Marseille Cedex*
JF Rey, *Saint Laurent Du Var Cedex*
José Sahel, *Marseille*
Nathalie Salles, *Pessac*

Germany

Marcel Binnebösel, *Aachen*
P Born, *Munich*
Stefan von Delius, *München*
Dirk Domagk, *Muenster*
Christoph Eisenbach, *Heidelberg*
Ines Gockel, *Mainz*
Arthur Hoffman, *Mainz*
Georg FBA Kähler, *Mannheim*
Günter Kampf, *Hamburg*
Ralf Kiesslich, *Mainz*
Andreas Kirschniak, *Tübingen*
Oliver Pech, *Wiesbaden*
Michael Pietsch, *Mainz*
Andreas Probst, *Augsburg*
Andrea Riphaus, *Bochum*
Raphael Rosch, *Aachen*
Claus Schäfer, *Munich*
Hubert J Scheidbach, *Magdeburg*
Peter Schemmer, *Heidelberg*
Hans Scherübl, *Berlin*
Thomas W Spahn, *Schwerte*
Holger Sudhoff, *Bielefeld*
Jens Tischendorf, *Aachen*
Michael Vieth, *Bayreuth*
Jochen Wedemeyer, *Hannover*
Uwe Will, *Gera*

Greece

Georgios K Anagnostopoulos, *Athens*
Anna Eleftheriadou, *Rethymnon*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanos, *Thessaloniki*
John A Karagiannis, *Athens*
Stefanos Karagiannis, *Kifissia*
Spiros D Ladas, *Athens*
Konstantinos A Papadakis, *Heraklion*
George H Sakorafas, *Athens*
Elias Xirouchakis, *Areos*

Hungary

Pal Demeter, *Budapest*
Lujber László, *Pecs*
Peter Lakatos, *Budapest*
István Rácz, *Gyor*

India

Ramanathan S Bharathi, *Uttar Pradesh*
Devendra C Desai, *Mumbai*
Evan L Fogel, *Indianapolis*
Uday Chand Ghoshal, *Lucknow*
Chittor M Habibullah, *Andhra Pradesh*
Rakesh Kochhar, *Chandigarh*
Rakesh Kumar, *New Delhi*
Sri Prakash Misra, *Allahabad*
Sandeep Nijhawan, *Rajasthan*
Kaushal Kishor Prasad, *Chandigarh*
Surinder Singh Rana, *Chandigarh*
Muthukumaran Rangarajan, *Tamil Nadu*
D Nageshwar Reddy, *Hyderabad*
Omar Javed Shah, *Kashmir*
Virendra Singh, *Chandigarh*

Iran

Tahereh Falsafi, *Tehran*
Mohammad Rahnavardi, *Tehran*

Ireland

Colm Ó'Moráin, *Dublin*
Eamonn M Quigley, *Cork*

Israel

Simon Bar-Meir, *Ramat Gan*
Rami Eliakim, *Haifa*
Zvi Fireman, *Hadea*
Irina Hirsh, *Haifa*
Tiberiu Hershcovici, *Jerusalem*
Jesse Lachter, *Haifa*

Italy

Paola De Angelis, *Rome*
Paolo G Arcidiacono, *Milan*
Alberto Arezzo, *Torino*
Gabrio Bassotti, *San Sisto*
Giampaolo Bresci, *Pisa*
Carlo Calabrese, *Bologna*
Salvatore MA Campo, *Rome*
Federico Carpi, *Pisa*
Livio Cipolletta, *Torre del Greco*
Sandro Contini, *Parma*
Salvatore Cucchiara, *Rome*
Gabriele Curcio, *Palermo*
Luigi Familiari, *Cavalluccio*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Napoli*
Giovanni B Gasbarrini, *Rome*
Carlo M Girelli, *Busto Arsizio*
Mauro Manno, *Baggiovara di Modena*
Hugo Martines, *Savona*
Gabriele Masselli, *Rome*
Emanuele Meroni, *Milan*
Andrea Moglia, *Pisa*
Raffaele Pezzilli, *Bologna*
Venerino Poletti , *Forlì*
Salvatore Pucciarelli, *Padova*
Franco Radaelli, *Como*
Marmo Riccardo, *Luigi Curto Polla*
Maria Elena Riccioni, *Rome*
Stefania Romano, *Naples*
Emanuele Rondonotti, *Milano*
Gianluca Rotondano, *Torre del Greco*
Vittorio Terruzzi, *Como*
Cristina Trovato, *Milano*
Antonio Tucci, *Bologna*
Maurizio Vecchi, *Milan*
Maurizio Ventrucci, *Bologna*

Japan

Mitsuhiro Asakuma, *Osaka*
Hiroki Endo, *Kanagawa*
Shotaro Enomoto, *Wakayama*
Kuang-I Fu, *Kashiwa*
Makoto Hashizume, *Fukuoka*
Toru Hiyama, *Higashihiroshima*
Akira Hokama, *Okinawa*
Akira Horiuchi, *Komagane*
Kinichi Hotta, *Nagano*
Atsushi Imagawa, *Kagawa*
Hiroo Imazu, *Tokyo*
Haruhiro Inoue, *Yokohama*
Ryu Ishihara, *Osaka*
Naoki Ishii, *Tokyo*
Hajime Isomoto, *Nagasaki*
Takao Itoi, *Tokyo*
Satoru Kakizaki, *Gunma*
Hiroshi Kakutani, *Tokyo*
Terumi Kamisawa, *Tokyo*
Yoshihide Kanno, *Sendai*
Mototsugu Kato, *Sapporo*
Takashi Kawai, *Tokyo*

Hirofumi Kawamoto, *Okayama*
Hiroto Kita, *Saitama*
Koga Komatsu, *Akita*
Hitoshi Kondo, *Sapporo*
Hiroaki Kubo, *Fukuoka*
Keiichiro Kume, *Kitakyusyu*
Iruru Maetani, *Tokyo*
Hiroto Miwa, *Hyogo*
Akihiro Mori, *Aichi*
Akihiro Mori, *Aichi*
Yoshihiro Moriwaki, *Yokohama*
Naoki Muguruma, *Tokushima*
Shinji Nishiwaki, *Gifu*
Ichiro Oda, *Tokyo*
Kazuichi Okazaki, *Osaka*
Yasuhiro Oono, *Chiba*
Taro Osada, *Tokyo*
Yutaka Saito, *Tokyo*
Yuzo Sakai, *Chiba*
Naoto Sakamoto, *Tokyo*
Nobuyuki Sakurazawa, *Tokyo*
Yasushi Sano, *Hyogo*
Tomoyuki Shibata, *Toyoake*
Takashi Shida, *Chiba*
Atsushi Sofuni, *Tokyo*
Kazuki Sumiyama, *Tokyo*
Nobumi Tagaya, *Tochigi*
Hirokazu Takahashi, *Yokohama*
Kyosuke Tanaka, *Mie*
Shinji Tanaka, *Hiroshima*
Gen Tohda, *Fukui*
Tomoyuki Tsujikawa, *Shiga*
Noriya Uedo, *Osaka*
Shuji Yamamoto, *Kyoto*
Takayuki Yamamoto, *Yokkaichi*
Hideo Yanai, *Yamaguchi*
Kenjiro Yasud, *Kyoto*
Naohisa Yoshida, *Kyoto*

Lebanon

Kassem A Barada, *Beirut*

Lithuania

Laimas Virginijus Jonaitis, *Kaunas*

Malaysia

Sanjiv Mahadeva, *Kuala Lumpur*
Sreenivasan Sasidharan, *Pulau Pinang*

Mexico

OT Teramoto-Matsubara, *México*

Netherlands

Marco Bruno, *Rotterdam*
Dirk Joan Gouma, *Amsterdam*
Iris Lansdorp-Vogelaar, *Rotterdam*
Chris JJ Mulder, *Amsterdam*
Vasileios Panteris, *Rotterdam*
Harald Erwin Vonkeman, *Enschede*

New Zealand

Michael PG Schultz, *Dunedin*

Norway

Magdy El-Salhy, *Stord*
Odd Helge Gilja, *Bergen*

Pakistan

Syed H Ali Shah, *Karachi*
Lubna Kamani, *Karachi*

Poland

Stanislaw A Hac, *Gdansk*
Maciej Michalik, *Pomorskie*

Portugal

Miguel T Coimbra, *Porto*
Marie I Cremers, *Setúbal*
Mário Dinis-Ribeiro, *Porto*
Pedro N Figueiredo, *Coimbra*
Rui MA da Silva, *Porto*

Romania

Mihai Ciocirlan, *Bucharest*
Lucian Negreanu, *Bucharest*

Singapore

Zhiwei Huang, *Singapore*
Surendra K Mantoo, *Singapore*

South Africa

Roland N Ndip, *Alice*

South Korea

Young-Tae Bak, *Seoul*
Dong Kyung Chang, *Seoul*
Youn-Seok Cho, *Uijeongbu*
Seong Woo Jeon, *Daegu*
Jong-Man Kang, *Seoul*
Yong Sung Kim, *Gyeonggi-do*
Hang Lak Lee, *Sungdonggu*
Suck-Ho Lee, *Cheonan*
Jong Ho Moon, *Bucheon*
Dong Kyun Park, *Incheon*
Dae Kyung Sohn, *Gyeonggi*
Jaekyu Sung, *Daejeon*
Si-Young Song, *Seoul*

Spain

Jose FN Aguilar, *Palma*
Adolfo P Blanco, *Asturias*
Andres Cardenas, *Barcelona*
Gloria Fernández-Esparrach, *Barcelona*
Jesús García-Cano, *Cuenca*
Angels Gines, *Barcelona*
Angel Lanas, *Zaragoza*
G Payeras Llodrá, *Madrid*
Alfredo José Lucendo, *Tomelloso*
Enrique F Perez-Cuadrado Martinez, *Murcia*
Luis Rabago, *Madrid*
Eduardo Redondo-Cerezo, *Cuenca*
Luis Rodrigo, *Oviedo*
Jaume Boix Valverde, *Badalona*
Josep Llach Vila, *Barcelona*
Santiago Vivas, *León*

Sweden

George Dafnis, *Eskilstuna*
Per-Ola Park, *Borås*
Carlos A Rubio, *Stockholm*

Thailand

Somchai Amornyotin, *Bangkok*
Thawatchai Akaraviputh, *Bangkok*
Udom Kachintorn, *Bangkok*
Varut Lohsiriwat, *Bangkok*
Rungsun Rerknimitr, *Bangkok*

Turkey

Selcuk Disibeyaz, *Nkara*
Mehmet Eken, *Istanbul*
Muammer Kara, *Ankara*
Taylan Kav, *Ankara*
Nevin Oruc, *İzmir*
Burhan Ozdil, *Adana*
Nurdan Ozmeric, *Emek Ankara*
Sema Zer Toros, *Istanbul*

United Arab Emirates

Margit Gabriele Muller, *Abu Dhabi*

United Kingdom

Basil J Ammori, *Manchester*
Simon HC Anderson, *London*
Adam D Farmer, *London*
Annette Fritscher-Ravens, *Landon*
Gianpiero Gravante, *Bristol*
Abdulzahra Hussain, *London*
United KV Kodogiannis, *London*
Seamus J Murphy, *Newry*
Perminder Phull, *Aberdeen*

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 4 Number 11 November 16, 2012

World Journal of Gastrointestinal Endoscopy
Volume 4 Number 11 November 16, 2012

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITING
Editorial Board of *World Journal of Gastrointestinal Endoscopy*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080038
Fax: +86-10-85381893
E-mail: wjge@wjgnet.com
http://www.wjgnet.com

EDITORIAL OFFICE
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-85381893

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
November 16, 2012

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

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

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i11.479

World J Gastrointest Endosc 2012 November 16; 4(11): 479-488
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

Ilaria Tarantino, Assistant Professor, *Series Editor*

Endoscopic ultrasound-guided drainage of pancreatic fluid collections

Carlo Fabbri, Carmelo Luigiano, Antonella Maimone, Anna Maria Polifemo, Ilaria Tarantino, Vincenzo Cennamo

Carlo Fabbri, Carmelo Luigiano, Anna Maria Polifemo, Antonella Maimone, Vincenzo Cennamo, Unit of Gastroenterology and Digestive Endoscopy, AUSL Bologna Bellaria-Maggiore Hospital, 40135 Bologna, Italy
Ilaria Tarantino, Endoscopy Unit, ISMETT/UPMC, 90100 Palermo, Italy
Author contributions: Each author was involved with all stages of the manuscript development.
Correspondence to: Carlo Fabbri, MD, Unit of Gastroenterology and Digestive Endoscopy, AUSL Bologna Bellaria-Maggiore Hospital, Largo Nigrisoli 2, 40135 Bologna, Italy. carlo.fabbri@ausl.bologna.it
Telephone: +39-51-6225162 Fax: +39-51-6225247
Received: October 14, 2011 Revised: October 5, 2012
Accepted: October 26, 2012
Published online: November 16, 2012

Abstract

Pancreatic fluid collections (PFCs) develop secondary to either fluid leakage or liquefaction of pancreatic necrosis following acute pancreatitis, chronic pancreatitis, surgery or abdominal trauma. Pancreatic fluid collections include acute fluid collections, acute and chronic pancreatic pseudocysts, pancreatic abscesses and pancreatic necrosis. Before the introduction of linear endoscopic ultrasound (EUS) in the 1990s and the subsequent development of endoscopic ultrasound-guided drainage (EUS-GD) procedures, the available options for drainage in symptomatic PFCs included surgical drainage, percutaneous drainage using radiological guidance and conventional endoscopic transmural drainage. In recent years, it has gradually been recognized that, due to its lower morbidity rate compared to the surgical and percutaneous approaches, endoscopic treatment may be the preferred first-line approach for managing symptomatic PFCs. Endoscopic ultrasound-guided drainage has the following advantages, when compared to other alternatives such as surgical, percutaneous and non-EUS-guided endoscopic drainage. EUS-GD is less invasive than surgery and therefore does not require general anesthesia. The morbidity rate is lower, recovery is faster and the costs are lower. EUS-GD can avoid local complications related to percutaneous drainage. Because the endoscope is placed adjacent to the fluid collection, it can have direct access to the fluid cavity, unlike percutaneous drainage which traverses the abdominal wall. Complications such as bleeding, inadvertent puncture of adjacent viscera, secondary infection and prolonged periods of drainage with resultant pancreatico-cutaneous fistulae may be avoided. The only difference between EUS and non-EUS drainage is the initial step, namely, gaining access to the pancreatic fluid collection. All the subsequent steps are similar, i.e., insertion of guide-wires with fluoroscopic guidance, balloon dilatation of the cystogastrostomy and insertion of transmural stents or nasocystic catheters. With the introduction of the EUS-scope equipped with a large operative channel which permits drainage of the PFCs in "one step", EUS-GD has been increasingly carried out in many tertiary care centers and has expanded the safety and efficacy of this modality, allowing access to and drainage of overly challenging fluid collections. However, the nature of the PFCs determines the outcome of this procedure. The technique and review of current literature regarding EUS-GD of PFCs will be discussed.

Key words: Endoscopic ultrasound-guided drainage; Pancreatic fluid collections; Pseudocysts; Pancreatic abscesses; Infected necrosis

Peer reviewers: Viktor Ernst Eysselein, MD, Professor of Medicine, Division of Gastroenterology, Harbor-UCLA Medical Center, 1000 W. Carson Street, Box 483, Torrance, CA 90509, United States; Fauze Maluf-Filho, MD, Hospital das Clínicas, São Paulo University School of Medicine, 488 Olegario Mariano, São Paulo 05508-010, Brazil

Fabbri C, Luigiano C, Maimone A, Polifemo AM, Tarantino I, Cennamo V. Endoscopic ultrasound-guided drainage of pancreatic fluid collections. *World J Gastrointest Endosc* 2012; 4(11): 479-488 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i11/479.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i11.479

INTRODUCTION

Pancreatic fluid collections (PFCs) develop secondary to either fluid leakage or liquefaction of pancreatic necrosis following acute pancreatitis, chronic pancreatitis, surgery or abdominal trauma[1,2]. PFCs include acute fluid collections, acute and chronic pancreatic pseudocysts, pancreatic abscesses and pancreatic necrosis (Table 1). Up to a few years ago, drainage was recommended if the PFCs were larger than 6 cm, continued to increase in size or did not resolve after 6 wk as well as in asymptomatic patients, in order to avoid subsequent development of complications such as hemorrhage, perforation or secondary infections. Presently, drainage is recommended only for symptomatic collections. Symptomatic PFCs, presenting with pain and mechanical obstruction of the gastric outlet or biliary system, require drainage. Drainage of pancreatic abscesses and infected necrosis is required for the effective control of sepsis[3,4].

In recent years, it has gradually been recognized that, due to its lower morbidity rate compared to the surgical and percutaneous approaches, endoscopic treatment may be the preferred first-line approach for managing symptomatic PFCs[1,2,4]. Endoscopic ultrasound-guided drainage (EUS-GD) has the following advantages, when compared to other alternatives such as surgical, percutaneous and non-EUS-guided endoscopic drainage[4,5].

EUS-GD is less invasive than surgery and therefore does not require general anesthesia. The morbidity rate is lower, recovery is faster and the costs are lower[4,5]. EUS-GD can avoid local complications related to percutaneous drainage. Because the endoscope is placed adjacent to the fluid collection, it can have direct access to the fluid cavity, unlike percutaneous drainage which traverses the abdominal wall. Complications such as bleeding, inadvertent puncture of adjacent viscera, secondary infection and prolonged periods of drainage with resultant pancreatico-cutaneous fistulae may be avoided. In addition, it is not possible to remove solid necrotic debris through percutaneous drainage, whereas endoscopic necrosectomy may be performed *via* a transmural approach[4].

The only difference between EUS and non-EUS drainage is the initial step, namely, gaining access to the pancreatic fluid collection. All the subsequent steps are similar, i.e., insertion of guide-wires with fluoroscopic guidance, balloon dilatation of the cystogastrostomy, insertion of transmural stents or nasocystic catheters and endoscopic necrosectomy.

The specific advantages of using EUS-GD include: (1) EUS can distinguish PFCs from masqueraders as cystic tumors, the gallbladder, lymphoceles, true cysts and pseudoaneurysm; (2) EUS can determine the content of the PFC, such as whether it is a simple abscess or if significant necrotic debris is present, which would then require a more aggressive endoscopic approach; (3) EUS can identify interposed blood vessels and potentially reduce the risk of bleeding; (4) EUS can determine the distance between the PFC cavity and gut wall, thus potentially decreasing the risk of perforation; and (5) EUS permits drainage of non-bulging PFCs.

PROCEDURE AND TECHNIQUE

Antibiotic prophylaxis is generally administered in order to reduce the risk of infections. An adequate surgical back-up is mandatory. Drainage can be performed with the patient under moderate sedoanalgesia, although it may be helpful to carry out the procedure under general anaesthesia. Fluoroscopy is necessary, even although it is technically feasible to drain a PFC with a single stent using only EUS guidance.

Drainage should be performed using a linear echoendoscope with a working channel of 3.7 mm or 3.8 mm which allows the insertion of a 10 Fr stent or metallic stent. Echoendoscopes with smaller working channels, such as 2.8 mm or 3.2 mm, permit only the insertion of 7 Fr and 8.5 Fr stents, respectively.

If only echoendoscopes with small working channels are available, the echoendoscope can be exchanged with a therapeutic endoscope over the guide-wire and the drainage can be performed using this endoscope following initial EUS-guided puncture and guide-wire placement into the cavity.

There are several methods for performing EUS-GD of a PFC. The choice of technique is largely based on personal preference and experience, but four general steps are required: (1) Ultrasonographic imagery to identify an appropriate puncture route which has no interposing vessels (Figure 1); (2) Needle puncture of the PFC and insertion of a guide-wire (Figure 2A, B); (3) Dilation of the punctured tract, creating a fistula between gut wall and the PFC (Figure 3); and (4) Insertion of the drainage tubes (Figure 4A, B).

Two different approaches are described, the "single guide-wire approach" and the "double guide-wire approach"[4]. By using the traditional single guide-wire approach, a linear echoendoscope is used to visualize the pancreatic fluid collection; the collection is then punctured with a needle after Doppler US evaluation. Several needles, such as the 19-gauge EUS-fine needle aspiration (FNA) needles, access 19-gauge needle and the cystotome are alternatively employed. A guide-wire is then inserted through the needle into the collection under fluoroscope guidance. Usually, the puncture site is dilated by a balloon catheter to 6 to 8 mm and a double-pigtail transmural stent is then inserted for drainage. When multiple stents or an additional nasocystic catheter is required, the PFC

Table 1 Classification of pancreatic fluid collections

Term	Definition
Acute fluid collection	A collection of enzyme-rich pancreatic juice occurring early (within 48 h) in the course of acute pancreatitis, located in or near the pancreas and always lacking a well-defined wall of granulation tissue or fibrous tissue
Acute pseudocyst	A collection of pancreatic juice enclosed by a wall of nonepithelialized granulation tissue, arising as a consequence of acute pancreatitis, requiring at least 4 wk to form and devoid of significant solid debris
Chronic pseudocyst	A collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, arising as a consequence of chronic pancreatitis
Early pancreatic necrosis	A diffuse or focal area of nonviable pancreatic parenchyma greater than 30% of the gland by CT-scan, typically associated with peripancreatic fat necrosis
Late organized pancreatic necrosis	Evolution of acute necrosis to a partially encapsulated, well-defined collection of pancreatic juice and necrotic debris
Pancreatic abscess	A circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, arising as a consequence of acute pancreatitis or pancreatic trauma

is recannulated by using a catheter and guide-wire, followed by insertion of the second transmural stent or nasocystic catheter.

To circumvent the problem of having to recannulate the PFC after gaining initial transmural access and catheter or transmural stent placement, the concept of a "double-wire" approach, in which 2 guide-wires are inserted through the same catheter before stent placement, has been advocated. Three methods have been described. The initial publication of the procedure used a prototype 3-layer puncture kit which allowed the simultaneous insertion of 2 guide-wires at the initial puncture. This puncture kit consisted of a 6 Fr inner teflon catheter (DuPont, Wilmington, Del) inserted through an outer 8.5 Fr teflon catheter and a 22-gauge FNA needle, which was inserted through the inner catheter. The 6 Fr inner catheter reduces step formation and facilitates the insertion of the assembled kit into the PFC cavity after needle puncture. By using the assembled kit with the needle protruding out at the distal end of the catheter, the PFC is punctured under EUS-guidance, using electrocautery. The assembled inner and outer catheters are then pushed into the cavity. Once entry into the PFC is confirmed by EUS and by aspiration of fluid, the needle and the 6 Fr inner catheter are withdrawn, which leaves behind the 8.5 Fr outer catheter. Two 0.035-inch guide-wires are simultaneously inserted into the PFC cavity. An 8.5 Fr double-pigtail stent and a 7 Fr nasocystic catheter or another stent can be sequentially placed. Other investigators reported inserting either the 10 Fr outer catheter of a cystotome or a 10 Fr Soehendra biliary dilator into the PFC cavity through the single guide-wire inserted at the initial EUS-guided puncture, followed by insertion of a second guide-wire through these catheters. Sequential transmural stent and drainage catheter placement can then be performed without loss of access to the PFC cavity and obviates the need for recannulation, which may be difficult because of a tangential axis of puncture or from poor visibility caused by the fluids flowing from the PFC.

In some cases, EUS-GD fails to reduce the size of the PFC due to the presence of persistent infection with necrotic material. In such cases, endoscopic necrosectomy using a gastroduodenoscope is indicated. A balloon dilator for esophageal strictures is used to dilate the fistula where the stents are inserted. After dilation of the cystogastrostomy or cystoduodenostoma with the balloon dilator, a gastroduodenoscope is directly inserted into the PFC. Mural trabeculation and necrotic substances are then identified in the PFC and necrotic tissue is irrigated by spraying water from a flushing pump and removing the tissue with a basket catheter[4].

OUTCOME AND RESULTS

One of the most important steps in the development of interventional EUS was taken by Grimm *et al*[6] in 1992. They created a fistula between the stomach and a cyst with the aid of a linear echoendoscope. Owing to the small working channel of only 2 mm, the EUS-scope had to be exchanged for a regular side-viewing endoscope after a puncture and guide-wire placement in the PFC under EUS guidance. With the introduction of the therapeutic linear EUS-scope with working channels of 3.7 or 3.8 mm, it is now possible to achieve adequate drainage by placing multiple large-bore stents and a nasocystic catheter without changing the endoscope. As a result of these developments, EUS-GD has currently been tested in 1134 published cases and, in experienced hands, is now considered a safe and effective technique for the treatment of PFCs, with a very low complication rate (Table 2)[6-78].

There are a large number of case reports and case series including PFCs with different characteristics and different methods of drainage and using diverse EUS-scopes and endoscopes.

Recently, a web-based survey was sent to United States and international members of the American Society for Gastrointestinal Endoscopy[79]. Of the 3054 endoscopists to whom the survey was sent, 266 (8.7%) replied: 198 performed pseudocyst drainage [103 (52%)] and the transgastric route was the most commonly used drainage route (65%). The number of stents placed ranged from 1 to 5 and these remained in place for 2 to 30 wk. A CT-scan was used before drainage by 95% of all respondents. EUS imaging was used before drainage by 72 of 103 United States endoscopists (70%) compared with 56 of 95 international endoscopists (59%). EUS-guided drainage was used by 56% of United States endoscopists compared with 43% of international endoscopists. The most common site of transmural entry for drainage of collections appears to be the transgastric route. Although CT-scan is the most commonly used pre-drainage imaging modality, EUS is used before and during transmural drainage of pseudocysts.

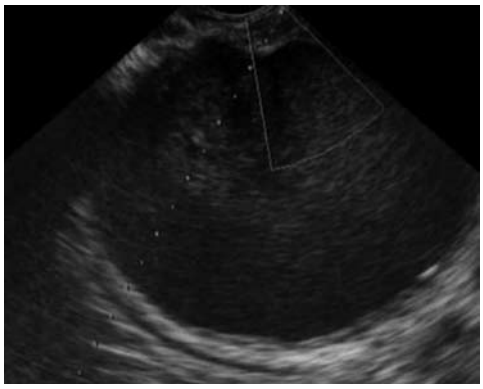


Figure 1 Ultrasonographic image of the pancreatic fluid collection to identify an appropriate puncture route which has no interposing vessels.

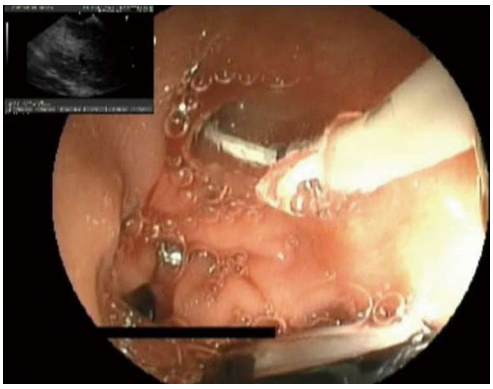


Figure 3 Dilation of the punctured tract, creating a fistula between gut wall and the pancreatic fluid collection.

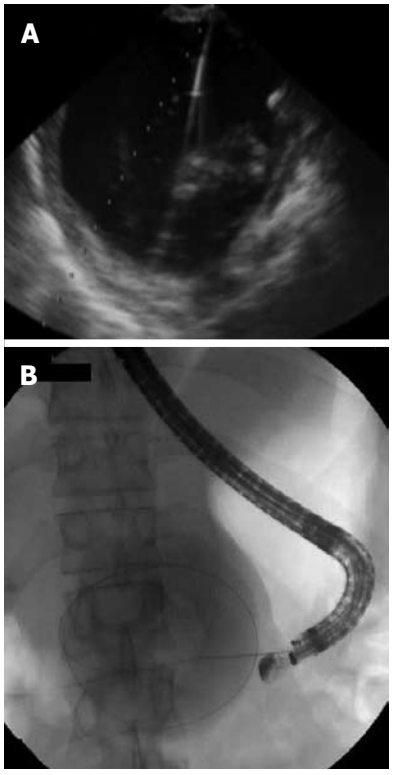


Figure 2 Needle puncture of the pancreatic fluid collection and insertion of a guide-wire. A: Ultrasonographic image of needle puncture of the pancreatic fluid collection; B: Radiological image of insertion of a guide-wire in the pancreatic fluid collection.

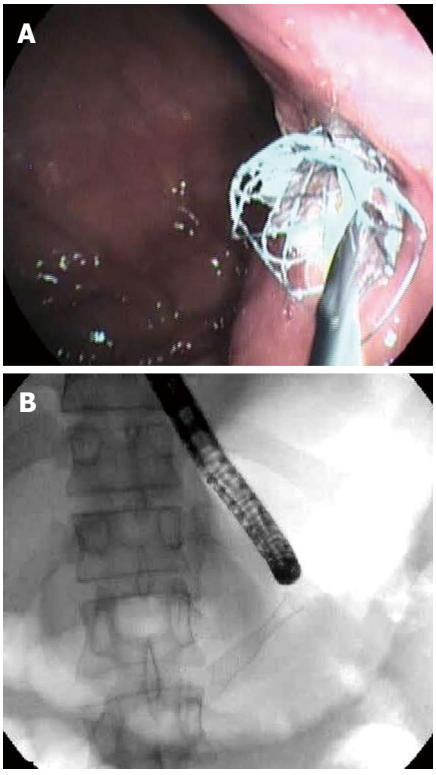


Figure 4 Insertion of the drainage tubes. A: Endoscopic image of insertion of a fully covered self-expanding metal stent; B: Radiological image of insertion of a fully covered self-expanding metal stent.

However, several nonrandomized case series have suggested that EUS-GD is safer than traditional "blind" techniques[36,80].

Kahaleh *et al*[36] published the first nonrandomized study which compared endoscopic conventional transmural drainage (CTD) with EUS-GD. In that study, PFCs with bulging and no obvious portal hypertension underwent conventional transmural drainage, while all remaining patients underwent EUS-GD. There were no significant differences between the groups in terms of efficacy or safety. Indirectly, this study supported the concept that EUS-GD is superior, because it can be used to drain PFCs not amenable to CTD, without any increased risks.

Varadarajulu *et al*[80], in a nonrandomised study, evaluated the CTD with EUS-GD of PFCs in 53 patients. CTD was successful in only 30 patients (57%). To achieve successful drainage, luminal compression was required and at least five puncture attempts were made, potentially increasing the complication risk. On the other hand, EUS allowed a diagnosis of mucinous tumor to be made in two patients and was successful in all cases. Bleeding occurred in one patient who underwent CTD, whereas no complications occurred among those who underwent EUS-GD.

To date only two randomized trials have been pub-

Table 2 Results of endoscopic ultrasound-guided drainage of pancreatic fluid collections

Ref.	Year	Number of PFCs	Technical success (%)	Clinical success (%)	Complications (%)	Recurrence (%)
Grimm *et al*[6]	1992	1	100	100	0	0
Binmoeller *et al*[7]	1995	27	93	78	52	22
Wiersema[8]	1996	1	100	100	0	0
Chan *et al*[9]	1996	1	100	100	0	0
Gerolami *et al*[10]	1997	3	100	100	0	0
Ardengh *et al*[11]	1998	2	100	100	0	0
Giovannini *et al*[12]	1998	6	100	83	0	16
Pfaffenbach *et al*[13]	1998	11	91	82	0	18
Vilmann *et al*[14]	1998	1	100	100	0	0
Seifert *et al*[15]	2000	3	100	100	0	0
Seifert *et al*[16]	2000	6	100	83	0	0
Fuchs *et al*[17]	2000	3	100	100	0	0
Baron *et al*[18]	2000	1	100	100	0	0
Wiersema *et al*[19]	2001	1	100	100	0	0
Inui *et al*[20]	2001	3	100	100	0	33
Giovannini *et al*[21]	2001	35	100	89	3	9
Norton *et al*[22]	2001	14	93	93	14	23
Seifert *et al*[23]	2001	4	100	75	0	0
Vosoghi *et al*[24]	2002	14	100	93	7	7
Enya *et al*[25]	2003	13	100	85	0	0
Kakutani *et al*[26]	2004	1	100	100	0	0
Seewald *et al*[27]	2005	13	100	85	30	15
Sriram *et al*[28]	2005	8	100	100	12	0
Benyoumes *et al*[29]	2006	1	100	100	0	0
Raczynski *et al*[30]	2006	2	100	100	0	0
Charnley *et al*[31]	2006	13	100	92	0	0
Hookey *et al*[32]	2006	32	96	93	11	12
Krüger *et al*[33]	2006	35	94	88	33	12
Azar *et al*[34]	2006	23	91	82	4	18
Antillon *et al*[35]	2006	33	94	87	15	4
Kahaleh *et al*[36]	2006	46	100	93	19	NA
Itoi *et al*[37]	2006	3	100	100	0	0
Rout *et al*[38]	2006	1	100	100	0	0
Seewald *et al*[39]	2006	8	100	100	0	0
Ahlawat *et al*[40]	2006	11	100	82	18	18
Arvanitakis *et al*[41]	2007	46	100	94	22	11
Lopes *et al*[42]	2007	51	94	84	25	17
Jansen *et al*[43]	2007	8	100	100	0	0
Voermans *et al*[44]	2007	7	100	100	14	0
Voermans *et al*[45]	2007	25	100	93	40	7
Kang *et al*[46]	2008	1	100	100	0	0
Escourrou *et al*[47]	2008	13	100	100	46	0
Ardengh *et al*[48]	2008	77	94	91	6	11
Hocke *et al*[49]	2008	30	97	83	23	3
Varadarajulu *et al*[50]	2008	24	100	96	4	NA
Varadarajulu *et al*[51]	2008	60	95	93	2	4
Barthet *et al*[52]	2008	28	100	89	25	NA
Jah *et al*[53]	2008	1	100	100	0	0
Reddy *et al*[54]	2008	6	100	100	16	0
Talreja *et al*[55]	2008	18	100	95	44	0
Schrover *et al*[56]	2008	8	100	75	13	0
Mathew *et al*[57]	2008	6	100	100	16	0
Tarantino *et al*[58]	2009	1	100	100	0	0
Park *et al*[59]	2009	39	95	100	7	6
Yasuda *et al*[60]	2009	26	92	95	0	17
Itoi *et al*[61]	2009	13	100	100	0	0
Trevino *et al*[62]	2009	3	100	100	0	0
Varadarajulu *et al*[63]	2009	10	100	90	0	0
Piraka *et al*[64]	2009	2	100	100	50	0
Ang *et al*[65]	2009	10	100	100	10	0
Okabe *et al*[66]	2009	2	100	100	0	0
Antillon *et al*[67]	2009	1	100	100	0	0
Chase *et al*[68]	2009	1	100	100	0	0
Becker *et al*[69]	2009	7	100	100	57	14
Ahn *et al*[70]	2010	47	98	100	11	11
Khashab *et al*[71]	2010	6	100	NA	0	NA
Tarantino *et al*[72]	2010	1	100	100	0	0

Koo *et al*[73]	2010	1	100	100	0	0
Pallapothu *et al*[74]	2011	6	100	77	16	16
Jazrawi *et al*[75]	2011	10	100	100	0	10
Larghi *et al*[76]	2011	1	100	100	0	0
Sadik *et al*[77]	2011	26	100	88	15	4
Will *et al*[78]	2011	132	97	96	29	15

NA: Not available; PFCs: Pancreatic fluid collections.

lished comparing the CTD with EUS-GD of PFCs[50,59]. Varadarajulu *et al*[50] in 2008 published the first prospective randomized trial to compare the rate of technical success between EUS-GD and CTD of PFCs. Thirty patients were randomised to undergo PFC drainage by EUS (15) or CTD (15) over a 6 mo period. Of the 15 patients randomized to EUS, drainage was not undertaken in one because an alternative diagnosis of biliary cystadenoma was made and this patient was excluded. All 14 patients randomised to an EUS underwent successful drainage (100%), while the procedure was technically successful in only 5 of 15 patients (33%) randomized to CTD. All 10 patients who failed drainage by CTD underwent successful drainage of the PFC on a crossover to EUS. Major procedure-related bleeding was encountered in 2 patients in whom CTD was performed.

Park *et al*[59] conducted a prospective randomised trial to compare the technical success and clinical outcomes of EUS-GD and CTD for treating pancreatic pseudocysts. A total of 60 consecutive patients with pancreatic pseudocysts were randomly divided into two groups to undergo either EUS-GD (31) or CTD (29). The rate of technical success of the drainage was significantly higher for the EUS group (94 %) than for the CTD group (72 %) (P = 0.039) in intention-to-treat analysis. In cases where CTD failed (8 patients) because the pseudocysts were nonbulging, a crossover was made to EUS-GD, which was successfully performed in all these patients. Complications occurred in 7 % of the EUS group and in 10% of the CTD group (P = 0.67). During follow-up, pseudocyst resolution was achieved in 97% in the EUS group and in 91 % in the CTD group (P = 0.565).

Varadarajulu *et al*[81] also published the only experience which compares the clinical outcomes of EUS-GD with surgical cyst-gastrostomy for the management of patients with uncomplicated PFCs and a cost analysis of each treatment modality was also performed. Ten patients who underwent surgical cyst-gastrostomy were matched with 20 patients who underwent an EUS-GD. There were no significant differences in rates of treatment success (100% *vs* 95%), procedural complications (none in either cohort) or reinterventions (10% *vs* 0%) between surgery and EUS-GD. The mean length of a post-procedure hospital stay for the EUS group was shorter than for the surgical group (2.5 d *vs* 6.5 d) and the average direct cost per case for EUS-GD was significantly lower when compared with surgical cyst-gastrostomy.

These studies showed that when EUS-GD is performed, the rate of iatrogenic hemorrhage and perforation is lower and the success rate is markedly higher.

Portal hypertension with gastric varices was traditionally a contraindication for endoscopic drainage because of the possibility of iatrogenic hemorrhage. However, in the series by Antillon *et al*[35], 24% of patients treated had perigastric varices and other groups have also reported a similar ability to perform transenteric drainage in the setting of portal hypertension and intervening perigastric vessels using endoscopic ultrasound-guided drainage[28].

The technical and clinical success mean rates reported for EUS-GD of PFCs in series with more than 10 patients were 97% and 91% respectively and the mean overall recurrence rate was 9%[6-78].

Pancreatic fluid collections that arise in the setting of acute pancreatitis tend to respond better to endoscopic drainage than those arising in patients with chronic pancreatitis; however, in one study, higher success rates were actually seen in those patients with chronic pancreatitis (92% *vs* 74%), with the difference potentially related to timing of drainage in the acute pancreatitis group[82-84].

For PFCs which contain a clear fluid, such as pseudocysts, the treatment success rates are very high, exceeding 95% and even reaching 100%, while for PFCs in which at EUS the contents can appear to be completely anechoic, with nonfluid/hyperechoic material and a homogenous layer (probably debris) or as focal lesions consistent with necrotic tissue, such as pancreatic abscesses or walled-off pancreatic necrosis, the results for clinical resolution are generally poorer than pseudocyst.

Hookey *et al*[32] compared etiologies, drainage techniques and outcomes in 116 patients (32 EUS-GD) who underwent endoscopic drainage of PFCs. Of the 116 patients, 8 patients had pancreatic necrosis and 9 had pancreatic abscesses. In this study, drainage of organized necrosis was associated with a significantly higher failure rate than other collections. Drainage of necrosis resulted in clinical success in only 25% of cases and technical success in 50%. Six of eight patients had a nasocystic catheter placed and one patient experienced recurrence. There were two procedure-related complications in this subgroup. Nine patients underwent endoscopic drainage for pancreatic abscesses. Seven of nine patients had a nasocystic catheter placed. All procedures were technically successful and eight of nine (88.9%) patients had clinical success. One abscess recurred and there were no procedure related complications.

Seifert *et al*[15] were the first group to describe the combination of EUS-GD transmural puncture in necrotizing pancreatitis or abscess followed by tract dilation and repeated, direct endoscopic debridements of the lesser sac. In this series, fenestration of the gastric wall

and debridement of infected necrosis by direct retroperitoneal endoscopy was performed on three patients. This strategy led to rapid clinical improvement and no serious complications.

In 2001, Giovannini *et al*[21] reported their experience with EUS-guided drainage of pancreatic pseudocysts and pancreatic abscesses in 35 patients. Twenty of these patients had pancreatic abscesses, located either in the tail of the pancreas (17 patients) or adjacent to the gastric wall (3 patients). Placement of a 7 Fr nasocystic drain was successful in 18 of 20 patients. The remaining two patients required surgery. Over a mean follow-up period of 27 mo, two relapses occurred.

In 2005, Seewald *et al*[27] performed a retrospective study of the outcome of patients with pancreatic necrosis and abscesses, all unfit to undergo surgery. The treatment included synchronous EUS-GD procedures followed by balloon dilation of the cystogastrostomy or cystoduodenostoma, daily endoscopic necrosectomy and saline solution washing, and sealing of pancreatic fistulae by *N*-butyl-2-cyanoacrylate. This study was performed over a 7 year period with 13 consecutive patients, 5 with infected pancreatic necrosis and 8 with pancreatic abscesses. Endoscopic therapy was successful in resolving the infected necrosis or abscess in 12 of 13 patients over a median follow-up period of 9.5 mo. One patient required additional surgery to evacuate necrosis that extended into the paracolic gutter. Two patients with a disconnected duct gland syndrome developed recurrent fluid collections after 2 and 4 mo. These patients ultimately required pancreatic head resections. Two patients had their persistent ductal leaks glued. Complications included three episodes of locally controlled bleeding. The median number of daily necrosectomy and lavage was 7 (range 2-23) and 12 (range 2-41), respectively.

In 2007, Lopes *et al*[42] performed a retrospective analysis of 51 patients who underwent EUS-GD of PFCs. Twenty-six of these patients had pancreatic abscesses. What is notable in this study regarding pancreatic abscesses is that the endoscopic approach was not more hazardous for abscesses in regard to the complications rate when compared to other pancreatic fluid collections. Placement of a nasocystic drain did not reduce the complication rate but the placement of two stents narrowed the rate of complications.

Recently, Sadik *et al*[77] compared the outcome for EUS-GD of clear fluid pancreatic pseudocysts (15 patients) with the outcome for abscess drainage (10 patients). The EUS-GD drainage was successful in 94% of the pseudocysts and in 80% of the abscesses ($P = 0.04$). The complication rate in pseudocysts was 6% and in abscesses was 30% ($P = 0.02$).

Will *et al*[78] have published the largest series reported in the literature with 81 abscess and 34 infected necrosis drained transluminally with EUS, with an overall clinical success rate of 97% and 94% and a recurrence rate of 16% and 18%, respectively.

However, EUS-GD for PFCs presents some challenges and disadvantages. One of the challenges encountered during EUS-GD, especially in infected PFCs, is the process of sequential transgastric stenting and nasocystic catheter placement, which may be difficult because of the collapse of the cystic cavity, the presence of a notable quantity of fluid or pus being emitted by the cavity which obscures the endoscopic view and the tangential axis of the punctured tract[39].

Other challenges encountered, especially when the content of the collection is non-fluid, are: (1) the small diameter of the 10 Fr plastic stents used which limits the efficacy in draining; (2) the need, in some cases, to place more stents for drainage, which has been associated with the need for multiple revisions in 17.7% to 27% of cases due to obstruction; and (3) when the placement of a naso-cystic catheter is required, patient discomfort and dislodgement of the catheter are often reported[3,4].

For the above reasons, the type of stent used for endoscopic drainage is currently a major area of interest. In a small number of cases, covered self-expandable metal stents (CSEMSs), with different diameters and different endoscopic techniques of placement, have recently been adopted for drainage[55,58,67,72].

Talreja *et al*[55] evaluated the efficacy and safety of transenteric drainage of PFCs by using CSEMSs. In that study, 18 patients underwent drainage of PFCs and a median of 1 session was required to achieve drainage. The technical and clinical success rates were 100% and 95%, respectively; with 14 patients (78%) achieving complete resolution of their PFC. The mean follow-up period until final resolution was 77 d and complications included superinfection (5), bleeding (2) and inner migration (1).

Antillon *et al*[67] report a case in which they used a large diameter removable metallic esophageal stent to facilitate drainage of infected pancreatic necrosis after multiple failed conventional necrosectomies.

A CSEMS can be an alternative to conventional drainage with plastic stents because it offers the option of a larger diameter access fistula for drainage and may increase the final success rate while it reduces the time to PFC resolution. A larger prospective randomised study should be carried out to compare this technique with conventional drainage with plastic stents in order to validate these findings.

COMPLICATIONS

The main potential complications of concern are superinfection, bleeding and perforation.

The complication rate reported ranges between 0% and 52% (Table 2), with a mean overall complication rate of 15% in series with more than 10 patients[6-78].

To minimise risk, only collections with a mature wall and within 1 cm of the gastrointestinal lumen should undergo endoscopic drainage. Any coagulopathy, if present, should be corrected. Patients with pseudocysts undergoing drainage should also receive prophylactic antibiotics in order to prevent secondary infection of a

sterile collection.

The risk of complication is low thus far in the context of EUS-GD of PFCs without endoscopic necrosectomy and debridement. Perforation rates ranging between 3%-5% were reported in the context of endoscopic necrosectomy[45,49,78]. The risk can be reduced by adhering to key principles, such as draining only a collection with a mature wall, performing stepwise balloon dilatation of the cystogastrostomy, avoiding over-insufflations of the cavity with air and performing gentle debridement using saline lavage and aspiration, baskets, soft snares and retrieval nets when required.

In conclusion, the availability of curved linear array echoendoscopes has resulted in EUS-GD of PFCs as a credible alternative to drainage via the surgical or percutaneous route. The development of new instruments and devices is the basis for alternative less invasive approaches to various pathologies. Further progress in instrumentation is required to make this technique safer and more effective. In the meantime, the endoscopic approach should be dictated by local expertise and individual patient presentation.

In addition, it must be recognized that not all endosonographers have the technical expertise to perform such complex procedures. Apart from the ability to perform linear EUS, a background in endoscopic retrograde cholangiopancreatography is important and additional exposure and specific training are required. EUS-GD is mandatory for non-bulging PFCs and in high-risk patients, such as those with portal hypertension.

REFERENCES

1 **Jacobson BC**, Baron TH, Adler DG, Davila RE, Egan J, Hirota WK, Leighton JA, Qureshi W, Rajan E, Zuckerman MJ, Fanelli R, Wheeler-Harbaugh J, Faigel DO. ASGE guideline: The role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. *Gastrointest Endosc* 2005; **61**: 363-370

2 **Habashi S**, Draganov PV. Pancreatic pseudocyst. *World J Gastroenterol* 2009; **15**: 38-47

3 **Chak A**. Endosonographic-guided therapy of pancreatic pseudocysts. *Gastrointest Endosc* 2000; **52**: S23-S27

4 **Seewald S**, Ang TL, Kida M, Teng KY, Soehendra N. EUS 2008 Working Group document: evaluation of EUS-guided drainage of pancreatic-fluid collections (with video). *Gastrointest Endosc* 2009; **69**: S13-S21

5 **Seewald S**, Ang TL, Teng KY, Groth S, Zhong Y, Richter H, Imazu H, Omar S, Polese L, Seitz U, Bertschinger P, Altorfer J, Soehendra N. Endoscopic ultrasound-guided drainage of abdominal abscesses and infected necrosis. *Endoscopy* 2009; **41**: 166-174

6 **Grimm H**, Binmoeller KF, Soehendra N. Endosonography-guided drainage of a pancreatic pseudocyst. *Gastrointest Endosc* 1992; **38**: 170-171

7 **Binmoeller KF**, Soehendra N. Endoscopic ultrasonography in the diagnosis and treatment of pancreatic pseudocysts. *Gastrointest Endosc Clin N Am* 1995; **5**: 805-816

8 **Wiersema MJ**. Endosonography-guided cystoduodenostomy with a therapeutic ultrasound endoscope. *Gastrointest Endosc* 1996; **44**: 614-617

9 **Chan AT**, Heller SJ, Van Dam J, Carr-Locke DL, Banks PA. Endoscopic cystgastrostomy: role of endoscopic ultrasonography. *Am J Gastroenterol* 1996; **91**: 1622-1625

10 **Gerolami R**, Giovannini M, Laugier R. Endoscopic drainage of pancreatic pseudocysts guided by endosonography. *Endoscopy* 1997; **29**: 106-108

11 **Ardengh JC**, Della Libera E, Ferrari AP. Endosonography-guided drainage of pancreatic pseudocyst without gastric or duodenal compression. *Endoscopy* 1998; **30**: S71-S72

12 **Giovannini M**, Bernardini D, Seitz JF. Cystogastrotomy entirely performed under endosonography guidance for pancreatic pseudocyst: results in six patients. *Gastrointest Endosc* 1998; **48**: 200-203

13 **Pfaffenbach B**, Langer M, Stabenow-Lohbauer U, Lux G. [Endosonography controlled transgastric drainage of pancreatic pseudocysts]. *Dtsch Med Wochenschr* 1998; **123**: 1439-1442

14 **Vilmann P**, Hancke S, Pless T, Schell-Hincke JD, Henriksen FW. One-step endosonography-guided drainage of a pancreatic pseudocyst: a new technique of stent delivery through the echo endoscope. *Endoscopy* 1998; **30**: 730-733

15 **Seifert H**, Wehrmann T, Schmitt T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. *Lancet* 2000; **356**: 653-655

16 **Seifert H**, Dietrich C, Schmitt T, Caspary W, Wehrmann T. Endoscopic ultrasound-guided one-step transmural drainage of cystic abdominal lesions with a large-channel echo endoscope. *Endoscopy* 2000; **32**: 255-259

17 **Fuchs M**, Reimann FM, Gaebel C, Ludwig D, Stange EF. Treatment of infected pancreatic pseudocysts by endoscopic ultrasonography-guided cystogastrostomy. *Endoscopy* 2000; **32**: 654-657

18 **Baron TH**, Wiersema MJ. EUS-guided transesophageal pancreatic pseudocyst drainage. *Gastrointest Endosc* 2000; **52**: 545-549

19 **Wiersema MJ**, Baron TH, Chari ST. Endosonography-guided pseudocyst drainage with a new large-channel linear scanning echoendoscope. *Gastrointest Endosc* 2001; **53**: 811-813

20 **Inui K**, Yoshino J, Okushima K, Miyoshi H, Nakamura Y, Watanabe S, Takashima T, Nakazawa S, Hattori T. EUS-guided one-step drainage of pancreatic pseudocysts: experience in 3 patients. *Gastrointest Endosc* 2001; **54**: 87-89

21 **Giovannini M**, Pesenti C, Rolland AL, Moutardier V, Delpero JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. *Endoscopy* 2001; **33**: 473-477

22 **Norton ID**, Clain JE, Wiersema MJ, DiMagno EP, Petersen BT, Gostout CJ. Utility of endoscopic ultrasonography in endoscopic drainage of pancreatic pseudocysts in selected patients. *Mayo Clin Proc* 2001; **76**: 794-798

23 **Seifert H**, Faust D, Schmitt T, Dietrich C, Caspary W, Wehrmann T. Transmural drainage of cystic peripancreatic lesions with a new large-channel echo endoscope. *Endoscopy* 2001; **33**: 1022-1026

24 **Vosoghi M**, Sial S, Garrett B, Feng J, Lee T, Stabile BE, Eysselein VE. EUS-guided pancreatic pseudocyst drainage: review and experience at Harbor-UCLA Medical Center. *MedGenMed* 2002; **4**: 2

25 **Enya M**, Yasuda I, Tomita E, Shirakami Y, Otsuji K, Shinoda T, Moriwaki H. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts using a large-channel echoendoscope and a conventional polypectomy snare. *Dig Endosc* 2003; **15**: 323-328

26 **Kakutani H**, Hino S, Ikeda K, Uchiyama Y, Sumiyama K, Kuramochi A, Kawamura M, Tajiri H. A case of pancreatic pseudocyst successfully treated with endoscopic cystgastrostomy using a new therapeutic echoendoscope. *Dig Endosc* 2004; **16**: 337–339

27 **Seewald S**, Groth S, Omar S, Imazu H, Seitz U, de Weerth A, Soetikno R, Zhong Y, Sriram PV, Ponnudurai R, Sikka S, Thonke F, Soehendra N. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm (videos). *Gastrointest Endosc*

2005; **62**: 92-100
28 **Sriram PV**, Kaffes AJ, Rao GV, Reddy DN. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts complicated by portal hypertension or by intervening vessels. *Endoscopy* 2005; **37**: 231-235
29 **Benyoumes M**, Deprez PH. A single therapeutic echo endoscope used for combined transgastric and transpapillary drainage of a pancreatic abscess. *Endoscopy* 2006; **38**: 98
30 **Raczynski S**, Teich N, Borte G, Wittenburg H, Mössner J, Caca K. Percutaneous transgastric irrigation drainage in combination with endoscopic necrosectomy in necrotizing pancreatitis (with videos). *Gastrointest Endosc* 2006; **64**: 420-424
31 **Charnley RM**, Lochan R, Gray H, O'Sullivan CB, Scott J, Oppong KE. Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. *Endoscopy* 2006; **38**: 925-928
32 **Hookey LC**, Debroux S, Delhaye M, Arvanitakis M, Le Moine O, Devière J. Endoscopic drainage of pancreatic-fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes. *Gastrointest Endosc* 2006; **63**: 635-643
33 **Krüger M**, Schneider AS, Manns MP, Meier PN. Endoscopic management of pancreatic pseudocysts or abscesses after an EUS-guided 1-step procedure for initial access. *Gastrointest Endosc* 2006; **63**: 409-416
34 **Azar RR**, Oh YS, Janec EM, Early DS, Jonnalagadda SS, Edmundowicz SA. Wire-guided pancreatic pseudocyst drainage by using a modified needle knife and therapeutic echoendoscope. *Gastrointest Endosc* 2006; **63**: 688-692
35 **Antillon MR**, Shah RJ, Stiegmann G, Chen YK. Single-step EUS-guided transmural drainage of simple and complicated pancreatic pseudocysts. *Gastrointest Endosc* 2006; **63**: 797-803
36 **Kahaleh M**, Shami VM, Conaway MR, Tokar J, Rockoff T, De La Rue SA, de Lange E, Bassignani M, Gay S, Adams RB, Yeaton P. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. *Endoscopy* 2006; **38**: 355-359
37 **Itoi T**, Tsuchiya T, Sofuni A, Itokawa F, Kurihara T, Moriyasu F, Kawai T. Endoscopic ultrasonography-guided simultaneous internal and external drainage of infected pancreatic pseudocysts. *Dig Endosc* 2006; **18**: 71-74
38 **Rout S**, Rahman SH, Sheridan MB, Guillou PJ, Menon KV. Endoscopic ultrasound guided transgastric stenting of traumatic pancreatic pseudocyst. *JOP* 2006; **7**: 423-426
39 **Seewald S**, Thonke F, Ang TL, Omar S, Seitz U, Groth S, Zhong Y, Yekebas E, Izbicki J, Soehendra N. One-step, simultaneous double-wire technique facilitates pancreatic pseudocyst and abscess drainage (with videos). *Gastrointest Endosc* 2006; **64**: 805-808
40 **Ahlawat SK**, Charabaty-Pishvaian A, Jackson PG, Haddad NG. Single-step EUS-guided pancreatic pseudocyst drainage using a large channel linear array echoendoscope and cystotome: results in 11 patients. *JOP* 2006; **7**: 616-624
41 **Arvanitakis M**, Delhaye M, Bali MA, Matos C, De Maertelaer V, Le Moine O, Devière J. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. *Gastrointest Endosc* 2007; **65**: 609-619
42 **Lopes CV**, Pesenti C, Bories E, Caillol F, Giovannini M. Endoscopic-ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts and abscesses. *Scand J Gastroenterol* 2007; **42**: 524-529
43 **Jansen JM**, Hanrath A, Rauws EA, Bruno MJ, Fockens P. Intracystic wire exchange facilitating insertion of multiple stents during endoscopic drainage of pancreatic pseudocysts. *Gastrointest Endosc* 2007; **66**: 157-161
44 **Voermans RP**, Eisendrath P, Bruno MJ, Le Moine O, Devière J, Fockens P. Initial evaluation of a novel prototype forward-viewing US endoscope in transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2007; **66**: 1013-1017
45 **Voermans RP**, Veldkamp MC, Rauws EA, Bruno MJ, Fockens P. Endoscopic transmural debridement of symptomatic organized pancreatic necrosis (with videos). *Gastrointest Endosc* 2007; **66**: 909-916
46 **Kang SG**, Park do H, Kwon TH, Park JY, Park SH, Park JH, Lee SH, Chung IK, Kim HS, Kim SJ. Transduodenal endoscopic necrosectomy via pancreaticoduodenal fistula for infected peripancreatic necrosis with left pararenal space extension (with videos). *Gastrointest Endosc* 2008; **67**: 380-383
47 **Escourrou J**, Shehab H, Buscail L, Bournet B, Andrau P, Moreau J, Fourtanier G. Peroral transgastric/transduodenal necrosectomy: success in the treatment of infected pancreatic necrosis. *Ann Surg* 2008; **248**: 1074-1080
48 **Ardengh JC**, Coelho DE, Coelho JF, de Lima LF, dos Santos JS, Módena JL. Single-step EUS-guided endoscopic treatment for sterile pancreatic collections: a single-center experience. *Dig Dis* 2008; **26**: 370-376
49 **Hocke M**, Will U, Gottschalk P, Settmacher U, Stallmach A. Transgastral retroperitoneal endoscopy in septic patients with pancreatic necrosis or infected pancreatic pseudocysts. *Z Gastroenterol* 2008; **46**: 1363-1368
50 **Varadarajulu S**, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111
51 **Varadarajulu S**, Tamhane A, Blakely J. Graded dilation technique for EUS-guided drainage of peripancreatic fluid collections: an assessment of outcomes and complications and technical proficiency (with video). *Gastrointest Endosc* 2008; **68**: 656-666
52 **Barthet M**, Lamblin G, Gasmi M, Vitton V, Desjeux A, Grimaud JC. Clinical usefulness of a treatment algorithm for pancreatic pseudocysts. *Gastrointest Endosc* 2008; **67**: 245-252
53 **Jah A**, Jamieson N, Huguet E, Griffiths W, Carroll N, Praseedom R. Endoscopic ultrasound-guided drainage of an abdominal fluid collection following Whipple's resection. *World J Gastroenterol* 2008; **14**: 6867-6868
54 **Reddy DN**, Gupta R, Lakhtakia S, Jalal PK, Rao GV. Use of a novel transluminal balloon accessotome in transmural drainage of pancreatic pseudocyst (with video). *Gastrointest Endosc* 2008; **68**: 362-365
55 **Talreja JP**, Shami VM, Ku J, Morris TD, Ellen K, Kahaleh M. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents (with video). *Gastrointest Endosc* 2008; **68**: 1199-1203
56 **Schrover IM**, Weusten BL, Besselink MG, Bollen TL, van Ramshorst B, Timmer R. EUS-guided endoscopic transgastric necrosectomy in patients with infected necrosis in acute pancreatitis. *Pancreatology* 2008; **8**: 271-276
57 **Mathew A**, Biswas A, Meitz KP. Endoscopic necrosectomy as primary treatment for infected peripancreatic fluid collections (with video). *Gastrointest Endosc* 2008; **68**: 776-782
58 **Tarantino I**, Barresi L, Fazio V, Di Pisa M, Traina M. EUS-guided self-expandable stent placement in 1 step: a new method to treat pancreatic abscess. *Gastrointest Endosc* 2009; **69**: 1401-1403
59 **Park DH**, Lee SS, Moon SH, Choi SY, Jung SW, Seo DW, Lee SK, Kim MH. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. *Endoscopy* 2009; **41**: 842-848
60 **Yasuda I**, Iwata K, Mukai T, Iwashita T, Moriwaki H. EUS-guided pancreatic pseudocyst drainage. *Dig Endosc* 2009; **21** Suppl 1: S82-S86
61 **Itoi T**, Itokawa F, Tsuchiya T, Kawai T, Moriyasu F. EUS-guided pancreatic pseudocyst drainage: simultaneous placement of stents and nasocystic catheter using double-guidewire technique. *Dig Endosc* 2009; **21** Suppl 1: S53-S56
62 **Trevino JM**, Christein JD, Varadarajulu S. EUS-guided

transesophageal drainage of peripancreatic fluid collections. *Gastrointest Endosc* 2009; **70**: 793-797
63 **Varadarajulu S**, Trevino JM, Christein JD. EUS for the management of peripancreatic fluid collections after distal pancreatectomy. *Gastrointest Endosc* 2009; **70**: 1260-1265
64 **Piraka C**, Shah RJ, Fukami N, Chathadi KV, Chen YK. EUS-guided transesophageal, transgastric, and transcolonic drainage of intra-abdominal fluid collections and abscesses. *Gastrointest Endosc* 2009; **70**: 786-792
65 **Ang TL**, Teo EK, Fock KM. Endoscopic drainage and endoscopic necrosectomy in the management of symptomatic pancreatic collections. *J Dig Dis* 2009; **10**: 213-224
66 **Okabe Y**, Kaji R, Ishida Y, Sakamoto T, Maeda A, Kikuma K, Tsuruta O, Sata M. Trans-gastric endoscopic drainage using a large balloon for pancreatic necrosis and abscess - two case reports. *Dig Endosc* 2009; **21** Suppl 1: S71-S74
67 **Antillon MR**, Bechtold ML, Bartalos CR, Marshall JB. Transgastric endoscopic necrosectomy with temporary metallic esophageal stent placement for the treatment of infected pancreatic necrosis (with video). *Gastrointest Endosc* 2009; **69**: 178-180
68 **Chase MP**, Yarze JC, Gumustop B, Leach RP. Endoscopic ultrasound-guided aspiration and oral antibiotic therapy as definitive treatment of an asymptomatic pancreatic abscess. *Pancreas* 2009; **38**: 475-476
69 **Becker V**, Huber W, Meining A, Prinz C, Umgelter A, Ludwig L, Bajbouj M, Gaa J, Schmid RM. Infected necrosis in severe pancreatitis--combined nonsurgical multi-drainage with directed transabdominal high-volume lavage in critically ill patients. *Pancreatology* 2009; **9**: 280-286
70 **Ahn JY**, Seo DW, Eum J, Song TJ, Moon SH, Park do H, Lee SS, Lee SK, Kim MH. Single-Step EUS-Guided Transmural Drainage of Pancreatic Pseudocysts: Analysis of Technical Feasibility, Efficacy, and Safety. *Gut Liver* 2010; **4**: 524-529
71 **Khashab MA**, Lennon AM, Singh VK, Shin EJ, Canto MI, Kalloo AN, Okolo PI, Giday SA. EUS-guided pseudocyst drainage as a one-step procedure using a novel multiple wire insertion technique. *Endoscopy* 2010; **42** Suppl 2: E292-E293
72 **Tarantino I**, Traina M, Barresi L, Volpes R, Gridelli B. Transgastric plus transduodenal necrosectomy with temporary metal stents placement for treatment of large pancreatic necrosis. *Pancreas* 2010; **39**: 269-270
73 **Koo JE**, Park do H, Oh J, Lee YH, Moon SH, Lee SS, Seo DW, Lee SK, Kim MH. EUS-Guided Multitransgastric Endoscopic Necrosectomy for Infected Pancreatic Necrosis with Non-contagious Retroperitoneal and Peritoneal Extension. *Gut Liver* 2010; **4**: 140-145
74 **Pallapothu R**, Earle DB, Desilets DJ, Romanelli JR. NOTES(®) stapled cystgastrostomy: a novel approach for surgical management of pancreatic pseudocysts. *Surg Endosc* 2011; **25**: 883-889
75 **Jazrawi SF**, Barth BA, Sreenarasimhaiah J. Efficacy of endoscopic ultrasound-guided drainage of pancreatic pseudocysts in a pediatric population. *Dig Dis Sci* 2011; **56**: 902-908
76 **Larghi A**, Seerden TC, Galasso D, Perri V, Uchida N, Carnuccio A, Costamagna G. EUS-guided cystojejunostomy for drainage of a pseudocyst in a patient with Billroth II gastrectomy. *Gastrointest Endosc* 2011; **73**: 169-171
77 **Sadik R**, Kalaitzakis E, Thune A, Hansen J, Jönson C. EUS-guided drainage is more successful in pancreatic pseudocysts compared with abscesses. *World J Gastroenterol* 2011; **17**: 499-505
78 **Will U**, Wanzar C, Gerlach R, Meyer F. Interventional ultrasound-guided procedures in pancreatic pseudocysts, abscesses and infected necroses - treatment algorithm in a large single-center study. *Ultraschall Med* 2011; **32**: 176-183
79 **Yusuf TE**, Baron TH. Endoscopic transmural drainage of pancreatic pseudocysts: results of a national and an international survey of ASGE members. *Gastrointest Endosc* 2006; **63**: 223-227
80 **Varadarajulu S**, Wilcox CM, Tamhane A, Eloubeidi MA, Blakely J, Canon CL. Role of EUS in drainage of peripancreatic fluid collections not amenable for endoscopic transmural drainage. *Gastrointest Endosc* 2007; **66**: 1107-1119
81 **Varadarajulu S**, Lopes TL, Wilcox CM, Drelichman ER, Kilgore ML, Christein JD. EUS versus surgical cyst-gastrostomy for management of pancreatic pseudocysts. *Gastrointest Endosc* 2008; **68**: 649-655
82 **Baron TH**, Harewood GC, Morgan DE, Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc* 2002; **56**: 7-17
83 **Johnson MD**, Walsh RM, Henderson JM, Brown N, Ponsky J, Dumot J, Zuccaro G, Vargo J. Surgical versus nonsurgical management of pancreatic pseudocysts. *J Clin Gastroenterol* 2009; **43**: 586-590
84 **Morton JM**, Brown A, Galanko JA, Norton JA, Grimm IS, Behrns KE. A national comparison of surgical versus percutaneous drainage of pancreatic pseudocysts: 1997-2001. *J Gastrointest Surg* 2005; **9**: 15-20; discussion 20-21

S- Editor Song XX **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i11.489

World J Gastrointest Endosc 2012 November 16; 4(11): 489-499
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

Shigetaka Yoshinaga, MD, PhD, *Series Editor*

Pathological evaluation of gastrointestinal endoscopic submucosal dissection materials based on Japanese guidelines

Koji Nagata, Michio Shimizu

Koji Nagata, Michio Shimizu, Department of Pathology, Saitama Medical University, International Medical Center, 1397-1 Yamane, Hidaka, Saitama 169-8050, Japan
Author contributions: Nagata K wrote the paper and Shimizu M read proofs of the paper.
Correspondence to: Koji Nagata, MD, PhD, Department of Pathology, Saitama Medical University, International Medical Center, 1397-1 Yamane, Hidaka, Saitama 169-8050, Japan. tororia@saitama-med.ac.jp
Telephone: +81-42-9840609 Fax: +81-42-9840609
Received: October 13, 2011 Revised: October 17, 2012
Accepted: October 26, 2012
Published online: November 16, 2012

Abstract

Endoscopic surgery first started as snare polypectomy and then progressed to endoscopic mucosal resection (EMR). In order to resect a lesion that is more than 2 cm, endoscopic submucosal dissection (ESD) was developed. ESD therapy has now been established and is being used for early stage neoplastic lesions in the stomach, colon, esophagus, larynx and pharynx. In ESD specimens, we deal with relatively small lesions; therefore, more meticulous and precise pathological diagnosis is required compared to that in surgically resected specimens. In addition, we should be expert in the eligibility criteria of the different organs for ESD therapy. Here, we explain the biopsy diagnosis, including the Japanese group classification as well as the Vienna classification, handling the specimen, including fixation, photography, cutting and paraffin embedding, histological type, depth, vascular invasion and evaluation of the surgical margins, based on the latest Japanese guidelines. Japanese histopathology diagnostic criteria for the stomach, colon and esophagus are also described. We also demonstrate some examples of those mentioned above.

Key words: Esophagus; Stomach; Colon; Rectum; Biopsy; Endoscopic mucosal dissection; Surgical pathology; Diagnosis; Guideline; Immunohistochemistry

Peer reviewers: Wai-Keung Chow, Visiting Staff, Division of Gastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung 40001, Taiwan, China; Jochen Wedemeyer, MD, Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Carl Neuberg Str. 1, 30625 Hannover, Germany

Nagata K, Shimizu M. Pathological evaluation of gastrointestinal endoscopic submucosal dissection materials based on Japanese guidelines. *World J Gastrointest Endosc* 2012; 4(11): 489-499 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i11/489.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i11.489

INTRODUCTION

Endoscopic surgery for gastrointestinal epithelial neoplasms such as protruding early gastric cancer or adenoma of the colon first took the form of polypectomy for polypoid lesions and then progressed to endoscopic mucosal resection (EMR) for flat type lesions[1]. However, the resection of these lesions by EMR was generally less precise than that in surgical excision. This was because the lesion could be no larger than approximately 2 cm in diameter for resection and had to be resected separately, not *en bloc*. In addition, local recurrence was often encountered. In order to solve these problems in the stomach, a new method called endoscopic submucosal dissection (ESD) was developed, enabling a lesion to be excised *en bloc*[2,3]. Nowadays, ESD has been used for early stage neoplastic lesions in the esophagus[4], colorectum[5], pharynx[6,7] and larynx[8]. The development of this tech-

nique enabled an accurate pathological diagnosis of the lesion to be made and the endoscopic operation became established as a form of therapy. ESD therapy has been established not only as a procedure of ESD, but also as a system composed of the endoscopic diagnosis of the lesion, the pathological diagnosis of the biopsy, ESD enforcement, the pathological diagnosis of the ESD specimen and additional surgical resections (if necessary). It was completed based on the data amassed by Japanese physicians, surgeons, radiologists and pathologists' continuous efforts through more than 50 years of experience. Here, we describe the Japanese histopathology diagnostic criteria based on ESD treatment and the evaluation criteria of ESD specimens (especially in the esophagus, stomach and colorectum). In addition, critical points to be considered are also mentioned.

STOMACH

ESD treatment was first performed for early gastric cancer and nowadays ESD treatment can be utilized in other organs, including the esophagus and colon. Eligibility criteria for ESD therapy and pathological diagnosis by the Gastric Cancer Treatment Guidelines 2010 have been established.

According to the Gastric Cancer Treatment Guidelines 2010 (3rd edition) by the Japanese Gastric Cancer Association, the fundamental rule for ESD treatment is described as follows: the possibility of lymph node metastasis is extremely low and the tumor is of a size and location which enables it to be removed *en bloc*. The absolute indicative lesion for ESD is defined as follows: differentiated type adenocarcinoma which is diagnosed as macroscopically intramucosal carcinomas (cT1a) of 2 cm or less in diameter regardless of its macroscopic type, without ulcer/ulcer scar lesion. If the lesion has no vascular invasion, the pT1a lesion shows an extremely low risk of lymph node metastasis[9-13]. Since ESD treatment does not include lymph node dissection, it poses a greater risk for lymph node metastasis than surgical resection[14,15]. Recently, ESD has been performed for the lesions of "extended adaptation". These lesions include (1) differentiated type adenocarcinoma (cT1a), more than 2 cm in diameter, without ulceration; (2) differentiated type adenocarcinoma (cT1a), 3 cm or less in diameter, with ulceration; and (3) undifferentiated type adenocarcinoma (cT1a), 2 cm or less, without ulceration[16-18]. All three lesions should not have lymphatic or vascular invasion. The pathological diagnosis of ESD is important to determine whether a case is a "usual adaptation lesion" or an "extended adaptation lesion".

Biopsy diagnosis

Histological assessment of gastric and colorectal biopsy specimens is made in Japan by using the "group classification" system. This classification was originally made for epithelial neoplasm and is based on the grade of cellular and/or structural changes of the lesion. The group classification is not a diagnostic category and is used only for biopsy tissue diagnosis and not for resection materials. This classification consists of six groups (Table 1)[19,20]. Since there are very few esophageal glandular neoplasias in Japan, the group classification is not used in the esophagus. In other words, squamous epithelial lesions are just divided into three categories (normal, reactive atypia and neoplasia with low grade atypia and high grade atypia). In order to internationally standardize the pathological criteria, an international consensus meeting was held in Vienna and the "Vienna classification" was established[21]. Afterwards, the "group classification" was also revised by adding the concept of the "Vienna classification" (Table 1). However, a debatable portion between the "group classification" and the "Vienna classification" still remains. For example, intramucosal invasive lesions of the colon are not considered to be intramucosal carcinomas in the western point of view but they are in the Japanese point of view. We Japanese also think that the proliferation potency of the cancer differs between cancer with low grade atypia (low grade cancer) and cancer with high grade atypia (high grade cancer) and the grading of the cancer is recommended. Intraepithelial neoplasia of the esophagus and Group 3 lesions of the stomach and the colorectum are now considered to be eligible for polypectomy, EMR or ESD treatment in Japan. Considering the adaptation of future treatment, it is necessary to standardize the pathological nomenclature of intramucosal neoplasia internationally. For example, adenoma/dysplasia to carcinoma in situ with low grade atypia should be standardized to low grade intramucosal neoplasia and carcinoma in situ with high grade atypia to intramucosal invasive adenocarcinoma should be standardized to high grade intramucosal neoplasia.

Table 1 Histological assessment of biopsy specimens of colon and rectum and comparison with Vienna classification

Definition of group classification of Japan	Vienna classification
Group X: Inadequate material for histological diagnosis	
Group 1: Normal tissue and non-neoplastic lesion	Category 1
Group 2: Lesions in which it is difficult to determine whether the lesion is tumorous or non-tumorous	Category 2
Group 3: Adenoma (benign neoplasia)	Category 3
Group 4: Neoplastic lesion suspected of being carcinoma	Category 4.1
Group 5: Carcinoma	Category 4.1 to 5.2

Japanese classification is used only for biopsy tissue diagnosis (English edition of gastric carcinoma is now being prepared for publication).

Handling of endoscopic resection materials

In ESD materials, it is important to pathologically evaluate whether curative resection has been made or additional resection is required. Since specimens and lesions are both smaller than the surgical operation materials, careful and meticulous handling is desirable.

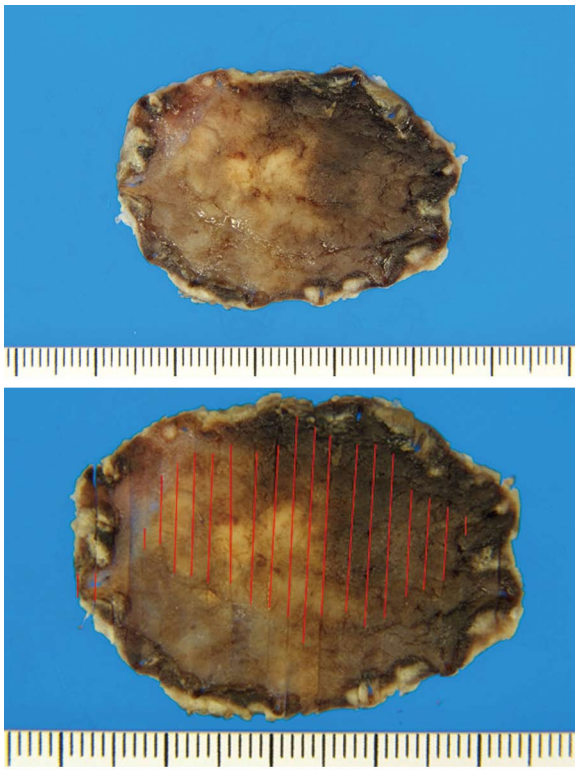


Figure 1 Endoscopic submucosal dissection materials with incidental lesions not found before treatment. These cases are found in a percentage of endoscopic submucosal dissection materials. The incidental lesion shows a positive margin. It should be kept in mind that a lesion may not be single but multiple in endoscopic submucosal dissection specimens. This accurate mapping of the lesion is helpful to make a treatment strategy after endoscopic submucosal dissection specimen.

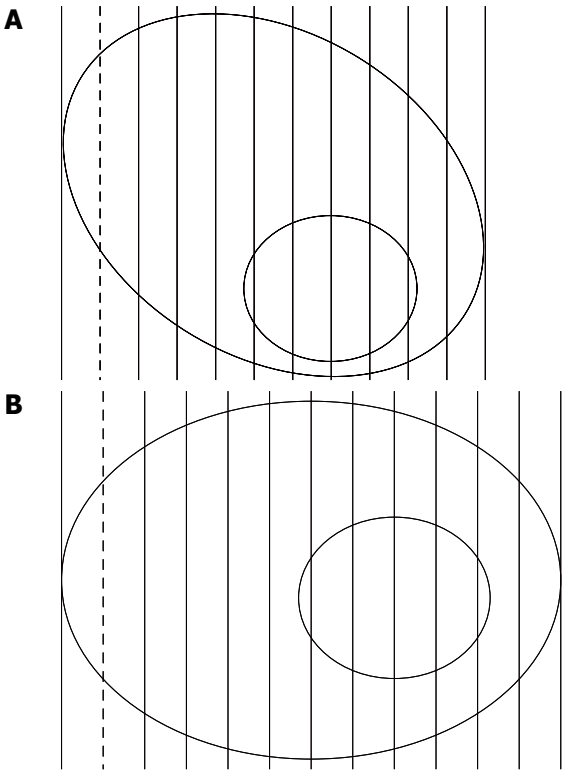


Figure 2 Cutting. A: General cutting of endoscopic submucosal dissection material. The final glass slide is of the reversed section of the solid line. Therefore, it is recommended that the tumor area should not be included in the portion of the dotted line; B: Cutting of endoscopic submucosal dissection material with a tumor close to the cut margin. Endoscopic submucosal dissection specimen should be cut in parallel sections which are perpendicular to the tangent of the closest margin.

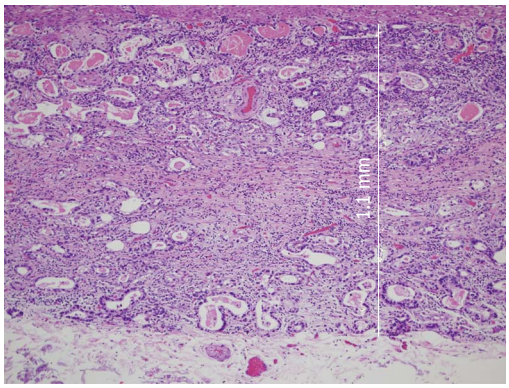


Figure 3 How to measure the depth in pT1b2 cases. Depth of a pT1b case indicates the distance from the lower edge of the muscularis mucosae to the invasive front of tumor.

Fixation of the specimen: Just as with surgical materials, an endoscopically resected specimen is placed on a formalin board, cork or styrofoam and stretched out to approximate the length to what is in the living body. Then the full thickness (mucosa, muscularis mucosae and submucosa) of the specimen is pinned with rustproof pins to identify the horizontal margin. Overextension of the specimen should be avoided since it can cause destruction of the material. A filter paper placed between the resection specimen and the fixation board should prevent poor fixation.

Macroscopic observation: In order to identify the proximal side, distal side, tumor location, size of lesion and marginal side, communication between endoscopists and pathologists is essential. Especially if there is a possibility of submucosal invasion or ulcer scar, it is necessary for pathologists to confirm the possible site with endoscopists.

Photography: Photographs of the specimen should be taken both before and after formalin fixation. In general, when taking a picture, the resection materials are positioned with the proximal side to the right and the distal side to the left. However, in the case of ESD, the specimen can be positioned with the major axis direction horizontally for the photograph, as this allows for the highest resolution. The gross photograph with cutting lines is recommended to compare macroscopic and microscopic findings (Figure 1). It is also useful to map and rebuild the lesion. The mucosal lesion can be clearly identified if a photograph is taken of the specimen immersed in water after hematoxylin staining.

Cutting: Importantly, the ESD specimen should be cut

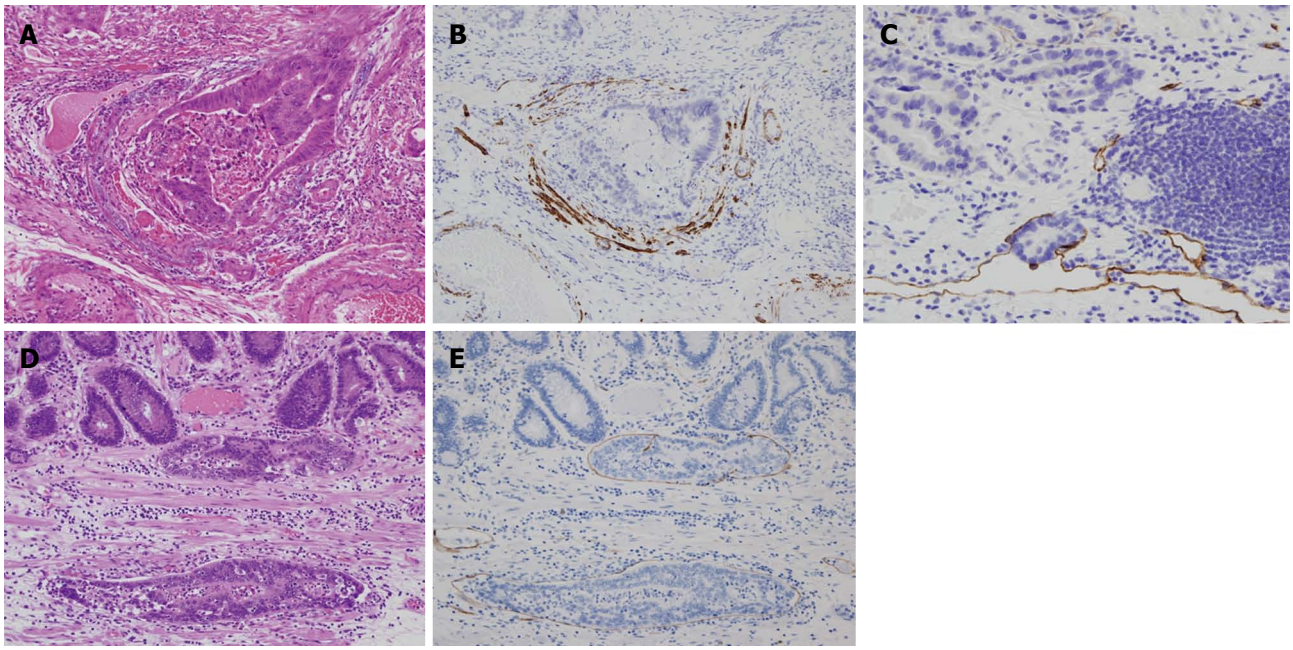


Figure 4 Evaluation of vessel invasion and lymphatic invasion. Venous invasion is evaluated by using a double staining with Victoria blue and hematoxylin-eosin (A) and immunohistochemistry of desmin (B). Lymphatic invasion is demonstrated by immunostaining of D2-40 (C). Lymphatic invasion is noted in the lamina propria (D: Hematoxylin-eosin stain; E: Immunohistochemistry of D2-40).

parallel to the closest margin direction (Figure 2A). When the negative margin is obvious, the specimens are step-sectioned along the minor axis of the specimen to obtain more information (Figure 2B).

The evidence of ESD treatment is based on the data of cases of surgically treated early gastric cancer in relation to lymph node metastases. In those cases, the lesion was step-sectioned at 4 mm to 5 mm intervals and then examined pathologically. Regarding the ESD material, the width of the sections is reduced to 2 mm intervals to allow for a more accurate diagnosis, as recommended by the Japanese Gastric Cancer Association. If any lesion is to be confirmed pathologically, tissue processing of the lesion should be performed.

Paraffin embedding: Larger tissue specimens should be divided properly. In such cases, care should be taken so that the divided portions do not contain the main lesion, a portion suspected of having invasion to the submucosa, or a site of an ulcer scar. Then, the tissues are put into the cassettes and the cassettes containing tissue are immersed in paraffin.

Histological evaluation

In Japan, the histological diagnosis of the ESD materials is made according to the gastric cancer handling rules. The most important thing in the pathological diagnosis of ESD is to evaluate the complete removal of the lesion[5,22]. Here, we will explain several important points for the pathological diagnosis in ESD specimens. These are the size of the lesion, histological type, depth of the lesion, vessel invasion, ulcer scar and surgical margin, each of which are described in detail below.

Histological type: Generally, the histological type of gastric cancer is divided into the differentiated type and undifferentiated type (so-called diffuse type in the Laurén classification)[23] and the major histological type within the tumor is taken as the final pathological diagnosis according to the gastric cancer handling rules in Japan[19]. If a lesion is composed of only the differentiated type, the chance of vascular invasion and lymph node metastasis is low. However, if there is some of the undifferentiated type mixed within the tumor, the risk becomes high. Therefore, it is recommended to write the presence of the undifferentiated type component in the pathology report. When submucosal invasion is present, the histological type of the invasive portion is important and it is necessary to mention whether the invasive part shows only the differentiated type component or if it includes the undifferentiated type component because the histological type will determine whether or not additional treatment may be required.

Depth: pT1b is classified into two categories, namely pT1b1 (tumor depth of less than 0.5 mm from the lower edge of muscularis mucosae) and pT1b2 (tumor depth of 0.5 mm or more from the lower edge of muscularis mucosae), because the risk of lymph node metastases is significantly higher in cases belonging to the latter category[16]. When the muscularis mucosae are obscure due to myofibroblastic proliferation, it is recommended to identify the muscularis mucosae by using the immunohistochemical staining of desmin.

There are several practical methods available for the measurement of 0.5 mm. These are: (1) putting a thin transparent ruler directly on the glass slide; (2) using a

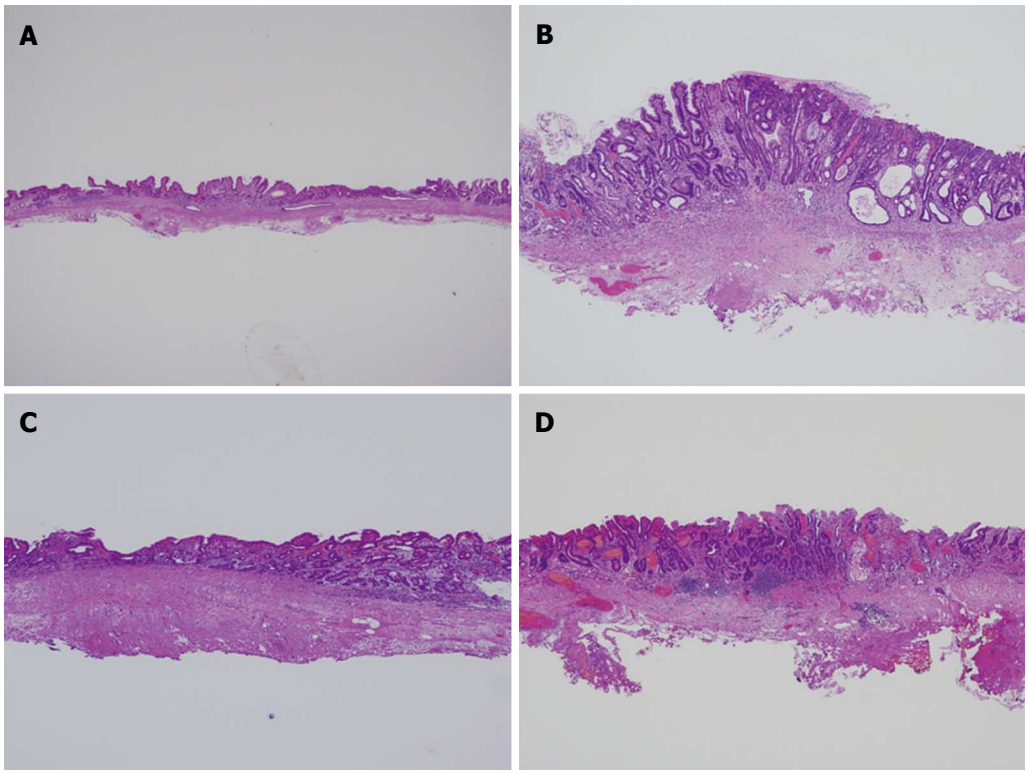


Figure 5 Ulcer scar *vs* biopsy scar. Biopsy scar is a very localized lesion (A and B) and is noted at the site of biopsy. Therefore, clinical information is important. On the other hand, ulcer scar due to tumor is usually an expansive lesion (C and D). Clinical information of no history of biopsy is also useful.

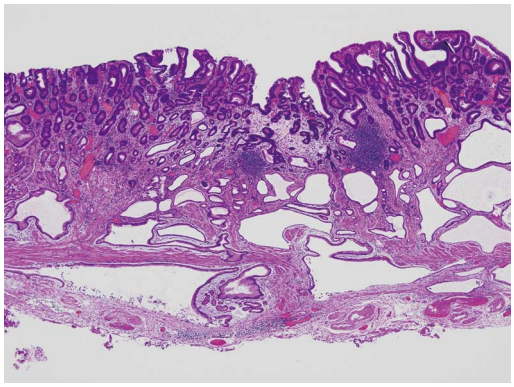


Figure 6 Heterotopic submucosal glands (= gastritis cystica profunda). Heterotopic submucosal glands can be misdiagnosed endoscopically as an ulcer due to submucosal invasion. These lesions should be described in the pathology report and the lesional mapping diagram.

measurement device of a microscopic digital camera; (3) measuring with the micrometer of the eyepiece; and (4) using a scale loupe (Figure 3). The depth of invasion in the ESD specimen is only determined in cases of negative vertical margin. In cases of positive vertical margin, the findings should be described, for example, as follows: "at least pT1b2/SM2: 1200 micrometers from muscularis mucosae".

Vessel invasion

The presence or absence of lymphatic permeation and vascular (vein) invasion is one of the important factors for the evaluation of additional therapy. In our institution, double staining with Victoria blue and hematoxylin-eosin (HE) for vascular invasion and immunohistochemistry of D2-40 for lymphatic invasion are routinely performed in all cases with submucosal invasion[24,25]. In addition, elastic Van Gieson stain and immunohistochemistry of CD31 or CD34 are widely used for the identification of vascular and lymphatic invasions (Figure 4)[26]. When special staining and immunohistochemistry are ordered, the lesion of vascular invasion may disappear due to a deeper cut. Therefore, caution should be made in cutting the block. In cases with obvious vascular invasion on HE-stained slides, we record its presence even if we cannot confirm such invasions by special staining or immunohistochemistry. Since lymphatic invasion can be present even in pT1a cases, careful microscopic examination is necessary (Figure 4).

ULCER SCAR AND BIOPSY SCAR

The determination of curability of the lesion may be changed depending on the presence or absence of an ulcer or ulcer scar. An ulcer scar should be confirmed histologically, not endoscopically. Since a biopsy scar is not regarded as a real ulcer scar, it is necessary to confirm previous biopsy histories, including the biopsy site (Figures 5 and 6). Confirmation with endoscopists may be required, depending on the case.

Evaluation of the surgical margins

Horizontal margin: To diagnose a negative horizontal margin, the first and last section should be free of can-

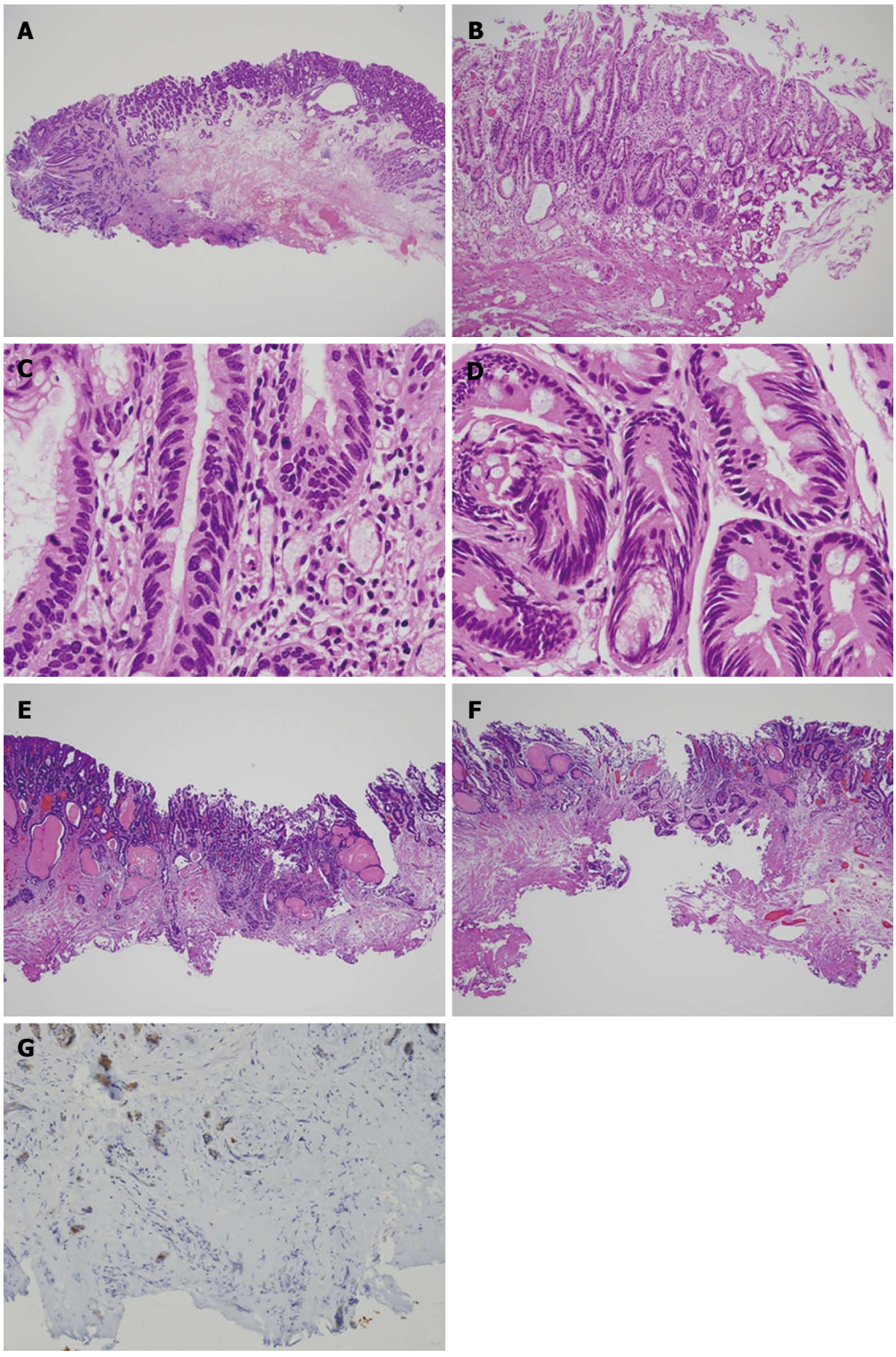


Figure 7 Cases of positive horizontal margin and vertical margin. In most cases, a positive margin is easily recognized (A); Some cases show marked degeneration by treatment (B); By careful microscopic examination, adenocarcinoma cells (C) can be distinguished from intestinalized epithelium (D). A positive vertical margin at the submucosal layer (E) or at the lamina propria (F) should be described in the pathology report. A positive vertical margin can be easily detected by using immunohistochemistry of keratin (G).

cer and both sides of all other sections should show no cancer. In the case of a negative horizontal margin, the distance (mm) to the margin should be recorded and in positive cases, it is recommended that the number of sections with positive margins be described. In cases with a cauterization effect, it is sometimes difficult to judge the horizontal margin (Figure 7). Although there is no conclusive solution in such cases, immunohistochemical staining of p53 and Ki-67 may be useful[27]. Detailed microscopic examination including nuclear and structural

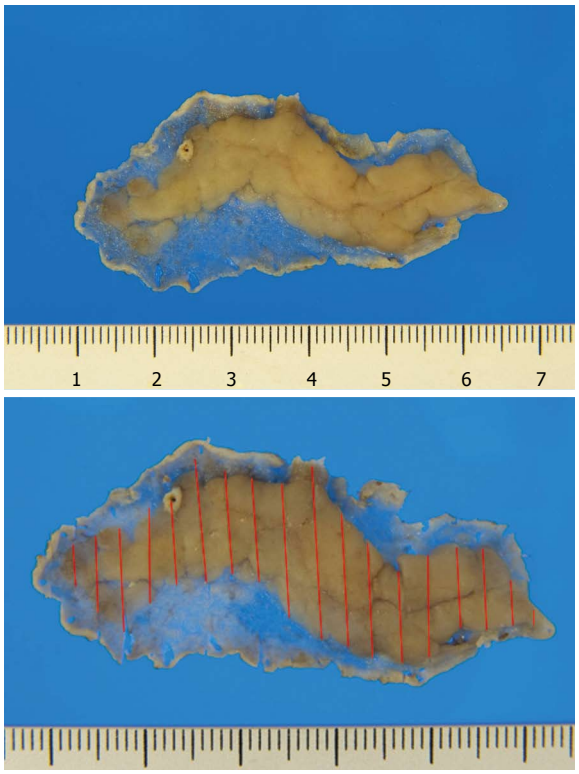


Figure 8 Cutting of a sessile polypoid lesion. Non-tumor areas around the polypoid lesion are very thin. The submucosal layer of the tumor portion is also thin. Therefore, caution should be taken when preparing the specimen so that a false positive diagnosis of the vertical margin will not be made.

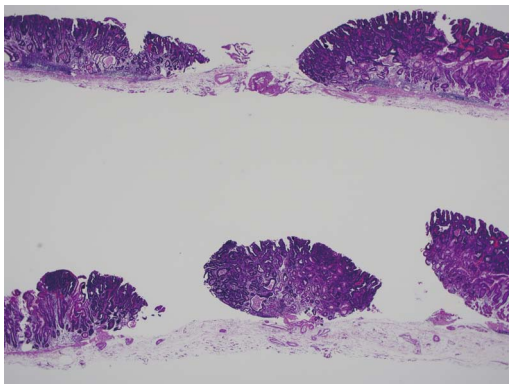


Figure 9 Mucosal tears due to overextension during the tissue fixation.

changes may be helpful in some cases. Recently, ESD has been performed for lesions measuring more than 5 cm. In such cases, an incidental lesion which was not detected preoperatively may be found and it may show a positive margin. Therefore, it should be kept in mind that multiple lesions may be present at the time of preoperative diagnosis.

Vertical margin: When cancer cells are not exposed to an abrasion side in all sections, we make the diagnosis of a negative vertical margin and confirm the depth of invasion. In cases with positive vertical margins, as previously described in the section of the depth, both the positive

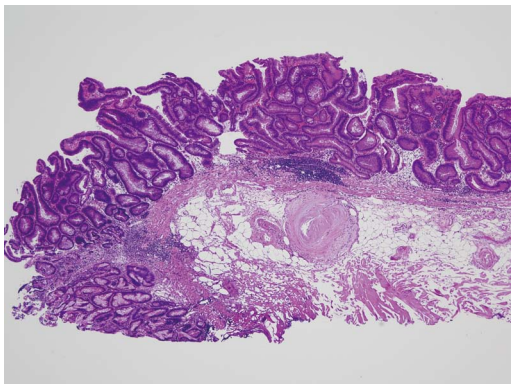


Figure 10 Positive horizontal margin in the colonic endoscopic submucosal dissection. In appropriate pathology specimens, the evaluation of the margin is relatively easy.

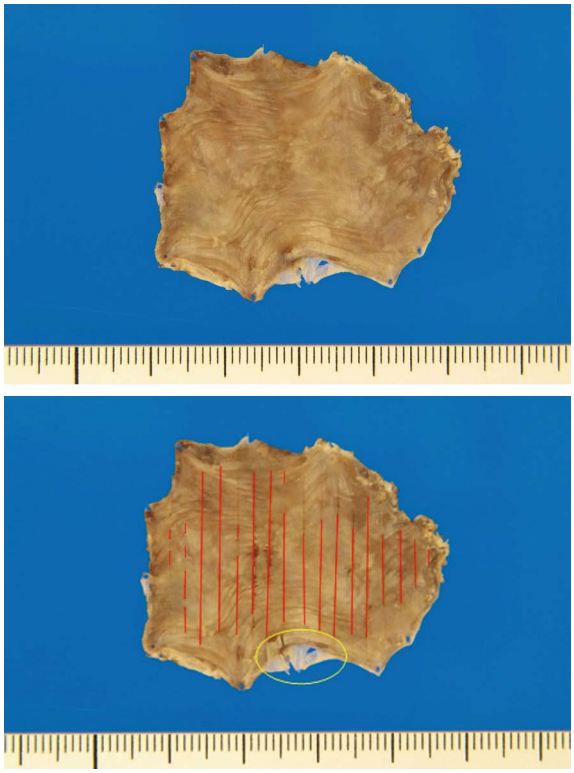


Figure 11 Early esophageal cancer in endoscopic submucosal dissection specimen. The marginal portion (squamous epithelium) of the specimen is very thin. Therefore, it is difficult to make a section (yellow circle) and may cause false positivity of the surgical margin.

site (either lamina propria or submucosa) and the distance from the lower edge of muscularis mucosae to the positive margin site should be recorded (Figure 7). When tumor cells are hard to identify due to cauterization, immunostains with keratin are useful. When the positive margin site shows no cauterization effect, the possibility of false positivity should be considered and recorded as such. Then, a more deeply cut section should be obtained. Since examination by re-embedding often does not work well, it is better to avoid such a preparation. In the case of a negative vertical margin, if tumor cells are

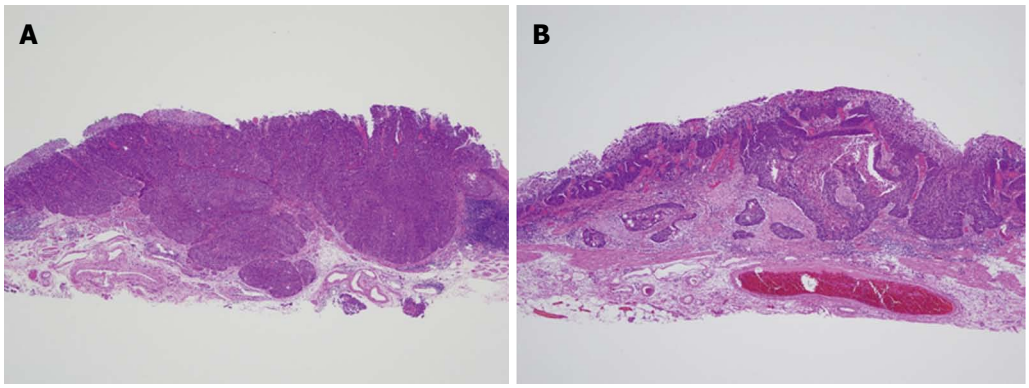


Figure 12 Invasive patterns in squamous cell carcinoma of the esophagus. Expansive pattern (A) and infiltrative pattern (B) should be described in the pathology report.

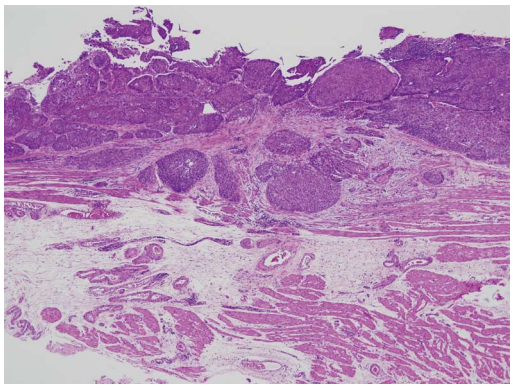


Figure 13 pT1a-superficial muscularis mucosae case. The lower portion of the picture shows two-layered muscularis mucosae. In esophageal cancers with pT1a-MM (M3), the depth of invasion is divided into three (pT1a-superficial muscularis mucosae, pT1a-lamina propria mucosae and pT1a-deep muscularis mucosae).

close to the vertical margin, recording the distance from the abrasion margins to the tumor cells may be useful as information during follow-up.

COLON AND RECTUM

As for the endoscopic treatment of colorectal lesions, polypectomy is the main treatment since most lesions are pedunculated. ESD is performed for so-called lateral spread lesions[28]. The evaluation of ESD specimens follows that of polypectomy materials.

Biopsy diagnosis

The definition/diagnostic criteria of colorectal cancer are different in Japan and the west. High-grade intraepithelial neoplasia can be called carcinoma in Japan, while only submucosal invasive lesions can be called carcinoma in the west. Namely, intramucosal invasive lesions are included in high-grade dysplasia in the west. Therefore, the so-called western high-grade dysplasia can be a target for endoscopic treatment in Japan.

Characteristics of colonic ESD material

In the colon, pedunculated polypoid lesions are much more common compared to those in the stomach. However, some show sessile lesions, or so-called laterally spreading tumors (LSTs). LSTs are the most common target lesions in colonic ESD. Characteristics of large bowel ESD materials include predominantly polypoid lesions, often papillary or villous lesions with fragility, and thin walls compared to those in the stomach (Figure 8). It is desirable that all of the layers of the specimen should be examined microscopically. The rupture of the material by the excessive extension at fixation handling disturbs an accurate diagnosis (Figure 9).

Eligibility criteria for endoscopic treatment are based on the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines (2010 edition). In the colorectal cancer treatment guidelines published in 2010, the principle of the endoscopic treatment is described as follows: "the size and the location of the lesion should be such that it can be excised *en bloc*, and there is a low risk of lymph node metastasis". Eligibility criteria for endoscopic excision are (1) intramucosal carcinoma, or mildly invasive cancer into the submucosa; (2) less than 2 cm at the greatest diameter; and (3) macroscopic type is not taken into consideration[29,30]. In addition, the adaptation of colonic ESD for adenoma includes lesions which are 2 cm or more at the greatest diameter with lateral spread lesions or sessile lesions, lesions with an ulcer scar and recurrent lesions; while that for carcinoma is adenocarcinoma with cT1b1 (SM1) which is 2 cm or less at the greatest diameter.

Eligibility criteria for additional treatment after endoscopic excision

In cases with positive horizontal or vertical margins, additional surgical resection is recommended (Figure 10)[5]. In addition, surgical resection is considered if any one of the following factors is present: (1) pT1b1 (deeper than 1000 micrometers from the lower border of muscularis mucosae); (2) positive lymphovascular invasion (ly, v); (3) poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous carcinoma; and (4) budding/sprouting at the invasive front showing Grade 2 to 3. Therefore, it is important to evaluate these factors in ESD materials of the colon[31-33].

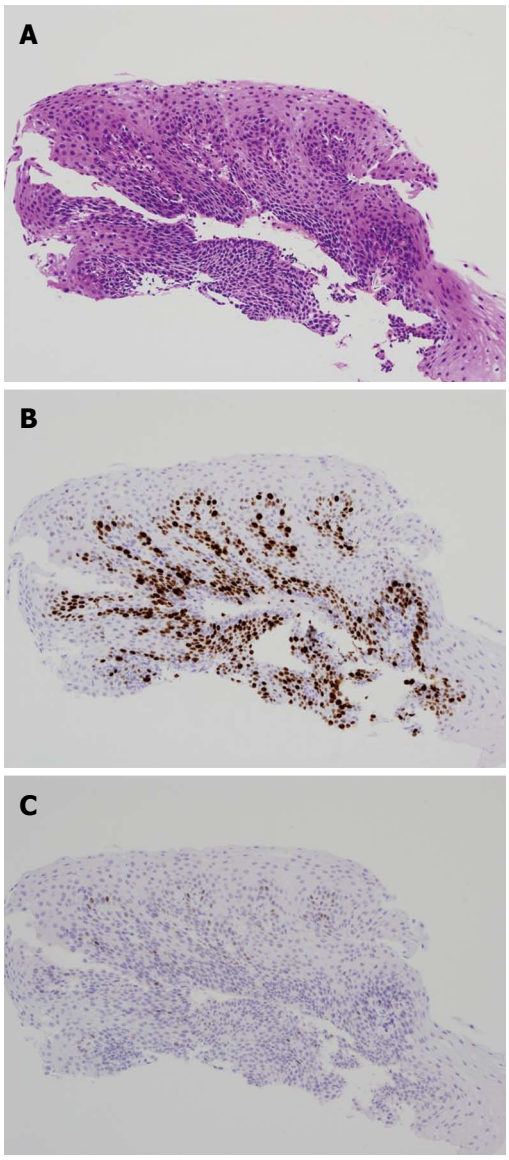


Figure 14 Evaluation of horizontal margin in the esophageal endoscopic submucosal dissection. Compared to hematoxylin-eosin stain (A); immunohistochemical stainings of Ki-67 (B) and p53 (C) highlight the lesion.

Pathological diagnosis specific to colonic lesions

Unlike gastric lesions, large intestinal lesions predominantly show pedunculated lesions. Therefore, special attention should be paid to submucosal invasion and the grading of budding/sprouting.

Evaluation of submucosal invasion

Most colorectal lesions are pedunculated or sub-pedunculated and are usually treated by polypectomy or EMR. In recent years, however, ESD has been used for the treatment of non-polypoid 0-IIc type lesions as well as LST type lesions. Regarding the evaluation of submucosal invasion, there are some differences between pedunculated lesions and non-pedunculated lesions in the colon. When it is possible to identify the muscularis mucosae, the depth of submucosal invasion is the distance from the deeper edge of the muscularis mucosae to the deepest invasive portion. When muscularis mucosae cannot be identified, the depth of submucosal invasion is the distance between the surface of the tumor and the deepest invasive portion. In polypoid tumors with disrupted muscularis mucosae, the depth of submucosal invasion is the distance between the deepest invasive site and the reference line, defined as the boundary between the tumor head and the pedicle. Migration of adenomatous glands (dysplastic glands in the west) should be differentiated from the true submucosal invasion[34].

Budding/sprouting grading

When cancer cells reveal an isolated or small cluster pattern in the invasive front in the large bowel pT1b cancer, it is most likely to be lymph node metastasis. Budding/sprouting is defined as a small cluster of cancer cells consisting of less than 5 tumor cells at the invasive front. When the most highly concentrated area is examined under × 200 magnification, 0-4 clusters can be graded as Grade 1, 5-9 clusters as Grade 2, and 10 or more clusters as Grade 3. Grade 2 and Grade 3 show a significantly higher risk of lymph node metastasis than Grade 1. Therefore, in cases with submucosal invasion, it is required to describe the budding/sprouting grading in the report[33,35-38].

ESOPHAGUS

Eligibility criteria for endoscopic treatment are based on Esophageal Cancer Diagnosis Treatment Guidelines (Second Edition, 2007).

The endoscopic ablative adaptation of esophageal cancer is as follows: carcinoma in situ [pT1a-EP (M1)], tumor-invaded lamina propria mucosa [pT1a-LPM (M2)], or tumor-invaded mucosa (pT1a). Since these lesions show extremely rare lymph node metastases, radical cure can be obtained by the ESD procedure. Because of the occurrence of cicatricial stenosis after ESD, adaptation of ESD is limited to the cases with less than two-thirds circumferential lesion. The lesions which have invaded the muscularis mucosa [pT1a-MM (M3)] or invaded the submucosa up to a depth of 200 micrometers or less from the lamina muscularis mucosa (pT1b-SM1 in ESD criteria) are a relatively indicative lesion because of the risk of lymph node metastasis. In addition, total circumferential lesion in pT1a-MM (M3) and pT1b-SM1 is a relative indicative lesion. The lesion invading the submucosa with a depth of more than 200 micrometers from the lamina muscularis mucosa (pT1b-SM2 in ESD criteria) has a 50% risk of lymph node metastasis[39]; therefore, these lesions are treated in accordance with the treatment of progressive cancer[40-42].

Characteristics of esophagus ESD materials

In esophageal ESD materials, the mucosal epithelium and lamina propria separates easily and the marginal portion is easily fragmented. Since a lesion can be recognizable by Lugol dispersion, cutting after Lugol staining is useful.

Caution should be made to examine all of the layers microscopically (Figure 11). In cases of esophageal cancer with invasion deeper than the lamina propria mucosa, the invasive pattern should be recorded, since the risk of lymphovascular invasion differs depending on the invasive patterns, namely expansive pattern or infiltrating pattern (Figure 12)[43-45].

In cases of Barrett's esophageal cancer, double layers of the muscularis mucosae is known[46]. Around the muscularis mucosae, vasculatures and lymphatic channels are well developed and there is the possibility of lymph node metastasis. However, the relationship between the depth of early stage Barrett's esophageal cancer and lymph node metastasis is not clear in Japan. Therefore, cases with pT1a-MM (M3) are divided into pT1a-superficial muscularis mucosae, pT1a- LPM and pT1a-deep muscularis mucosae in Japan and we are now collecting these cases for evaluation (Figure 13). In cases with esophageal ESD, it is sometimes difficult to judge the horizontal margin and in such cases, immunohistochemical staining of p53 and Ki-67 may be useful (Figure 14).

CONCLUSION

We described several important points to be considered in ESD materials. For accurate pathological diagnosis, it is essential to make appropriate pathology specimens, including HE glass slides. Furthermore, it is important for pathologists to understand the factors related to the prognosis and to communicate with endoscopists.

REFERENCES

1 **Kudo S**. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy* 1993; **25**: 455-461
2 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70
3 **Ono H**. Early gastric cancer: diagnosis, pathology, treatment techniques and treatment outcomes. *Eur J Gastroenterol Hepatol* 2006; **18**: 863-866
4 **Takahashi H**, Arimura Y, Masao H, Okahara S, Tanuma T, Kodaira J, Kagaya H, Shimizu Y, Hokari K, Tsukagoshi H, Shinomura Y, Fujita M. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). *Gastrointest Endosc* 2010; **72**: 255-264, 264. e1-2
5 **Tanaka S**, Oka S, Chayama K. Colorectal endoscopic submucosal dissection: present status and future perspective, including its differentiation from endoscopic mucosal resection. *J Gastroenterol* 2008; **43**: 641-651
6 **Kuwabara T**, Hiyama T, Oka S, Urabe Y, Tanaka S, Yoshihara M, Arihiro K, Shimamoto F, Chayama K. Clinical features of pharyngeal intraepithelial neoplasias and outcomes of treatment by endoscopic submucosal dissection. *Gastrointest Endosc* 2012; Epub ahead of print
7 **Hanaoka N**, Ishihara R, Takeuchi Y, Suzuki M, Uemura H, Fujii T, Yoshino K, Uedo N, Higashino K, Ohta T, Kanzaki H, Hanafusa M, Nagai K, Matsui F, Iishi H, Tatsuta M, Tomita Y. Clinical outcomes of endoscopic mucosal resection and endoscopic submucosal dissection as a transoral treatment for superficial pharyngeal cancer. *Head Neck* 2012; Epub ahead of print
8 **Fujishiro M**. Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 4289-4295
9 **Abe N**, Watanabe T, Suzuki K, Machida H, Toda H, Nakaya Y, Masaki T, Mori T, Sugiyama M, Atomi Y. Risk factors predictive of lymph node metastasis in depressed early gastric cancer. *Am J Surg* 2002; **183**: 168-172
10 **Kunisaki C**, Takahashi M, Nagahori Y, Fukushima T, Makino H, Takagawa R, Kosaka T, Ono HA, Akiyama H, Moriwaki Y, Nakano A. Risk factors for lymph node metastasis in histologically poorly differentiated type early gastric cancer. *Endoscopy* 2009; **41**: 498-503
11 **Yamao T**, Shirao K, Ono H, Kondo H, Saito D, Yamaguchi H, Sasako M, Sano T, Ochiai A, Yoshida S. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. *Cancer* 1996; **77**: 602-606
12 **Mita T**, Shimoda T. Risk factors for lymph node metastasis of submucosal invasive differentiated type gastric carcinoma: clinical significance of histological heterogeneity. *J Gastroenterol* 2001; **36**: 661-668
13 **Alvarez Herrero L**, Pouw RE, van Vilsteren FG, ten Kate FJ, Visser M, van Berge Henegouwen MI, Weusten BL, Bergman JJ. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. *Endoscopy* 2010; **42**: 1030-1036
14 **Japanese gastric cancer association**. Gastric cancer treatment guidelines 2010. 3 ed. Tokyo: Kanehara, 2010
15 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123
16 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225
17 **Hirasawa T**, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 2009; **12**: 148-152
18 **Hanaoka N**, Tanabe S, Mikami T, Okayasu I, Saigenji K. Mixed-histologic-type submucosal invasive gastric cancer as a risk factor for lymph node metastasis: feasibility of endoscopic submucosal dissection. *Endoscopy* 2009; **41**: 427-432
19 **Japanese gastric cancer association**. Japanese classification of gastric cancer. Tokyo: Kanehara, 2010
20 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112
21 **Schlemper RJ**, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Fléjou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251-255
22 **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
23 **Lauren P**. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49
24 **Sako A**, Kitayama J, Ishikawa M, Yamashita H, Nagawa H. Impact of immunohistochemically identified lymphatic invasion on nodal metastasis in early gastric cancer. *Gastric Cancer* 2006; **9**: 295-302

25 **Yonemura Y**, Endou Y, Tabachi K, Kawamura T, Yun HY, Kameya T, Hayashi I, Bandou E, Sasaki T, Miura M. Evaluation of lymphatic invasion in primary gastric cancer by a new monoclonal antibody, D2-40. *Hum Pathol* 2006; **37**: 1193-1199

26 **del Casar JM**, Corte MD, Alvarez A, García I, Bongera M, González LO, García-Muñiz JL, Allende MT, Astudillo A, Vizoso FJ. Lymphatic and/or blood vessel invasion in gastric cancer: relationship with clinicopathological parameters, biological factors and prognostic significance. *J Cancer Res Clin Oncol* 2008; **134**: 153-161

27 **Sugai T**, Inomata M, Uesugi N, Jiao YF, Endoh M, Orii S, Nakamura S. Analysis of mucin, p53 protein and Ki-67 expressions in gastric differentiated-type intramucosal neoplastic lesions obtained from endoscopic mucosal resection samples: a proposal for a new classification of intramucosal neoplastic lesions based on nuclear atypia. *Pathol Int* 2004; **54**: 425-435

28 **Kudo S**, Kashida H, Tamura T, Kogure E, Imai Y, Yamano H, Hart AR. Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. *World J Surg* 2000; **24**: 1081-1090

29 **Japanese society for cancer of the colon and rectum**. JSCCR guidelines 2010 for the treatment of colorectal cancer. Tokyo: Kanehara, 2010

30 **Watanabe T**, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2012; **17**: 1-29

31 **Kitajima K**, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004; **39**: 534-543

32 **Ueno H**, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K, Matsukuma S, Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004; **127**: 385-394

33 **Tateishi Y**, Nakanishi Y, Taniguchi H, Shimoda T, Umemura S. Pathological prognostic factors predicting lymph node metastasis in submucosal invasive (T1) colorectal carcinoma. *Mod Pathol* 2010; **23**: 1068-1072

34 **Japanese society for cancer of the colon and rectum**. Japanese classification of colorectal carcinoma. 2rd ed. Tokyo: Kanehara, 2009

35 **Nakamura T**, Mitomi H, Kanazawa H, Ohkura Y, Watanabe M. Tumor budding as an index to identify high-risk patients with stage II colon cancer. *Dis Colon Rectum* 2008; **51**: 568-572

36 **Okuyama T**, Nakamura T, Yamaguchi M. Budding is useful to select high-risk patients in stage II well-differentiated or moderately differentiated colon adenocarcinoma. *Dis Colon Rectum* 2003; **46**: 1400-1406

37 **Morodomi T**, Isomoto H, Shirouzu K, Kakegawa K, Irie K, Morimatsu M. An index for estimating the probability of lymph node metastasis in rectal cancers. Lymph node metastasis and the histopathology of actively invasive regions of cancer. *Cancer* 1989; **63**: 539-543

38 **Prall F**. Tumour budding in colorectal carcinoma. *Histopathology* 2007; **50**: 151-162

39 **Eguchi T**, Nakanishi Y, Shimoda T, Iwasaki M, Igaki H, Tachimori Y, Kato H, Yamaguchi H, Saito D, Umemura S. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: analysis of 464 surgically resected cases. *Mod Pathol* 2006; **19**: 475-480

40 **Kim DU**, Lee JH, Min BH, Shim SG, Chang DK, Kim YH, Rhee PL, Kim JJ, Rhee JC, Kim KM, Shim YM. Risk factors of lymph node metastasis in T1 esophageal squamous cell carcinoma. *J Gastroenterol Hepatol* 2008; **23**: 619-625

41 **Chiba T**, Kawachi H, Kawano T, Kumagai J, Kitagaki K, Sekine M, Uchida K, Kobayashi M, Sugihara K, Eishi Y. Independent histological risk factors for lymph node metastasis of superficial esophageal squamous cell carcinoma; implication of claudin-5 immunohistochemistry for expanding the indications of endoscopic resection. *Dis Esophagus* 2010; **23**: 398-407

42 **Japan esophageal society**. Japanese classification of esophageal cancer. 10th ed. Tokyo: Kanehara, 2008

43 **Miyata H**, Yoshioka A, Yamasaki M, Nushijima Y, Takiguchi S, Fujiwara Y, Nishida T, Mano M, Mori M, Doki Y. Tumor budding in tumor invasive front predicts prognosis and survival of patients with esophageal squamous cell carcinomas receiving neoadjuvant chemotherapy. *Cancer* 2009; **115**: 3324-3334

44 **Koike M**, Kodera Y, Itoh Y, Nakayama G, Fujiwara M, Hamajima N, Nakao A. Multivariate analysis of the pathologic features of esophageal squamous cell cancer: tumor budding is a significant independent prognostic factor. *Ann Surg Oncol* 2008; **15**: 1977-1982

45 **Roh MS**, Lee JI, Choi PJ. Tumor budding as a useful prognostic marker in esophageal squamous cell carcinoma. *Dis Esophagus* 2004; **17**: 333-337

46 **Takubo K**, Aida J, Naomoto Y, Sawabe M, Arai T, Shiraishi H, Matsuura M, Ell C, May A, Pech O, Stolte M, Vieth M. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. *Hum Pathol* 2009; **40**: 65-74

S- Editor Song XX **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i11.500

World J Gastrointest Endosc 2012 November 16; 4(11): 500-505
ISSN 1948-5190 (online)

REVIEW

Endoscopic management of inflammatory bowel disease strictures

Raluca Vrabie, Gerald L Irwin, David Friedel

Raluca Vrabie, Gerald L Irwin, David Friedel, Winthrop University Hospital, 259 First Street, Mineola, NY 11501, United States
Author contributions: Vrabie R wrote the article; Irwin GL provided the CT image; Friedel D is the senior author for this paper.
Correspondence to: Raluca Vrabie, Assistant Professor, Winthrop University Hospital, 259 First Street, Mineola, NY 11501, United States. rvrabie@winthrop.org
Telephone: +1-516-6636905 Fax: +1-516-6634655
Received: September 7, 2012 Revised: October 12, 2012
Accepted: October 26, 2012
Published online: November 16, 2012

Abstract

Stricture formation is a common complication of Crohn's disease, occurring in approximately one third of all patients with this condition. While the traditional management of such strictures has been largely surgical, there have been case series going back three decades highlighting the potential role of endoscopic balloon dilation in this clinical setting. This review article summarizes the stricture pathogenesis, focusing on known clinical and genetic risk factors. It then highlights the endoscopic balloon dilation research to date, with particular emphasis on three large recent case series. It concludes by describing the literature consensus regarding specific methodology and presenting avenues for future investigations.

Key words: Stricture; Endoscopic dilation; Crohn's disease

Peer reviewers: Kenneth KY Wong, MD, PhD, Assistant Professor, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China; Alfredo José Lucendo, MD, PhD, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n, 13700 Tomelloso (Ciudad Real), Spain

Vrabie R, Irwin GL, Friedel D. Endoscopic management of inflammatory bowel disease strictures. *World J Gastrointest Endosc* 2012; 4(11): 500-505 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i11/500.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i11.500

INTRODUCTION

Crohn's disease is a chronic autoimmune disorder of the gastrointestinal tract, characterized by periods of disease activity and quiescence. The treatment is focused on prolonging the periods of inactivity, and minimizing the amount of inflammation when a flare does occur. However, 10%-15% of patients will have a continuous, unremitting course and at present, the disease is incurable[1].

DEMOGRAPHIC INFORMATION

The highest incidence of Crohn's disease has been reported in northern Europe (4-10.7/10^5) the United Kingdom (0.7-6.7/10^5) and North America (5.8-7.9/10^5). The prevalence of Crohn's disease in North America is 44-201/10^5; in Europe, the range is more variable, between 8-214/10^5[2]. The number of patients affected is rising in the rest of the world as well. In South Korea, comparing the interval 1986-1990 to 2001-2005, the incidence of Crohn's disease increased significantly from 0.05/10^5 to 1.3/10^5[3]. In China, the incidence of Crohn's disease incidence was found to be 1×10^5 and tripled in a decade of follow-up[3].

NATURAL HISTORY

The natural disease progression begins with aphthous ulcers, which progress to fistulae or strictures, more often in patients with ileal rather than colonic disease[4] The digestive segment affected tends to be stable over time[5] Approximately 40% patients will need surgery after 10

years of disease[6,7] and about 10% will have a permanent stoma[8]. Crohn's disease patients have a 1.52 greater mortality than the general population[9].

Strictures, which occur in approximately 1/3 of patients after 10 years of disease[5], are thought of as either inflammatory or fibrotic. Strictures and fistulae are often found in proximity of one another, either both being caused by the inflammation or the fistula developing to decompress the lumen from the increased wall tension caused by the stricture (Figure 1)[10]. Lumenal dilation proximal to the stricture site is considered an indication that the wall has lost its elasticity and the stricture is permanent. Strictures also frequently occur at anastomotic sites, where generally the disease is likely to recur first[4].

While there are medical options for addressing inflammatory strictures, the management of fibrotic ones has traditionally been thought of as largely surgical[11-13]. The role of endoscopy in the management of fibrotic strictures has not been well-defined, but several recent studies have shed significant light on this topic. Advantages of using endoscopic dilation over the more established surgical methods (strictureplasty or resection with primary anastomosis) include decreased invasiveness and adhesion formation, as well as preservation of intestinal length. Disadvantages include the need for repeat dilation.

This review article will describe the known risk factors for stricture formation, summarize the historical literature regarding endoscopic dilation of these strictures, and subsequently focus on three recent large studies on this subject, describing their findings and limitations.

PREDISPOSING FACTORS FOR STRICTURE FORMATION

Known factors predisposing to stricture formation can be broadly categorized into clinical presentation parameters, serologic markers and genetic susceptibility.

An analysis of a database of 600 European patients, followed for 15 years, and published this year in Gut, reveals that parameters that have been proven to correlate with poorer disease outcome are smoking, lower educational level, younger age at diagnosis and shorter disease duration prior to inclusion in the database[14]. Similar data can be found in other demographic groups. An Israeli population of over 200 Crohn's disease patients with an average follow-up interval of 12 years demonstrated that smoking and male gender are correlated with increased risk of complications[15]. A New Zealand patient database of over 700 patients revealed that younger age at diagnosis, complicated disease and ileal disease all correlate with increased risk of perirectal disease[16]. The clinical factors demonstrated to correlate specifically with stricture formation, according to the TREAT registry, are severity of disease at the time of stricture formation, with a hazard ratio (HR) of 2.35, (95%CI 1.35-4.09), duration of Crohn's disease, HR 1.02, (95%CI 1-1.04), and new corticosteroid use, HR 2.85, (95% CI 1.23-6.57)[17].

The role of serologic markers in predicting disease course is at this point not well defined, though generally pANCA positivity is thought to correlate with a more benign, ulcerative colitis-like clinical presentation, while antibodies to oligomannan (anti-Saccharomyces cerevisiae antibody), OmpC (*Escherichia coli* outer membrane porin C), *Pseudomonas florescens* associated sequence I2 (bacterial sequence I2) and CBir1 (flagellin) correlate with more complicated Crohn's disease[18-22].

NOD2/CADR15 remains the most established genetic predictor of complicated Crohn's disease, though it is not currently able to predict which patients should be targeted for more aggressive early intervention. Located on chromosome 16q12, *NOD2* is a disease susceptibility gene, which when mutated increases the risk of developing Crohn's. It is expressed intracellularly and is considered part of the innate bacterial sensing mechanism. In a recent metanalysis of 36 studies studying the role of the *NOD2* genotype on Crohn's disease[23] the relative risk of stricturing disease with any (one or more) mutant *NOD2* allele was 1.17 (95%CI 1.10-1.24, $P < 0.001$). The 3 major polymorphisms reported with Crohn's are *Arg*702*Trp* (SNP8), *Gly*908*Arg* (SNP12), *Leu*1007*insC* (SNP13). These polymorphisms have been associated with ileal disease, stenosis, and need for surgery[24] In the 10 studies that were able to analyze this further, the most likely mutation associated with stricturing disease was *Gly*908*Arg*, with a risk ratio of complicated disease of 1.33, sensitivity of 0.11 (95%CI 0.07-0.13) and a specificity of 0.93 (95%CI 0.88-0.96). Overall, the mutation most likely to correlate with an aggressive course was a homozygous mutation of *Leu*1007*insC*, with a AuROC of 0.98 but the confidence intervals of both the positive 2.6 (95% CI 0.4-16.6) and the negative 0.98 (95%CI 0.94-1.03) likelihood ratios cross 1. A recent analysis of banked blood from 593 patients with Crohn's disease also revealed that *Leu*1007*insC* (SNP13) was the most high risk allele of *NOD2*, with a $P < 0.001$ for complication risk versus patients without *NOD2* mutations[25] and an odds ratio (OR) of 13.61 (95%CI 2.62-250.70). Apart from *NOD2*, other genetic markers for Crohn's confirmed in multiple populations include ATG16L1 (autophagy-related 16-like 1 gene) and IL23R (interleukin 23 receptor gene), the latter in a protective role[26].

ENDOSCOPIC BALLOON DILATION-HISTORICAL BACKGROUND

While the predisposing factors leading to stricture formation have not been fully elucidated, the generally accepted treatment paradigm has traditionally been surgical. This view has been challenged by novel endoscopic techniques. A review article[27] evaluated both surgical stricturoplasties and endoscopic balloon dilation studies performed between 1980 and 2009. 574 patients were studied in the endoscopic balloon dilation group, on whom a total of 1003 procedures were performed. There was a median technical success rate of 90%, a median intention-to-treat surgical recurrence rate of 27.6% (after

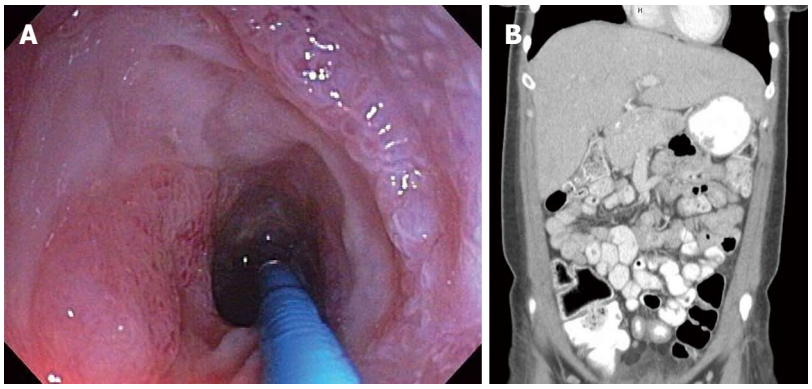


Figure 1 Endoscopic and computed tomography imaging of a terminal ileum stricture in a patient with Crohn's disease. A: Endoscopic imaging of a terminal ileum stricture in a patient with Crohn's disease; B: Computed tomography imaging of a terminal ileum stricture in a patient with Crohn's disease.

a mean follow-up period of 21 mo) and a major complications rate of 3%. There was no uniform approach in terms of the technique used (including balloon size, time of insufflation, or use of intralesional steroid injections) and very few of the 23 papers included reported the site-specific recurrence rate. The surgical data from the same review article, which analyzed 1958 patients, revealed an equivalent median surgical recurrence rate of 24% after a median follow-up of 46 mo. Of note, the surgical complication rate was higher than the endoscopic one, 5% *vs* 3%.

A smaller, earlier and more detailed review[28] focused only on endoscopic dilation demonstrates similar results. The observation interval was 1990-2007. The total number of Crohn's patients included in this review was 347, with 353 strictures and 695 dilation sessions. The technical success rate was 86%, long-term clinical success rate was 58% and the rate of major complications 2%. The vast majority of these complications were perforations. The majority of the patients in these studies (66%) had dilation at the site of a prior surgery. In contrast to the former review article, the percent of patients requiring surgery after dilation (after successful dilation) was higher at 42%, perhaps partially explained by the longer follow-up period of 33 mo. The mean interval between dilation and surgery was 15 mo, and more than 2/3 of the patients in whom the procedure was performed successfully were able to avoid surgery during the entire follow-up period. The average patient age was 54 years old, the average time between diagnosis and dilation was 13 years. 29% patients had been on immunosuppressive therapy at the time of the dilation. The mean stricture length was 2.7 cm, and < 5 cm in 84% patients. Most studies did not use intra-lesional steroid injections, and the maximum balloon caliber was 18-25 mm. There was no consensus on insufflation technique, with both incremental increase and initial largest possible diameter being used. The time spent dilating was also highly variable, from 2 min to 1 h. The mean number of dilations per patient was 2.2. 14% patients were considered endoscopic failures, with angulated stenosis being the most common reason for this. The endoscopists in these studies applied the same technique to all the patients in their respective studies, with no alteration of procedure based on stricture characteristics or general disease state. An interesting finding of this review was that a stricture of $\leqslant$ 4 cm in length had an OR of 4.01 for a surgery-free outcome.

ENDOSCOPIC BALLOON DILATION-RECENT DATA

The data on this topic is limited by very small numbers. The studies included in the above two reviews are all less than 60 patients, retrospective and without a control group. However, three recent larger studies have been performed to help determine the utility of endoscopic dilation of Crohn's strictures. These studies are larger, single center cohort studies. Two are prospective, and the largest and most recent one is a retrospective chart review. The patients included were generally middle-aged (40-50 s). A stricture was defined as inability to traverse a segment of colon with the scope or a radiographically determined area of luminal narrowing with corresponding obstructive symptoms. Therapeutic success was defined as the ability to pass the scope through the stricture post-dilation. All three studies averaged about 2 dilations per patient. All the studies used a Boston Scientific through the scope balloon, 12-25 mm in diameter, and conscious sedation (Table 1). Strictures were generally anastomotic with the exception of the Mueller *et al* study, in which 69% had *de novo* strictures. Only the Scimeca *et al*[29] study recorded the number of smokers in the group (43%), and this proved to be insignificant as an outcome variable in that study.

The Gustavsson *et al*[30] study was the largest one to date, including a total of 178 patients, and the one with the longest follow-up period (median 12 years). It is a retrospective case series. Most patients had either ileal or ileocolonic disease, and approximately 40% had stricturing disease at presentation. The management was homogeneous, which is a weakness of the study, in that patients enrolled earlier in the study were dilated whenever they were scoped (19%), whereas patients enrolled later were only dilated based on symptoms. 80% of the dilations were performed on anastomotic strictures. 1% of the cases were done with general anesthesia. Another study weakness is that the length of the strictures was not recorded. 1.4% of the cases were complicated by bowel perforation. The largest balloon diameter (25 mm) had an overall 9.3% complication rate, as compared to 3.5%

Table 1 Summary of significant endoscopic stricture dilation studies

Ref.	Study design	*n*	dilations	Stricture length (cm)	Stricture diameter (mm)	Maximum insufflation dia. (mm)	Insufflation interval (s)	Initial success rate (%)	Follow-up interval	Long-term success rate (%)	Major complication rate(%)
Scimeca *et al*[29]	Prospective, single center cohort	37	72	3.4 (2-6)	6 (3-8)	10-20	60-90	51	26.3 mo (2-61)	89	0
Gustavsson *et al*[30]	Retrospective single center cohort	178	776	NA	> 5 mm	12-25	60-180	89	12 yr	52	5.3
Mueller *et al*[31]	Prospective, single center cohort	55	93	3 (1-25)	NA	15-18	60	95	44 mo (1-103)	76	2

NA: Not available.

Table 2 Major complications related to endoscopic balloon dilation of strictures

Ref.	Complication
Gustavsson *et al*[29]	1.4% bowel perforation 1% major bleeding 1.3% minor bleeding 1.2% abdominal pain or fever
Scimeca *et al*[30]	None
Mueller *et al*[31]	2% bowel perforation

for the other sizes ($P < 0.01$). Patients fared equally well whether their strictures were anastomotic or *de novo*. At 5 years, 52% patients had at most one additional dilation, and 36% had a surgical resection. A strength of the study is that several different endoscopists of various skill level performed the dilations, which therefore makes this data more applicable to centers where there is at present no established expertise in this technique.

The Scimeca *et al*[29] study followed prospectively 37 Crohn's patients (39 strictures) during 72 dilations, at a single center in Italy. Almost all the strictures (97%) were post-surgical, with 77% being at ileo-colonic anastomosis sites. Patients included in the study had at least 2 episodes of clinical and radiologic obstruction in the 6 mo preceding the study, and at best an incomplete response to medical therapy. A maximum of four attempts at dilation were made per endoscopic session. There was a 51% rate of success after the first dilation, but an 89% rate of success after subsequent dilations. This group had no complications at all (Table 2), which perhaps is also related to the lower initial success rate compared to the other 2 studies cited (51% *vs* 89%-95% for the other 2). A weakness of the study is that patients were rescoped in 4-6 wk when the endoscopist judged the initial dilation to be incomplete, as this is a subjective assessment that is hard to replicate in other centers. 11% patients required surgery. An strength of the study is that there was no loss to follow-up, but this study has the shortest mean follow-up period of the three presented, namely about 2 years.

The Mueller *et al*[31] study is a German prospective single center study of 55 patients, with 74 symptomatic strictures, which resulted in 93 dilations. As opposed to the other studies cited here, the majority of patients in this study (69%) had *de novo* strictures. The inclusion criteria were clinical obstructive symptoms and sonographic or radiologic evidence of stricture. The default approach was direct visualization, but fluoroscopic guidance was employed when visualization was not possible (unclear how often this was necessary). There was no stricture diameter or length parameter used to determine eligibility, and some of the strictures dilated were as long as 25 cm. There was a 95% initial success rate, and 76% patients never required repeat treatment over the period of follow-up. 24% patients did eventually receive surgery over the follow-up period, on average within the first 6 wk (0-20 mo). There was a statistically significant correlation between the need for surgery and stricture length ($P = 0.006$) with the average stricture requiring surgery being 7.5 cm *vs* 2.5 cm for the strictures amenable to endoscopic therapy. One patient was perforated and 2 patients could not be dilated due to stricture anatomy.

RECOMMENDED ENDOSCOPIC APPROACH

In summary, these studies demonstrate an experience with endoscopic balloon dilation of Crohn's disease strictures dating back almost 2 decades. These procedures can be done with conscious sedation, on an outpatient basis. The perforation rate of up to 2% is considered acceptable, since the alternative as well as the perforation management is surgical. Boston Scientific balloons in the range of 10-20 mm are recommended, since larger 25 mm balloons do seem to increase the perforation risk. The response to dilation is similar whether the stricture is *de novo* or anastomotic. No consensus has been reached on the optimal length of stricture amenable to endoscopic manipulation, though based on the average length in the studies included 5 cm would be a reasonable cut-off. This would also make inherent sense considering the Boston Scientific balloon is 5.5 cm in length. The exact methodology by which the strictures should be dilated (i.e., how many minutes should the inflated balloon be held in position, or how many sequential insufflations should be attempted per procedure) has not been standardized yet, though dilating each balloon through the 3 diameters it can accommodate and holding the insufflated balloon at the stricture site for 30-60 s would be a reasonable starting point. Patients should be told that generally endoscopic balloon dilation requires two procedures to

achieve patency over a period of 5 years, and has long-term efficacy in at least half the patients it has been attempted in. These recommendations are concordant with expert opinions on this topic[32], though other sources still consider strictureplasty the first line approach[12].

It is difficult to compare the endoscopic results with the surgical literature. The data for segmental resection and anastomosis is homogeneous, as this surgery is not exclusively employed for stricture management. In addition, there are 15 distinct strictureplasty methods described[33], though the two most commonly employed for Crohn's are Heineke-Mikulicz and Finney. According to a 2007 metanalysis which analyzed 1112 patients with a total of 3259 strictureplasties, this approach has a complication rate of 4% (leak, fistula, abscess) and a recurrence rate of 28% by 5 years[34]. Though the average number of procedures per patient were > 2 in this period of time, the authors point out that only 3% of the repeat procedures involved re-instrumenting a site that had been operated on prior (the vast majority of the recurrences occurred at new sites of stricture). The majority of the strictures analyzed in the metanalysis were small bowel, which would not be amenable to dilation by traditional endoscopic techniques. In terms of laparoscopic resection, a large case series of over 300 patients from Mount Sinai Hospital in New York reported a postoperative complication rate of 13% (primarily obstruction and leak), which makes the endoscopic option more attractive, at least in the short term[35].

FUTURE RESEARCH AVENUES

It would be important to understand, in terms of the natural history of Crohn's disease, at which point intervening on a stricture would yield the maximum benefit. Perhaps it is not when the area has become fibrotic, but rather soon after a flare has resolved, that the initial dilation should be performed. It is unclear which of the medical treatment options available for the treatment of Crohn's would be most efficacious in preventing stricture formation. It would be useful to understand if injecting (with steroids or infliximab) or stenting the stricture would decrease the recurrence rate, as the current literature on this topic is scarce and lacking consensus[36-38]. It would also be important to determine the minimum number of dilations required to achieve operator proficiency, the optimal characteristics of a stricture that would make it amenable to endoscopic intervention, and the desirable diameter to which a stricture should be dilated such as to avoid both perforations and future obstructive symptoms.

REFERENCES

1 **Munkholm P**, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995; **30**: 699-706
2 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794
3 **Ahuja V**, Tandon RK. Inflammatory bowel disease in the Asia-Pacific area: a comparison with developed countries and regional differences. *J Dig Dis* 2010; **11**: 134-147
4 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963
5 **Louis E**, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; **49**: 777-782
6 **Solberg IC**, Vatn MH, Høie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol* 2007; **5**: 1430-1438
7 **Wolters FL**, Russel MG, Sijbrandij J, Schouten LJ, Odes S, Riis L, Munkholm P, Langholz E, Bodini P, O'Morain C, Katsanos K, Tsianos E, Vermeire S, Van Zeijl G, Limonard C, Hoie O, Vatn M, Moum B, Stockbrügger RW. Disease outcome of inflammatory bowel disease patients: general outline of a Europe-wide population-based 10-year clinical follow-up study. *Scand J Gastroenterol Suppl* 2006; (**243**): 46-54
8 **Cosnes J**. Crohn's disease phenotype, prognosis, and long-term complications: what to expect? *Acta Gastroenterol Belg* 2008; **71**: 303-307
9 **Canavan C**, Abrams KR, Mayberry JF. Meta-analysis: mortality in Crohn's disease. *Aliment Pharmacol Ther* 2007; **25**: 861-870
10 **Oberhuber G**, Stangl PC, Vogelsang H, Schober E, Herbst F, Gasche C. Significant association of strictures and internal fistula formation in Crohn's disease. *Virchows Arch* 2000; **437**: 293-297
11 **Saunders BP**, Brown GJ, Lemann M, Rutgeerts P. Balloon dilation of ileocolonic strictures in Crohn's disease. *Endoscopy* 2004; **36**: 1001-1007
12 **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62
13 **Samimi R**, Flasar MH, Kavic S, Tracy K, Cross RK. Outcome of medical treatment of stricturing and penetrating Crohn's disease: a retrospective study. *Inflamm Bowel Dis* 2010; **16**: 1187-1194
14 **Cosnes J**, Bourrier A, Nion-Larmurier I, Sokol H, Beaugerie L, Seksik P. Factors affecting outcomes in Crohn's disease over 15 years. *Gut* 2012; **61**: 1140-1145
15 **Mazor Y**, Maza I, Kaufman E, Ben-Horin S, Karban A, Chowers Y, Eliakim R. Prediction of disease complication occurrence in Crohn's disease using phenotype and genotype parameters at diagnosis. *J Crohns Colitis* 2011; **5**: 592-597
16 **Eglinton TW**, Roberts R, Pearson J, Barclay M, Merriman TR, Frizelle FA, Gearry RB. Clinical and genetic risk factors for perianal Crohn's disease in a population-based cohort. *Am J Gastroenterol* 2012; **107**: 589-596
17 **Lichtenstein GR**, Olson A, Travers S, Diamond RH, Chen DM, Pritchard ML, Feagan BG, Cohen RD, Salzberg BA, Hanauer SB, Sandborn WJ. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. *Am J Gastroenterol* 2006; **101**: 1030-1038
18 **Vasiliauskas EA**, Plevy SE, Landers CJ, Binder SW, Ferguson DM, Yang H, Rotter JI, Vidrich A, Targan SR. Perinuclear antineutrophil cytoplasmic antibodies in patients with Crohn's disease define a clinical subgroup. *Gastroenterology* 1996; **110**: 1810-1819
19 **Vasiliauskas EA**, Kam LY, Karp LC, Gaiennie J, Yang H, Targan SR. Marker antibody expression stratifies Crohn's disease into immunologically homogeneous subgroups with distinct clinical characteristics. *Gut* 2000; **47**: 487-496

20 **Mow WS**, Vasiliauskas EA, Lin YC, Fleshner PR, Papadakis KA, Taylor KD, Landers CJ, Abreu-Martin MT, Rotter JI, Yang H, Targan SR. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* 2004; **126**: 414-424

21 **Landers CJ**, Cohavy O, Misra R, Yang H, Lin YC, Braun J, Targan SR. Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. *Gastroenterology* 2002; **123**: 689-699

22 **Papadakis KA**, Yang H, Ippoliti A, Mei L, Elson CO, Hershberg RM, Vasiliauskas EA, Fleshner PR, Abreu MT, Taylor K, Landers CJ, Rotter JI, Targan SR. Anti-flagellin (CBir1) phenotypic and genetic Crohn's disease associations. *Inflamm Bowel Dis* 2007; **13**: 524-530

23 **Adler J**, Rangwalla SC, Dwamena BA, Higgins PD. The prognostic power of the NOD2 genotype for complicated Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2011; **106**: 699-712

24 **Rieder F**, Lawrance IC, Leite A, Sans M. Predictors of fibrostenotic Crohn's disease. *Inflamm Bowel Dis* 2011; **17**: 2000-2007

25 **Lichtenstein GR**, Targan SR, Dubinsky MC, Rotter JI, Barken DM, Princen F, Carroll S, Brown M, Stachelski J, Chuang E, Landers CJ, Stempak JM, Singh S, Silverberg MS. Combination of genetic and quantitative serological immune markers are associated with complicated Crohn's disease behavior. *Inflamm Bowel Dis* 2011; **17**: 2488-2496

26 **Weersma RK**, Stokkers PC, van Bodegraven AA, van Hogezand RA, Verspaget HW, de Jong DJ, van der Woude CJ, Oldenburg B, Linskens RK, Festen EA, van der Steege G, Hommes DW, Crusius JB, Wijmenga C, Nolte IM, Dijkstra G. Molecular prediction of disease risk and severity in a large Dutch Crohn's disease cohort. *Gut* 2009; **58**: 388-395

27 **Wibmer AG**, Kroesen AJ, Gröne J, Buhr HJ, Ritz JP. Comparison of strictureplasty and endoscopic balloon dilatation for stricturing Crohn's disease--review of the literature. *Int J Colorectal Dis* 2010; **25**: 1149-1157

28 **Hassan C**, Zullo A, De Francesco V, Ierardi E, Giustini M, Pitidis A, Taggi F, Winn S, Morini S. Systematic review: Endoscopic dilatation in Crohn's disease. *Aliment Pharmacol Ther* 2007; **26**: 1457-1464

29 **Scimeca D**, Mocciaro F, Cottone M, Montalbano LM, D' Amico G, Olivo M, Orlando R, Orlando A. Efficacy and safety of endoscopic balloon dilation of symptomatic intestinal Crohn's disease strictures. *Dig Liver Dis* 2011; **43**: 121-125

30 **Gustavsson A**, Magnuson A, Blomberg B, Andersson M, Halfvarson J, Tysk C. Endoscopic dilation is an efficacious and safe treatment of intestinal strictures in Crohn's disease. *Aliment Pharmacol Ther* 2012; **36**: 151-158

31 **Mueller T**, Rieder B, Bechtner G, Pfeiffer A. The response of Crohn's strictures to endoscopic balloon dilation. *Aliment Pharmacol Ther* 2010; **31**: 634-639

32 **Felley C**, Vader JP, Juillerat P, Pittet V, O'Morain C, Panis Y, Vucelic B, Gonvers JJ, Mottet C, Froehlich F, Michetti P. Appropriate therapy for fistulizing and fibrostenotic Crohn's disease: Results of a multidisciplinary expert panel - EPACT II. *J Crohns Colitis* 2009; **3**: 250-256

33 **Ambe R**, Campbell L, Cagir B. A comprehensive review of strictureplasty techniques in Crohn's disease: types, indications, comparisons, and safety. *J Gastrointest Surg* 2012; **16**: 209-217

34 **Yamamoto T**, Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2007; **50**: 1968-1986

35 **Nguyen SQ**, Teitelbaum E, Sabnis AA, Bonaccorso A, Tabrizian P, Salky B. Laparoscopic resection for Crohn's disease: an experience with 335 cases. *Surg Endosc* 2009; **23**: 2380-2384

36 **East JE**, Brooker JC, Rutter MD, Saunders BP. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. *Clin Gastroenterol Hepatol* 2007; **5**: 1065-1069

37 **Swaminath A**, Lichtiger S. Dilation of colonic strictures by intralesional injection of infliximab in patients with Crohn's colitis. *Inflamm Bowel Dis* 2008; **14**: 213-216

38 **Rejchrt S**, Kopacova M, Brozik J, Bures J. Biodegradable stents for the treatment of benign stenoses of the small and large intestines. *Endoscopy* 2011; **43**: 911-917

S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i11.506

World J Gastrointest Endosc 2012 November 16; 4(11): 506-512
ISSN 1948-5190 (online)

BRIEF ARTICLE

Losartan to prevent hyperenzymemia after endoscopic retrograde cholangiopan-creatography: A randomized clinical trial

Tomas Sjöberg Bexelius, John Blomberg, Yun-Xia Lu, Hans-Olof Håkansson, Peter Möller, Carl-Eric Nordgren, Urban Arnelo, Jesper Lagergren, Mats Lindblad

Tomas Sjöberg Bexelius, John Blomberg, Yun-Xia Lu, Jesper Lagergren, Mats Lindblad, Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, 176 70 Stockholm, Sweden
John Blomberg, Urban Arnelo, Mats Lindblad, Department of Surgery, Gastro Center, Karolinska University Hospital, 176 70 Stockholm, Sweden
Hans-Olof Håkansson, Peter Möller, Carl-Eric Nordgren, Department of Surgery, Kalmar County Hospital, 391 85 Kalmar, Sweden
Urban Arnelo, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, 176 70 Stockholm, Sweden
Author contributions: Bexelius TS conceived the study and performed the study design and drafted the manuscript; Blomberg J performed endoscopies and wrote the manuscript; Lu YX performed the statistical analysis and helped with the study design; Arnelo U, Håkansson HO and Möller P recruited patients, performed endoscopies and revised the manuscript; Nordgren CE contributed to manuscript writing; Lagergren J conceived the study, its design and edited the manuscript; Lindblad M concieved the study, performed endoscopies, and aided in writing the manuscript; All authors read and approved the final manuscript.
Supported by The Swedish Society of Medicine, The Lisa and Johan Grönberg Foundation
Correspondence to: Tomas Sjöberg Bexelius, MD, PhD, Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, Norra Stationsgatan 67, 176 70 Stockholm, Sweden. tomas.s.bexelius@ki.se
Telephone: +46-8-517769-40 Fax: +46-8-51776280
Received: August 30, 2011 Revised: August 27, 2012
Accepted: October 26, 2012
Published online: November 16, 2012

Abstract

AIM: To study if the angiotensin Ⅱ receptor blockers (ARB) losartan counteracts pancreatic hyperenzymemia as measured 24 h after endoscopic retrograde cholangiopancreatography (ERCP).

METHODS: A triple-blind and placebo-controlled randomized clinical trial was performed at two Swedish hospitals in 2006-2008. Patients over 18 years of age undergoing ERCP, excluding those with current pancreatitis, current use of ARB, and severe disease, such as sepsis, liver and renal failure. One oral dose of 50 mg losartan or placebo was given one hour before ERCP. The relative risk of hyperenzymemia 24 h after ERCP was estimated using multivariable logistic regression, and expressed as odds ratio with 95% confidence intervals (CIs), including adjustment for potential remaining confounding.

RESULTS: Among 76 participating patients, 38 were randomized to the losartan and the placebo group, respectively. The incidence rates of hyperenzymemia and acute pancreatitis among all 76 participating patients were 21% and 12%, respectively. Hyperenzymemia was detected in 9 and 7 patients in the losartan and placebo group, respectively. There were no major differences between the comparison groups regarding cannulation difficulty, findings, or proportion of patients requiring drainage of the bile ducts. There were, however, more pancreatic duct injections, a greater extent of pancreatography, and more biliary sphincterotomies in the losartan group than in the placebo group. Losartan was not associated with risk of hyperenzymemia compared to the placebo group after multi-varible logistic regression analysis (odds ratio 1.6, 95%CI 0.3-7.8).

CONCLUSION: In this randomized trial 50 mg losartan given orally had no prophylactic effect on development of hyperenzymemia after ERCP.

Key words: Renin-angiotensin system; Pancreatitis; Prophylaxis; Placebo-controlled trial

Peer reviewers: Mohammad Al-Haddad, MD, Assistant Professor of Clinical Medicine, Director, Endoscopic Ultrasound Fellowship Program, Indiana University School of Medicine, 550 N. University Blvd, Suite 4100, Indianapolis, IN 46202, United States; Viktor Ernst Eysselein, MD, Professor of Medicine, Division of Gastroenterology, Harbor-UCLA Medical Center, 1000 W. Carson Street, Box 483, Torrance, CA 90509, United States

Bexelius TS, Blomberg J, Lu YX, Håkansson HO, Möller P, Nordgren CE, Arnelo U, Lagergren J, Lindblad M. Losartan to prevent hyperenzymemia after endoscopic retrograde cholangiopancreatography: A randomized clinical trial. *World J Gastrointest Endosc* 2012; 4(11): 506-512 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i11/506.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i11.506

INTRODUCTION

Acute pancreatitis is a serious complication after endoscopic retrograde cholangio-pancreatography (ERCP) affecting 1%-10% of the patients[1-5]. Elevation of pancreatic enzymes in serum (hyperenzymemia) is linked with pancreatitis, and occurs in 25%-40% of the patients after ERCP[1,2,6,7]. Known risk factors for post-ERCP pancreatitis include female sex, previous pancreatitis, and procedure-related factors, including pancreatic duct injection, cannulation difficulties, and use of sphincterotomy[3-5]. Several agents have been evaluated in the prevention of post-ERCP pancreatitis in clinical trials. Some groups of medications have not been associated with convincing effects, e.g., anti-secretary drugs[6,8-15], protease inhibitors[1,2,6,16-21], heparin[22], and other anti-inflammatory drugs[7,23-25]. Other drugs, however, have shown promising effects, e.g., interleukin 10[26], glyceryl trinitrate[27], and antibiotics[28]. To date, however, there is no established medical prophylaxis against pancreatitis after ERCP. There is support for the new hypothesis that angiotensin Ⅱ type 1 receptor blockers (ARB) prevent the development of pancreatitis or pancreatic hyperenzymemia after ERCP. Acute pancreatitis activates a local pancreatic renin-angiotensin system as well as the circulating renin-angiotensin system[29,30]. Experimental research has shown that the angiotensin Ⅱ type receptor and angiotensinogen are highly expressed in inflamed pancreatic tissue, and that administration of angiotensin Ⅱ increases the secretion of pancreatic enzymes[31]. This increased secretion can in turn be blocked by the ARB losartan (Cozaar®)[31,32]. Moreover, losartan can prevent induced acute pancreatitis in rats[32-34]. Furthermore, a recent case-control study by our group indicated a decreased risk of acute pancreatitis among patients treated with ARB[35]. We have therefore conducted a clinical trial to test whether losartan prevents pancreatic hyperenzymemia after ERCP.

MATERIALS AND METHODS

A triple-blind, placebo-controlled randomized trial was performed at two Swedish hospitals, Karolinska University Hospital and Kalmar County Hospital, during the study period May 1, 2006 through October 31, 2008. There was a temporary intermission in the inclusion of patients during the period October 31, 2007 to May 1, 2008 to allow manufacturing of additional placebo capsules because of a restricted durability. The performing endoscopists recruited study patients. A capsule of 50 mg losartan or an identical capsule of placebo was given orally one hour before the ERCP. The dose was selected to minimize adverse side effects and yet ensure adequate penetration to the pancreatic tissue[36,37]. The capsules were manufactured by Apoteket AB Produktion och Laboratoriers. The primary study outcome was occurrence of hyperenzymemia 24 h after ERCP. Hyperenzymemia was defined as plasma levels of pancreatic amylase or lipase at least three times above the upper reference level. Post-ERCP pancreatitis was a secondary outcome, defined as persistent upper abdominal pain combined with hyperenzymemia 24 h after ERCP.

Patients

Eligible for the study were patients older than 18 years, scheduled for ERCP. The study aimed to investigate first-time ERCP patients, and therefore set an arbitrarily chosen time limit to one year since last ERCP to be included in the study. Other exclusion criteria were: previous ERCP within one year, current elevation of pancreatic amylase or lipase, ongoing acute or chronic pancreatitis, current use of ARB or angiotensin I converting enzyme inhibitor, bilateral renal artery stenosis (or unilateral in patients with a single kidney), known hypersensitivity to ARB, pregnancy, breastfeeding, or predefined severe disease (ongoing sepsis, disseminated intravascular coagulopathy, acute circulatory collapse, severe dehydration, hypovolemia, severe renal insufficiency, or severe liver failure). The participating patients were asked about their medical history and underwent a physical examination. Measurements of blood pressure and heart rate, and assessment of pain on a Visual Analogue Scale were performed at baseline (one hour before the ERCP) and 24 h after the ERCP. Blood pressure and heart rate were also registered hourly until 6 h after the procedure, and later if needed. Blood samples were collected at baseline, and at one, four, and 24 h after the ERCP. In all other respects, the ERCP procedure and ensuing patient care followed the standard clinical routines.

Randomization and blinding

The included patients were randomized to the losartan group or the placebo group by use of consecutive closed study envelopes containing the individual study code, the case report form and the selected capsule. The study coordinator assigned active or placebo drug using computer generated random numbers. The randomization was made in blocks of 10 with equal distribution of active and placebo drugs at the participating centres. The study coordinator, who was not involved either in the patient care or in the analysis of the data, held the key to the

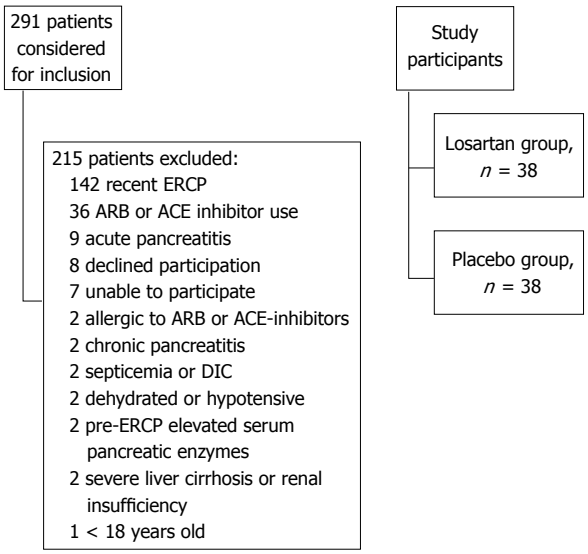


Figure 1 Flowchart of the patients who underwent endoscopic retrograde cholangio-pancreatography and were considered for inclusion in the study. DIC: Disseminated intravascular coagulation; ECRP: Endoscopic retrograde cholangiopancreatography; ARB: Angiotensin Ⅱ receptor blockers; ACE: Angiotensin Ⅰ converting enzyme.

study code. The participating patients, the endoscopists performing the ERCP, and the evaluators of the outcome were all kept unaware of the drug used until after the analyses.

Endoscopic retrograde cholangiopancreatography

The included patients fasted for 6 h before the ERCP. During the ERCP procedure, the patients received midazolam or diazepam for sedation and ketobemidone (Ketogan®) for analgesia. Glucagon or butylscopolamine (Buscopan®) was given to reduce intestinal motility if needed. Omnipaque [140-240 mgI/mL (GE Healthcare, CA, United States)] was used as contrast medium to visualize the biliary and pancreatic ducts. All participating endoscopists were experienced in ERCP. The endoscopist documented the following data immediately after completing the ERCP: indication for ERCP, degree of cannulation difficulty [easy, medium, difficult (> 15 attempts or > 5 min for deep cannulation after initial cholangio- or pancreatography), or failed], findings, degree of contrast filling of the pancreatic duct, number of contrast injections in the pancreatic duct, endoscopic procedures and interventions performed, and duration of the procedure.

Ethics

All participants signed written informed consent before inclusion. The regional ethical committee in Stockholm and the Medical Products Agency in Sweden approved the study. The trial was registered according to regulation formulated by the European Medicines Agency and Good Clinical Practice[38,39].

Statistical analysis

The sample size was estimated on the basis of the following assumptions: (1) an incidence of hyperenzymemia of 40%; (2) a reduction of hyperenzymemia to 10% in the losartan group; (3) a significance level (alpha) of 0.05; and (4) a power of 80%. Using two-sample comparison of proportions, the corresponding sample size was 38 patients in each group. We evaluated all patients included in the group to which they were randomized, i.e., according to the analytical rule of intention to treat. To assess the impact of missing outcome data, we analyzed the data using the method of last observation carried forward[40]. The Fisher exact test or χ^2 test was used for analysis of categorical variables. An analysis of variance or median test was performed for continuous data. To adjust for any imbalance of potentially confounding factors occurring in spite of randomization, we used multivariable logistic regression to estimate the relative risk of hyperenzymemia by calculating odds ratios (OR) with 95% confidence interval (CI). The following variables were adjusted for in the final multivariable model: sex, age (grouped into < or ⩾ 65 years), body mass index (BMI, expressed as kg/m^2 and categorized as < 20, 20-25, or > 25), history of pancreatitis (yes or no), study center (Karolinska University Hospital or Kalmar County Hospital), and ERCP duration (continuous variable). Other potential confounders, including degree of technical difficulties during ERCP, sphincterotomy, biliary drainage, and time between drug intake and ERCP, were tested in the regression model, but since they did not influence the risk estimates but only diluted the precision of the estimates they were not included in the final model. The statistical analyses were performed with SAS Statistical Package (version 9.0, SAS Institute Inc., Cary, NC, United States).

RESULTS

Study participants and procedures

Among 291 patients considered for inclusion, 215 were excluded. The reasons for these exclusions are listed in Figure 1. The most common reason for exclusion was recent ERCP (n = 142). Among the remaining 76 patients, 38 were randomized to the losartan group and 38 to the placebo group. Some characteristics of the study participants are presented in Table 1. The distribution of patients between the participating centres was equal in the comparison groups. Men were overrepresented in the losartan group. The distributions by age, BMI, history of pancreatitis, and the indications for the ERCP were equal between the groups, although there were fewer patients with jaundice and cholangitis in the losartan group (Table 1). However, there were no statistically significant differences in between the groups. At baseline the mean arterial blood pressure was the same, 100 mm Hg, in the two groups, but 24 h after the ERCP it was lower in the losartan group than in the placebo group (93 mmHg *vs* 98 mmHg; P < 0.05). As shown in Table 2, there were no major differences between the comparison groups regarding cannulation difficulty, findings, or proportion of patients requiring drainage of the bile ducts. There were,

Table 1 Characteristics of the 76 participating patients and indications for their endoscopic retrograde cholangiopancreatography *n* (%)

Characteristic	Losartan group	Placebo group
Total	38 (100)	38 (100)
Study centre		
Karolinska	19 (50)	19 (50)
Kalmar	19 (50)	19 (50)
Sex		
Male	22 (58)	16 (42)
Female	16 (42)	22 (58)
Age, yr		
< 65	13 (34)	14 (37)
⩾ 65	25 (66)	24 (63)
Body mass index, kg/m^2		
< 20	3 (8)	2 (5)
20-25	14 (37)	14 (37)
> 25	7 (18)	9 (24)
Unknown	14 (37)	13 (34)
Previous pancreatitis		
No	34 (89)	35 (92)
Yes	4 (11)	3 (8)
Indication for ERCP[1]		
Jaundice without cholangitis	20 (53)	21 (55)
Jaundice with cholangitis	7 (18)	9 (24)
Suspected tumour in pancreas or bile ducts	10 (26)	13 (34)
Suspected benign disease, i.e., biliary lithiasis, stricture or other disease	20 (53)	16 (42)

[1]Since each procedure could have several indications, the sum of percentages could be > 100. ECRP: Endoscopic retrograde cholangiopancreatography.

however, more pancreatic duct injections, a greater extent of pancreatography, and more biliary sphincterotomies in the losartan group than in the placebo group (Table 2). No patient received pancreatic stent. No patients with especially high risk of post-ERCP pancreatitis entered the study, e.g., individuals with sphincter Oddi's dysfunction, and no high risk procedures, e.g., sphincter Oddi manometry, duct balloon dilatation, or pancreatic sphincterotomy, were performed.

Pancreatic enzyme levels

The incidence rates of hyperenzymemia and acute pancreatitis among all 76 participating patients were 21% and 12%, respectively. In total, 9 patients in the losartan group and 7 patients in the placebo group showed hyperenzymemia 24 h after ERCP (P = 0.51) (Table 3). No decreased risk of hyperenzymemia was found in the losartan group compared to the placebo group in the multivariable adjusted regression model (OR 1.6, 95%CI 0.3-7.8). The median serum amylase concentration at baseline was similar in the two groups (0.44 in the losartan group and 0.46 in the placebo group; P = 0.64). No significant differences in the amylase or lipase values one hour post-ERCP in the comparison groups were seen (data not shown). There was no statistically significant difference in median serum amylase between the groups 24 h after ERCP (0.62 in the losartan group and 0.82 in the placebo group, P = 0.33). Hyperamylasemia occurred

Table 2 Distribution of procedure-related findings at endoscopic retrograde cholangiopancreatography in the 76 participating patients *n* (%)

Finding/procedure[1]	Losartan group	Placebo group
Total	38 (100)	38 (100)
Cannulation of the common bile duct		
Cannulation difficulty[2]		
Easy or medium	27 (71)	27 (71)
Difficult or failed	10 (26)	9 (24)
Pancreatography		
Number of pancreatic duct injections[2]		
None	21 (55)	24 (63)
1-3	15 (39)	11 (29)
⩾ 4	1 (3)	2 (5)
Extent of pancreatography[2]		
None	21 (55)	24 (63)
Main duct	12 (31)	11 (29)
First branch, second branch, and acinarisation	4 (11)	2 (5)
Procedure-related findings in bile ducts[2]		
Normal	5 (13)	3 (8)
Gallstone	13 (34)	14 (37)
Suspected cancer	6 (16)	8 (21)
Dilatation, benign or undetermined stricture, or anomaly	14 (37)	10 (26)
Procedure-related findings in pancreas[2]		
Not contrast-filled	21 (55)	24 (63)
Normal	13 (34)	10 (26)
Suspected cancer	0 (0)	1 (3)
Dilatation	3 (8)	1 (3)
Endoscopic procedure		
Biliary sphincterotomy		
No	11 (29)	14 (37)
Yes	27 (71)	24 (63)
Biliary stenting		
No	24 (63)	23 (61)
Yes	14 (37)	15 (39)
ERCP time, min[2]		
< 30	13 (34)	10 (26)
⩾ 30	22 (58)	26 (68)
Time between intake of losartan or placebo capsule and ERCP, min		
< 60	9 (24)	7 (18)
⩾ 60	29 (76)	31 (82)

[1]The endoscopist assessed degree of technical difficulty; [2]The total number of participants was 38 patients in each variable, and a sum < 38 indicate missing values between n = 2-5. ECRP: Endoscopic retrograde cholangiopancreatography.

in 8 patients in the losartan group and in 4 patients in the placebo group (P = 0.53) (Table 3). Similarly, there was no substantial difference in serum lipase value between the groups either at baseline (0.53 and 0.48 in the losartan and placebo groups, respectively, P = 0.47) or 24 h after ERCP (0.77 and 1.07 in the losartan and placebo groups, respectively, P = 0.62). Eight patients had hyperlipasemia 24 h after ERCP in the losartan group, and 7 in the placebo group (P = 0.89) (Table 3).

The evaluation of the effect of missing outcome data using the enzyme levels 4 h after ERCP in patients with missing 24-h values did not change the main results (data not shown). Acute pancreatitis occurred in 5 patients in the losartan group and 4 in the placebo group (P = 0.57) (Table 3). All cases of pancreatitis were mild as defined according to the Atlanta criteria[41]. Among the cases of

Table 3 Serum pancreatic enzyme levels, abdominal pain, and pancreatitis after endoscopic retrograde cholangiopancreatography among 76 participating patients[1] *n* (%)

Pancreatic enzyme level in serum	Losartan group	Placebo group	*P* value
Amylase (microkat/L), median, (interquartile range)			
At baseline	0.44 (0.3)	0.46 (0.4)	0.64
4 h after ERCP	0.75 (2.5)	0.68 (1.0)	0.81
24 h after ERCP	0.62 (2.3)	0.82 (1.0)	0.33
Hyperamylasemia[2] 24 h after ERCP, number (%)	8 (24)	4 (13)	0.53
Missing data	5 (13)	6 (16)	
Lipase (microkat/L), median, (interquartile range)			
At baseline	0.53 (0.3)	0.48 (0.5)	0.47
4 h after ERCP	1.02 (5.9)	0.76 (1.4)	0.47
24 h after ERCP	0.77 (1.1)	1.07 (1.5)	0.62
Hyperlipasemia[2] 24 h after ERCP, number (%)	8 (21)	7 (18)	0.89
Missing data	5 (13)	7 (18)	
Hyperenzymemia[3] 24 h after ERCP, number (%)	9 (24)	7 (18)	0.51
Missing data	4 (11)	3 (8)	
Abdominal pain 24 h after ERCP, number (%)	8 (23)	9 (26)	0.93
Missing data	3 (8)	3 (8)	
Acute pancreatitis (hyperenzymemia and abdominal pain after 24 h), number (%)	5 (13)	4 (11)	0.57
Missing data	7 (18)	4 (11)	

[1]In all analyses missing values were included as a separate category; *P*-values refer to overall differences between groups; [2]Defined as 3 times higher than the normal reference value; [3]Occurrence of hyperamylasemia or hyperlipasemia. ECRP: Endoscopic retrograde cholangiopancreatography.

pancreatitis the losartan treated group had more difficult cannulations compared to the placebo group, while there was no difference regarding degree of contrast filling.

DISCUSSION

This study provided no support for the hypothesis that losartan has a protective effect against the development of pancreatic hyperenzymemia after ERCP.

The randomized design, the blinding of all patients, clinical staff and evaluators, the use of identical capsules for losartan and placebo, and the objective outcome measurement, i.e., assessment for predefined pancreatic enzyme levels 24 h after the intervention, are among the strengths of the study. There are, however, several weaknesses to consider. The large number of patients found not to be eligible for inclusion extended the study period. The limited sample size meant that it was not possible to detect weak associations, which meant that type 2 errors could have occurred. The sample size estimation was, however, deliberately carried out with the purpose of detecting a strong decrease in hyperenzymemia only. Despite the randomization, the limited sample size could have introduced confounding if important covariates were not evenly distributed between the comparison groups. The distribution of the evaluated potential confounding factors was, however, fairly equal. Moreover, to avoid confounding due to any remaining imbalances, we analyzed the data using multivariable regression with adjustment for several covariates. Hyperenzymemia was used as a surrogate marker for increased risk of acute post-ERCP pancreatitis. This was justified by the strong link between these conditions[42]; further, hyperenzymemia has previously been used as a marker for pancreatic damage and pancreatitis after ERCP[1,16,26,27]. Since the occurrence of hyperenzymemia is markedly more common than pancreatitis, such a surrogate marker provided an opportunity to have a more limited sample size. If the results of the present study had indicated a prophylactic effect of losartan on hyperenzymemia, we had intended to expand the study to comprise a sufficient number of patients to address the outcome acute pancreatitis. The rate of post-ERCP pancreatitis was somewhat higher than expected, partly due to detection bias. Also, the study is small and therefore the high reported incidence of post-ERCP pancreatitis could be due to chance.

Experimental and clinical findings suggest that ARB's will protect against development of acute pancreatitis[31-33,35], but our study did not support this hypothesis. Apart from a true lack of effect, our negative results could have been due to several other factors: The tested dose (50 mg) of losartan might have been too low to have any preventive effect, and earlier administration of losartan could have been more beneficial, since a peak plasma concentration is obtained 4-6 h after an oral dose. The dose was predefined, however, and chosen on the basis of an experimental report of a protective effect on cerulein induced acute pancreatitis using 0.2 mg/kg in rats[32]. Moreover, losartan did decrease the blood pressure, suggesting that the dosage was at least sufficient to affect peripheral vasoconstriction. To date, the tissue concentration of losartan in the pancreas remains unknown. Thus, the study hypothesis cannot be dismissed on the basis of the present trial only. Before considering another randomized trial, e.g., with a longer pre-treatment latency and a higher dose of ARB, we suggest further observational investigations of the risk of post-ERCP pancreatitis among ARB users.

In conclusion, one oral capsule of 50 mg of the ARB losartan given one hour before ERCP did not prevent pancreatic hyperenzymemia after the ERCP procedure in this randomized, blinded and placebo-controlled clinical trial.

ACKNOWLEDGEMENTS

Eja Fridsta contributed to building the study database and designed the case reports form. Neither of the funding bodies influenced the scientific content of the study.

COMMENTS

Background

This experimental randomized trial based on experimental research, which have

shown beneficial effects on pancreatitis using angiotensin receptor blockers. Also, clinical evidence exists from an epidemiological study showing reduced risk of acute pancreatitis in hypertensive patients in a primary care setting in United Kingdom. Endoscopic retrograde cholangio-pancreatography is usually successful, e.g., removing gallstones and accessing bile ducts for other therapeutic purposes. However, there exist a small risk of the potential lethal complication of acute pancreatitis. This is the reason they are investigating the potential lowering risk of losartan on the risk of development of hyperenzymemia.

Research frontiers

Many different approaches both pharmacological and intervention-related have been tried to reduce the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Promising results have been seen pharmacologically with drugs, e.g., gabexate and ulinastatin, and with increased use of pancreatic stenting have also been successful in some studies. Still the need for better prophylactic strategies is large to reduce a potential life-threatening complication like pancreatitis.

Innovations and breakthroughs

In general, losartan, which belongs to the pharmacological class of angiotensin receptor blockers, are used broadly to treat high blood pressure, and heart failure. Experimentally, a role for angiotensin Ⅱ receptor blockers (ARB) is suggested in conditions such as inflammation, and cancer. Previously, experimental animal research have tested ARB on pancreatic inflammation with promising results, but the authors aimed to investigate this in humans, with the effect on pancreatic enzymatic secretion, in turn potentially leading to pancreatic inflammation.

Applications

This study suggests no benefit of losartan on the development of hyperenzymemia after ERCP. However, due to limited sample size, larger well-designed controlled trials could evaluate this question further to rule out an unseen effect so far.

Terminology

Endoscopic retrograde cholangio-pancreatography is an investigation using a flexible endoscope accessing the bile ducts allowing both therapeutic and diagnostic interventions. Losartan is anti-hypertensive drug acting on the renin-angiotensin system, which has effects on blood pressure, inflammation and salt balance.

Peer review

This is a well-designed randomized double-blind study, which examines the effect of the well-known anti-hypertensive drugs. Advantages include the strict randomized design, the identical capsules used for placebo and active drugs, objective outcome measurement using pancreatic enzymes, and strict adherence to intention-to-treat principle while analyzing the results. Disadvantages include sample-size, because a larger study would make the results more reliable and also possible to analyze the effect on acute pancreatitis, rather than the proxy variable hyperenzymemia.

REFERENCES

1 **Tsujino T**, Komatsu Y, Isayama H, Hirano K, Sasahira N, Yamamoto N, Toda N, Ito Y, Nakai Y, Tada M, Matsumura M, Yoshida H, Kawabe T, Shiratori Y, Omata M. Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 2005; **3**: 376-383

2 **Yoo JW**, Ryu JK, Lee SH, Woo SM, Park JK, Yoon WJ, Lee JK, Lee KH, Hwang JH, Kim YT, Yoon YB. Preventive effects of ulinastatin on post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients: a prospective, randomized, placebo-controlled trial. *Pancreas* 2008; **37**: 366-370

3 **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88

4 **Christensen M**, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: a prospective study. *Gastrointest Endosc* 2004; **60**: 721-731

5 **Freeman ML**. Post-ERCP pancreatitis: patient and technique-related risk factors. *JOP* 2002; **3**: 169-176

6 **Andriulli A**, Leandro G, Federici T, Ippolito A, Forlano R, Iacobellis A, Annese V. Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis. *Gastrointest Endosc* 2007; **65**: 624-632

7 **Zheng M**, Bai J, Yuan B, Lin F, You J, Lu M, Gong Y, Chen Y. Meta-analysis of prophylactic corticosteroid use in post-ERCP pancreatitis. *BMC Gastroenterol* 2008; **8**: 6

8 **Poon RT**, Yeung C, Liu CL, Lam CM, Yuen WK, Lo CM, Tang A, Fan ST. Intravenous bolus somatostatin after diagnostic cholangiopancreatography reduces the incidence of pancreatitis associated with therapeutic endoscopic retrograde cholangiopancreatography procedures: a randomised controlled trial. *Gut* 2003; **52**: 1768-1773

9 **Poon RT**, Yeung C, Lo CM, Yuen WK, Liu CL, Fan ST. Prophylactic effect of somatostatin on post-ERCP pancreatitis: a randomized controlled trial. *Gastrointest Endosc* 1999; **49**: 593-598

10 **Arcidiacono R**, Gambitta P, Rossi A, Grosso C, Bini M, Zanasi G. The use of a long-acting somatostatin analogue (octreotide) for prophylaxis of acute pancreatitis after endoscopic sphincterotomy. *Endoscopy* 1994; **26**: 715-718

11 **Kisli E**, Baser M, Aydin M, Guler O. The role of octreotide versus placebo in the prevention of post-ERCP pancreatitis. *Hepatogastroenterology* 2007; **54**: 250-253

12 **Li ZS**, Pan X, Zhang WJ, Gong B, Zhi FC, Guo XG, Li PM, Fan ZN, Sun WS, Shen YZ, Ma SR, Xie WF, Chen MH, Li YQ. Effect of octreotide administration in the prophylaxis of post-ERCP pancreatitis and hyperamylasemia: A multicenter, placebo-controlled, randomized clinical trial. *Am J Gastroenterol* 2007; **102**: 46-51

13 **Thomopoulos KC**, Pagoni NA, Vagenas KA, Margaritis VG, Theocharis GI, Nikolopoulou VN. Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. *Gastrointest Endosc* 2006; **64**: 726-731

14 **Chang FY**, Guo WS, Liao TM, Lee SD. A randomized study comparing glucagon and hyoscine N-butyl bromide before endoscopic retrograde cholangiopancreatography. *Scand J Gastroenterol* 1995; **30**: 283-286

15 **Silvis SE**, Vennes JA. The role of glucagon in endoscopic cholangiopancreatography. *Gastrointest Endosc* 1975; **21**: 162-163

16 **Cavallini G**, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. Gabexate in digestive endoscopy--Italian Group. *N Engl J Med* 1996; **335**: 919-923

17 **Masci E**, Cavallini G, Mariani A, Frulloni L, Testoni PA, Curioni S, Tittobello A, Uomo G, Costamagna G, Zambelli S, Macarri G, Innocenti P, Dragonetti C. Comparison of two dosing regimens of gabexate in the prophylaxis of post-ERCP pancreatitis. *Am J Gastroenterol* 2003; **98**: 2182-2186

18 **Ueki T**, Otani K, Kawamoto K, Shimizu A, Fujimura N, Sakaguchi S, Matsui T. Comparison between ulinastatin and gabexate mesylate for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized trial. *J Gastroenterol* 2007; **42**: 161-167

19 **Zheng M**, Chen Y, Yang X, Li J, Zhang Y, Zeng Q. Gabexate in the prophylaxis of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. *BMC Gastroenterol* 2007; **7**: 6

20 **Brust R**, Thomson AB, Wensel RH, Sherbaniuk RW, Costopoulos L. Pancreatic injury following ERCP. Failure of prophylactic benefit of Trasylol. *Gastrointest Endosc* 1977; **24**: 77-79

21 **Fujishiro H**, Adachi K, Imaoka T, Hashimoto T, Kohge N, Moriyama N, Suetsugu H, Kawashima K, Komazawa Y, Ishimura N, Ishihara S, Amano Y, Kinoshita Y. Ulinastatin shows preventive effect on post-endoscopic retrograde

cholangiopancreatography pancreatitis in a multicenter prospective randomized study. *J Gastroenterol Hepatol* 2006; **21**: 1065-1069
22 **Rabenstein T**, Roggenbuck S, Framke B, Martus P, Fischer B, Nusko G, Muehldorfer S, Hochberger J, Ell C, Hahn EG, Schneider HT. Complications of endoscopic sphincterotomy: can heparin prevent acute pancreatitis after ERCP? *Gastrointest Endosc* 2002; **55**: 476-483
23 **De Palma GD**, Catanzano C. Use of corticosteriods in the prevention of post-ERCP pancreatitis: results of a controlled prospective study. *Am J Gastroenterol* 1999; **94**: 982-985
24 **Sherman S**, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Earle D, Temkit M, Lehman GA. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. *Gastrointest Endosc* 2003; **58**: 23-29
25 **Murray B**, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2003; **124**: 1786-1791
26 **Devière J**, Le Moine O, Van Laethem JL, Eisendrath P, Ghilain A, Severs N, Cohard M. Interleukin 10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2001; **120**: 498-505
27 **Moretó M**, Zaballa M, Casado I, Merino O, Rueda M, Ramírez K, Urcelay R, Baranda A. Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: A randomized double-blind trial. *Gastrointest Endosc* 2003; **57**: 1-7
28 **Räty S**, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post-ERCP pancreatitis: reduction by routine antibiotics. *J Gastrointest Surg* 2001; **5**: 339-345; discussion 345
29 **Greenstein RJ**, Krakoff LR, Felton K. Activation of the renin system in acute pancreatitis. *Am J Med* 1987; **82**: 401-404
30 **Leung PS**, Chan WP, Nobiling R. Regulated expression of pancreatic renin-angiotensin system in experimental pancreatitis. *Mol Cell Endocrinol* 2000; **166**: 121-128
31 **Tsang SW**, Cheng CH, Leung PS. The role of the pancreatic renin-angiotensin system in acinar digestive enzyme secretion and in acute pancreatitis. *Regul Pept* 2004; **119**: 213-219
32 **Tsang SW**, Ip SP, Leung PS. Prophylactic and therapeutic treatments with AT 1 and AT 2 receptor antagonists and their effects on changes in the severity of pancreatitis. *Int J Biochem Cell Biol* 2004; **36**: 330-339
33 **Oruc N**, Ozutemiz O, Nart D, Yuce G, Celik HA, Ilter T. Inhibition of renin-angiotensin system in experimental acute pancreatitis in rats: a new therapeutic target? *Exp Toxicol Pathol* 2010; **62**: 353-360
34 **Chan YC**, Leung PS. Angiotensin II type 1 receptor-dependent nuclear factor-kappaB activation-mediated proinflammatory actions in a rat model of obstructive acute pancreatitis. *J Pharmacol Exp Ther* 2007; **323**: 10-18
35 **Sjöberg Bexelius T**, García Rodríguez LA, Lindblad M. Use of angiotensin II receptor blockers and the risk of acute pancreatitis: a nested case-control study. *Pancreatology* 2009; **9**: 786-792
36 **Dickstein K**, Gottlieb S, Fleck E, Kostis J, Levine B, DeKock M, LeJemtel T. Hemodynamic and neurohumoral effects of the angiotensin II antagonist losartan in patients with heart failure. *J Hypertens Suppl* 1994; **12**: S31-S35
37 **Gottlieb SS**, Dickstein K, Fleck E, Kostis J, Levine TB, LeJemtel T, DeKock M. Hemodynamic and neurohormonal effects of the angiotensin II antagonist losartan in patients with congestive heart failure. *Circulation* 1993; **88**: 1602-1609
38 **Lakemedelsverket**. Lakemedelsverkets foreskrifter och allmanna rad om klinisk provning av lakemedel for humant bruk. Lakemedelsverket: Director General Gunnar Alvan, 2003: 1-25
39 **European Medical Agency**. Guideline for Good Clinical Practice. London: European Medical Agency, 2006: 59
40 **European Medical Agency**. Guideline on missing data in confirmatory clinical trials. London: European Medical Agency, 2009: 13
41 **Bradley EL**. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993; **128**: 586-590
42 **Brunicardi CAD**, Billiar T, Dunn D, Hunter J, Matthews J, Pollock R. Schwartz's Principles of Surgery. 9th ed. Pancreas: McGraw-Hill, 2009

S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i11.513

World J Gastrointest Endosc 2012 November 16; 4(11): 513-517
ISSN 1948-5190 (online)

BRIEF ARTICLE

Awareness and attitudes of Greek medical students on colorectal cancer screening

Ioannis S Papanikolaou, Athanasios D Sioulas, Stylianos Kalimeris, Persephone Papatheodosiou, Ioannis Karabinis, Olga Agelopoulou, Iosif Beintaris, Dimitrios Polymeros, George Dimitriadis, Konstantinos Triantafyllou

Ioannis S Papanikolaou, Athanasios D Sioulas, Stylianos Kalimeris, Persephone Papatheodosiou, Ioannis Karabinis, Olga Agelopoulou, Iosif Beintaris, Dimitrios Polymeros, George Dimitriadis, Konstantinos Triantafyllou, Hepatogastroenterology Unit, 2nd Department of Internal Medicine and Research Unit, Attikon University General Hospital, Medical School, Athens University, 12462 Haidari, Greece
Author contributions: Papanikolaou IS conceived and designed the study, initially revised and approved the manuscript; Sioulas AD drafted, revised and approved the manuscript; Kalimeris S, Papatheodosiou P, Karabinis I, Agelopoulou O, Beintaris I and Polymeros D collected data, revised and approved the manuscript; Dimitriadis G and Triantafyllou K conceived the study, critically revised and approved the manuscript.
Correspondence to: Dr. Athanasios D Sioulas, Hepatogastroenterology Unit, 2nd Department of Internal Medicine and Research Unit, Attikon University General Hospital, Medical School, Athens University, Rimini 1, 12462 Haidari, Greece. athsioulas@yahoo.gr
Telephone: +30-210-5832090 Fax: +30-210-5326422
Received: December 10, 2011 Revised: September 25, 2012
Accepted: October 26, 2012
Published online: November 16, 2012

Abstract

AIM: To prospectively assess the knowledge and attitudes of medical students (MS), as tomorrow's physicians, about colorectal cancer (CRC) and its screening modalities.

METHODS: Three hundred fourth year MS of the University of Athens were enrolled in this survey. Their selection was random, based on student identification card number. All participants completed an anonymous written questionnaire over a 4 month period. The questionnaire was divided into 4 sections and included queries about CRC-related symptoms, screening with colonoscopy and MS awareness and attitudes in this field. Following collection and analysis of the data, the results are presented as percentages of answers for each separate question.

RESULTS: Two hundred and sixty-five students answered the questionnaire over a 4 mo period. Interestingly, only 69% of the study population considered CRC to be a high-risk condition for public health. However, the vast majority of participants identified CRC-related symptoms and acknowledged its screening to be of great value in reducing CRC incidence and mortality. A very small proportion (38%) had received information material regarding CRC screening (either during their medical training or as a part of information provided to the general public) and only 60% of the participants declared willingness to receive further information. Regarding colonoscopy, 85% would prefer an alternative to colonoscopy methods for CRC screening. Moreover, 53% considered it to be a painful method and 68% would appreciate more information about the examination.

CONCLUSION: MS in Greece need to be better informed about CRC screening and screening colonoscopy.

Key words: Screening; Medical students; Colorectal cancer; Attitudes

Peer reviewers: Jin Gu, MD, FACS, Professor, Chief of Colorectal Surgery, Peking University School of Oncology, 52 Fu Cheng Lu, Beijing 100142, China; Shinji Tanaka, MD, PhD, Professor, Department of Endoscopy, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Papanikolaou IS, Sioulas AD, Kalimeris S, Papatheodosiou P, Karabinis I, Agelopoulou O, Beintaris I, Polymeros D, Dimitriadis G, Triantafyllou K. Awareness and attitudes of Greek medical students on colorectal cancer screening. *World J Gastrointest Endosc* 2012; 4(11): 513-517 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i11/513.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i11.513

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States and Western Europe. Lately, both the incidence and mortality rates of CRC seem to be declining in the United States, a fact that has been associated with the increased understanding of its pathogenesis, recent advances in medical and surgical care and the widespread implementation of screening programs[1,2]. Screening for CRC can identify premalignant lesions and detect asymptomatic early stage malignancy, thus decreasing its incidence and mortality[3,4]. Tests available for screening include stool-based tests (guaiac-based or immunochemical fecal tests, as well as stool DNA sampling), radiological methods (computed tomography colonography, double-contrast barium enema) and endoscopic examinations (colonoscopy, flexible sigmoidoscopy, capsule endoscopy). Screening colonoscopy aimed at early detection and removal of precancerous polyps seems to reduce the incidence of CRC[4]. Even flexible sigmoidoscopy can lead to a 60% decrease of CRC-associated deaths, provided screening was done before development of symptoms[5]. However, compliance of the asymptomatic population, as well as that of individuals with a high risk for CRC, with screening programs remains low[6-8]. Physician's beliefs on CRC screening has been shown to have a significant influence on whether or not their patients participate in CRC screening programs[9-11].

The objective of this survey was to prospectively assess the knowledge and specific attitudes of a series of fourth year medical students (MS) from the University of Athens about CRC and its screening programs, with an emphasis on colonoscopy.

MATERIALS AND METHODS

Three hundred MS from the University of Athens were enrolled in this survey. All students were in the fourth year and selection was based on student identification card number. The participants anonymously completed a written questionnaire between March and June, 2010. This was divided into 4 sections (Table 1). The first section included questions about CRC-related symptoms. In the second part, the survey asked questions regarding MS beliefs about CRC and its screening with colonoscopy. The third part provided questions pertaining to the availability and source of student's information on this subject. The questionnaire concluded with inquires addressing MS pre- and post-study attitudes towards CRC and its screening. MS willingness to enrich their knowledge in this area and subsequently inform their relatives and friends was also investigated. The results of this survey are presented as percentages of answers for each separate question.

RESULTS

Two hundred and sixty-five students (88.3%) answered the questionnaire. Respondents' mean age was 22.8 years (range 21-25 years) and 53% were male. Most (85%-99%) of the participants could identify CRC-related symptoms and 95% was aware of the fact that CRC screening significantly reduces its incidence and mortality. A significant proportion of MS (83%) was informed about the recommended age to start screening in average-risk population. However, only 69% viewed CRC as a major public health issue. Additionally, an even smaller proportion (38%) had received information material regarding CRC screening (either within their study curriculum or as a part of information directed to the general public); most interestingly, only 60% of the study group declared an interest to obtain further information. Regarding colonoscopy as a screening tool, 85% would prefer an alternative method and 53% considered it painful. Finally, 68% of the students would appreciate more information about colonoscopy and 78% agreed to subsequently inform their families and friends about the importance of CRC screening. The results of our survey are summarized in Table 1.

DISCUSSION

We ran the present survey in order to evaluate the awareness of a series of MS of CRC and its screening modalities, especially focusing on colonoscopy. The rationale behind the study population selection was that it is tomorrow's physicians who will be recruited from today's MS who will refer patients or who can influence the public to participate in CRC screening. Therefore, their attitude and information about CRC screening modalities, especially colonoscopy, may have a great impact on the public's compliance[12]. As the participants' parents belong to the age group primarily targeted to start CRC screening, their children's motivation to undergo colonoscopy would also be an immediate benefit.

It is encouraging that a remarkably high percentage (85%-99%) of the participants identified the alarm symptoms suggestive of CRC. This finding possibly reflects their medical education, since clear gaps in knowledge about CRC symptoms were recently reported by Ramos *et al*[13] in 625 primary healthcare patients. The vast majority of respondents (95%) admitted that screening for CRC leads to a decline in its incidence and mortality. This result is consistent with that of a recent

Table 1 Greek fourth year medical student responses to a 4 item questionnaire about colorectal cancer and colorectal cancer screening (%)

	Yes	No
Which of the following may be a CRC-related symptom?		
Rectal bleeding	99	1
Altered bowel habits	92	8
Constipation	95	5
Diarrhea	85	5
Which of the following is true about CRC and its screening?		
Screening begins at the age of 50 in average risk individuals	83	17
Screening reduces CRC mortality	95	5
CRC is a major public health problem	69	31
Is colonoscopy painful?	57	43
Would you prefer an alternative to colonoscopy for CRC screening	85	15
Polyps removal and lesional tissue sampling are feasible during colonoscopy	87	13
Information about CRC screening		
Have you ever received any information material regarding CRC screening	38	62
Would you like to receive more information material?	60	40
Your knowledge about CRC and colonoscopy originates from medical school or elsewhere (e.g. family, media, internet)	Medical school: 80 Elsewhere: 20	
Pre- and post-study attitude regarding CRC and its screening		
Have you ever encouraged anyone to undergo colonoscopy?	73	27
Are you willing to increase your knowledge in this area?	68	32
Are you planning to inform your family/friends about the benefits of CRC screening?	78	22

CRC: Colorectal cancer.

survey among MS in two American schools assessing knowledge and attitudes regarding CRC screening. In terms of the age to start screening tests for CRC in average risk individuals, a higher proportion of Greek than American MS gave the correct answer. However, differences in the setting of the relevant question may be responsible for this discrepancy[14].

Interestingly, only 69% of MS in our study considered CRC to be a major public health issue. This may have an unfavorable impact on their future role as healthcare providers and may most probably be attributed to the restricted information they have received so far on this topic (38%). An argument could be made that fourth year MS in the University of Athens have just started their clinical education; therefore, their perception of the value of cancer prevention strategies is limited. In accordance with this argument, it has been observed that the mean knowledge scores on CRC increase directly with level of training[15]. However, Zack *et al*[16] reported a significant discrepancy between the perceived, offered and actually implemented CRC screening by internal medicine residents in an Irish institution, despite their advanced medical education.

Numerous studies have been conducted in healthcare professionals to evaluate awareness and attitudes about CRC screening. According to our results, only 15% of the questioned MS would prefer colonoscopy as a personal screening tool. This percentage is markedly low, compared to the reported 97% and 27% among gastrointestinal specialists and general practitioners respectively, in the Netherlands[17]. Greek MS perception about colonoscopy being painful (57%), possibly reflecting their little information and clinical experience, may account for this finding. 78% of MS were planning to inform their family and friends about the benefits of CRC screening, whereas only 51% of the general practitioners in the above mentioned study favored population screening. On the other hand, 87.2% of obstetricians/gynecologists and 61.7% of nurse practitioners include CRC screening in their routine preventive practice[18]. These percentages lag far behind those of other common malignancies, such as breast and cervical cancer[19,20]. Similarly, a survey of internists' and surgeons' knowledge regarding CRC screening disclosed plenty of deficits[21].

Population adherence to CRC screening guidelines is disappointingly poor. In a survey carried out by Stock *et al*[8] in 11 European countries, the proportion of respondents aged 50 years and older who reported ever having undergone lower gastrointestinal endoscopy ranged from 8.2% in Greece to 35.7% in Austria. Several patient-related factors may contribute to the low adherence rate, including inappropriate perception of risk, burdensome enteric preparation, pain, discomfort and embarrassment related especially to colonoscopy[7]. Furthermore, CRC screening underutilization possibly represents the absence of information provided by the media and medical associations. Another factor that may contribute to these extremely low levels of compliance is the lack of knowledge in general practitioners or other medical specialties about the benefits of participation in CRC screening programs. This results in reduced referrals, especially for screening colonoscopy, which is generally considered a "difficult" or sometimes ineffective examination[22,23]; the latter seems to be an important factor, especially in light of recent cuts in spending for public health, as well as reductions in funding for health education, screening programs and investments to improve screening modalities[24,25].

To our best knowledge, this is the first report investigating MS awareness and attitudes towards CRC and its screening in Europe. However, it bears some limitations; it is restricted to fourth year MS, who actually have limited clinical experience and therefore their awareness and attitudes towards CRC screening may not be significantly different from the general population, although they have completed their preclinical education and started their clinical training. It may be reasonable to state that sixth year MS would perform significantly better. Furthermore, the inclusion of MS from only one of seven

Greek medical schools may have partly undermined the ability to generalize our conclusions. However, despite these limitations, we believe that our results are interesting and could possibly be enriched in the future by a similar survey in more advanced level MS attending medical schools all over Greece. Comparison with European MS attitudes would also be helpful since results might shed more light into the significantly different population's adherence rates observed in these countries and could serve as a "control group" to our MS in order to make interesting comparisons.

Collectively, our results highlight the need to better inform MS about CRC as a major public health problem and the available methods for its screening and surveillance. In this context, modifying medical schools' curricula to promote students' knowledge about preventive methods against CRC merits special consideration[26]. MS, as the future healthcare providers, through education in this area, are a crucial parameter in order to achieve maximum adherence of the general population in CRC screening programs aiming to decrease CRC-related deaths.

COMMENTS

Background

Colorectal cancer (CRC) is a common and potentially lethal disease. CRC screening tests can help identify cancers at an early and treatable stage. Colonoscopy in particular can also prevent the development of CRC by detecting precancerous lesions called adenomas, which can be removed before they become malignant. However, adherence to screening programs is relatively low, possibly reflecting the physician's awareness and attitudes towards this subject.

Research frontiers

Aiming to increase participation to CRC screening programs, an important hotspot is to assess and improve healthcare providers' knowledge in this field.

Innovations and breakthroughs

This study aims to assess the knowledge and attitudes of medical students (MS) about CRC and its screening methods, primarily colonoscopy. This is definitely of interest since MS are future physicians and should play a major role in public health system.

Applications

The results of the present study underline the need to better educate MS about CRC and its screening, in order to achieve higher adherence to screening programs and decrease CRC-related deaths.

Terminology

CRC: cancer that develops in the large intestine (colon) or rectum; Screening tests: methods that help identify cancer at an early stage or even detect precancerous lesions that can be removed, resulting in cancer prevention.

Peer review

The reviewers commented that the present study evaluates the awareness and attitudes of MS towards CRC and its screening by questionnaire given to Greek MS. They agree with the authors that Greek MS need to be better informed regarding this subject.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90

2 **Edwards BK**, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 2010; **116**: 544-573

3 **Winawer SJ**, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, Woolf SH, Glick SN, Ganiats TG, Bond JH, Rosen L, Zapka JG, Olsen SJ, Giardiello FM, Sisk JE, Van Antwerp R, Brown-Davis C, Marciniak DA, Mayer RJ. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997; **112**: 594-642

4 **Burt RW**, Barthel JS, Dunn KB, David DS, Drelichman E, Ford JM, Giardiello FM, Gruber SB, Halverson AL, Hamilton SR, Ismail MK, Jasperson K, Lazenby AJ, Lynch PM, Martin EW, Mayer RJ, Ness RM, Provenzale D, Rao MS, Shike M, Steinbach G, Terdiman JP, Weinberg D. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. *J Natl Compr Canc Netw* 2010; **8**: 8-61

5 **Atkin WS**, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; **375**: 1624-1633

6 **Centers for Disease Control and Prevention (CDC)**. Use of colorectal cancer tests--United States, 2002, 2004, and 2006. *MMWR Morb Mortal Wkly Rep* 2008; **57**: 253-258

7 **Bleiker EM**, Menko FH, Taal BG, Kluijt I, Wever LD, Gerritsma MA, Vasen HF, Aaronson NK. Screening behavior of individuals at high risk for colorectal cancer. *Gastroenterology* 2005; **128**: 280-287

8 **Stock C**, Brenner H. Utilization of lower gastrointestinal endoscopy and fecal occult blood test in 11 European countries: evidence from the Survey of Health, Aging and Retirement in Europe (SHARE). *Endoscopy* 2010; **42**: 546-556

9 **Shieh K**, Gao F, Ristvedt S, Schootman M, Early D. The impact of physicians' health beliefs on colorectal cancer screening practices. *Dig Dis Sci* 2005; **50**: 809-814

10 **Gennarelli M**, Jandorf L, Cromwell C, Valdimarsdottir H, Redd W, Itzkowitz S. Barriers to colorectal cancer screening: inadequate knowledge by physicians. *Mt Sinai J Med* 2005; **72**: 36-44

11 **Senore C**, Malila N, Minozzi S, Armaroli P. How to enhance physician and public acceptance and utilisation of colon cancer screening recommendations. *Best Pract Res Clin Gastroenterol* 2010; **24**: 509-520

12 **Hauer KE**, Wilkerson L, Teherani A. The relationship between medical students' knowledge, confidence, experience, and skills related to colorectal cancer screening. *J Cancer Educ* 2008; **23**: 209-213

13 **Ramos M**, Llagostera M, Esteva M, Cabeza E, Cantero X, Segarra M, Martín-Rabadán M, Artigues G, Torrent M, Taltavull JM, Vanrell JM, Marzo M, Llobera J. Knowledge and attitudes of primary healthcare patients regarding population-based screening for colorectal cancer. *BMC Cancer* 2011; **11**: 408

14 **Boehler M**, Advani V, Schwind CJ, Wietfeldt ED, Becker Y, Lewis B, Rakinic J, Hassan I. Knowledge and attitudes regarding colorectal cancer screening among medical students: a tale of two schools. *J Cancer Educ* 2011; **26**: 147-152

15 **Villarreal-Garza C**, García-Aceituno L, Villa AR, Perfecto-Arroyo M, Rojas-Flores M, León-Rodríguez E. Knowledge about cancer screening among medical students and internal medicine residents in Mexico City. *J Cancer Educ* 2010; **25**: 624-631

16 **Zack DL**, DiBaise JK, Quigley EM, Roy HK. Colorectal cancer screening compliance by medicine residents: perceived and actual. *Am J Gastroenterol* 2001; **96**: 3004-3008

17 **Terhaar Sive Droste JS**, Heine GD, Craanen ME, Boot H, Mulder CJ. On attitudes about colorectal cancer screening among gastrointestinal specialists and general practitioners

in the Netherlands. *World J Gastroenterol* 2006; **12**: 5201-5204
18 **Menees SB**, Patel DA, Dalton V. Colorectal cancer screening practices among obstetrician/gynecologists and nurse practitioners. *J Womens Health* (*Larchmt*) 2009; **18**: 1233-1238
19 **Menees SB**, Inadomi J, Elta G, Korsnes S, Punch M, Aldrich L. Colorectal cancer screening compliance and contemplation in gynecology patients. *J Womens Health* (*Larchmt*) 2010; **19**: 911-917
20 **Menees SB**, Fenner DE. Colon cancer screening in women. *Womens Health* (*Lond Engl*) 2007; **3**: 163-172
21 **Niv Y**, Niv G. Survey of surgeons' and internists' knowledge of colorectal cancer screening. *Cancer Detect Prev* 2004; **28**: 340-344
22 **Gaglia A**, Papanikolaou IS, Veltzke-Schlieker W. New endoscopy devices to improve population adherence to colorectal cancer prevention programs. *World J Gastrointest Endosc* 2010; **2**: 244-251
23 **Adler A**, Aschenbeck J, Aminalai A, Drossel R, Schröder A, Mayr M, Wettschureck E, Stange G, Papanikolaou IS, Wiedenmann B, Rösch T. Prospective Quality Assessment of Screening-Colonoscopy in Berlin (Berlin Colonoscopy Project, BECOP-3). *Gastrointest Endosc* 2009; **69**: AB287
24 **Triantafyllou K**, Angeletopoulou C. IMF and European coworkers attack public health in Greece. *Lancet* 2011; **378**: 1459-1460
25 **Kuehn BM**. Public health cuts threaten preparedness, preventive health services. *JAMA* 2011; **306**: 1965-1966
26 **Gaffan J**, Dacre J, Jones A. Educating undergraduate medical students about oncology: a literature review. *J Clin Oncol* 2006; **24**: 1932-1939

S- Editor Song XX **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2012 November 16; 4(11): I
ISSN 1948-5190 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Endoscopy*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

Hongchun Bao, PhD, Research Fellow, The Center for Micro-Photonics, Faculty of Engineering and Industrial Sciences, Swinburne University of Technology, PO Box 218, Hawthorn, Victoria 3122, Australia

Simon Bar-Meir, Professor, Director, Department of Gastroenterology, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel

Hajime Isomoto, MD, PhD, Associate Professor, Department of endoscopy, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Nevin Oruc, MD, Associate Professor, Ege University, Gastroenterology Department, Ege University Hospital, Bornova, İzmir 35100, Turkey

Krish Ragunath, Associate Professor, Consultant Gastroenterologist, Nottingham Digestive Diseases Centre and Biomedical Research Unit, Queens Medical Centre campus, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, United Kingdom

Sema Zer Toros, MD, Department of Otorhinolaryngology/Head and Neck Surgery, Haydarpaşa Numune Education and Research Hospital, M.Saadettin Sk. Mecidiye Mh. Saadet Apt. No:3 D:4 Ortaköy/Beşiktaş, Istanbul, Turkey

Dr. Antonio Tucci, Gastrointestinal Unit, Castel S. Pietro Terme Hospital, University of Bologna, Bologna, Italy

Jochen Wedemeyer, MD, Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Carl Neuberg Str. 1, 30625 Hannover, Germany

WJGE World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2012 November 16; 4(11): I
ISSN 1948-5190 (online)

Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA 94103, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
Kiev, Ukraine

October 4-6, 2012
EURO-NOTES 2012: NOTES and Advanced Interventional Endoscopy
Prague, Czech Republic

October 19-24, 2012
American College of Gastroenterology 77th Annual Scientific Meeting and Postgraduate Course
Las Vegas, NV 89085, United States

November 3-4, 2012
Modern Technologies in Diagnosis and Treatment of Gastroenterological Patients
Dnepropetrovsk, Ukraine

December 1-4, 2012
Advances in Inflammatory Bowel Diseases
Hollywood, FL 33028, United States

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2012 November 16; 4(11): I-V
ISSN 1948-5190 (online)

GENERAL INFORMATION

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253), is a monthly, open-access (OA), peer-reviewed online journal supported by an editorial board of 400 experts in gastrointestinal endoscopy from 45 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGE* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGE* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGE* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJGE* is to report rapidly the most recent results in basic and clinical research on gastrointestinal endoscopy including: gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy. Papers on advances and application of endoscopy-associated techniques, such as endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, endoscopic submucosal dissection and endoscopic balloon dilation are also welcome.

Columns

The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

Name of journal

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

Editor-in-chief

Editorial Office
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-8538-1893

Indexed and Abstracted in
PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

Published by
Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing
Statisital review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJGE* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should comform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Ab stract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the International Committee of Medical Journal Editors to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-acces sible registry at its outset. The only register now available, to our knowledge, is http://www. clinicaltrials.gov sponsored by the Uni ted States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions
Manuscripts should be submitted through the Online Submission System at: wjge@wjgnet.com. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may

send an email describing the problem to http://www.wjgnet.com/esps/, or by telephone: +86-10-59080038. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-59080039 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJGE*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. [a]$P <$

0.05, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data
Write as mean ± SD or mean ± SE.

Statistical expression
Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations
Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing
Editorial: http://www.wjgnet.com/1948-5190/g_info_20100316080004.htm

Frontier: http://www.wjgnet.com/1948-5190/g_info_20100313155344.htm

Topic highlight: http://www.wjgnet.com/1948-5190/g_info_20100316080006.htm

Observation: http://www.wjgnet.com/1948-5190/g_info_20100107124105.htm

Guidelines for basic research: http://www.wjgnet.com/1948-5190/g_info_20100313155908.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-5190/g_info_20100313160015.htm

Review: http://www.wjgnet.com/1948-5190/g_info_20100107124313.htm

Original articles: http://www.wjgnet.com/1948-5190/g_info_20100107133454.htm

Brief articles: http://www.wjgnet.com/1948-5190/g_info_20100313160645.htm

Case report: http://www.wjgnet.com/1948-5190/g_info_20100107133659.htm

Letters to the editor: http://www.wjgnet.com/1948-5190/g_info_20100107133856.htm

Book reviews: http://www.wjgnet.com/1948-5190/g_info_20100313161146.htm

Guidelines: http://www.wjgnet.com/1948-5190/g_info_20100313161315.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of WJGE. The revised version including manuscript and high-resolution image figures (if any) should be re-submitted online (http://www.wjgnet.com/1948-5190office/). The author should send the copyright transfer letter, responses to the reviewers, English language Grade B certificate (for non-native speakers of English) and final manuscript checklist to wjge@wjgnet.com.

Language evaluation
The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form
Please download a Copyright assignment form from http://www.wjgnet.com/1948-5190/g_info_20100107134847.htm.

Responses to reviewers
Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1948-5190/g_info_20100107134601.htm.

Proof of financial support
For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript
WJGE will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases
Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee
WJGE is an international, peer-reviewed, OA, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.