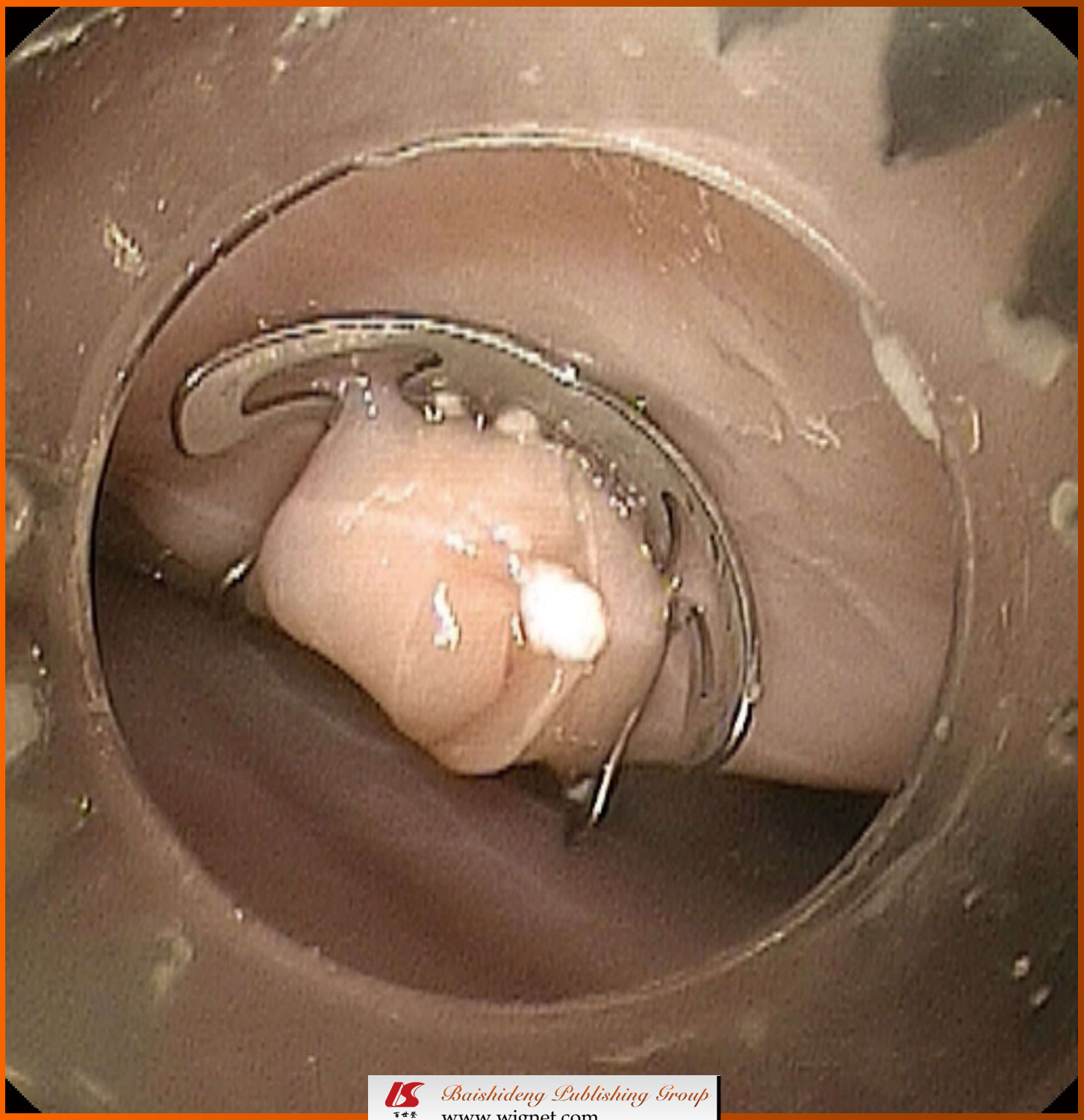
ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2013 August 16; 5(8): 359-419



Baishideng Publishing Group
www.wjgnet.com

WJGE

World Journal of Gastrointestinal Endoscopy

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

Editorial Board

2011-2015

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 402 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 46 countries, including Australia (7), Austria (1), Belgium (6), Brazil (7), Canada (5), Chile (2), China (25), Croatia (2), Cuba (1), Czech Republic (3), Denmark (1), Ecuador (1), Egypt (1), Finland (1), France (10), Germany (28), 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 (5), New Zealand (1), Norway (2), Pakistan (2), Poland (2), Portugal (5), Romania (2), Singapore (2), South Africa (1), South Korea (13), Spain (19), Sweden (3), Switzerland (1), Thailand (5), Turkey (8), United Arab Emirates (1), United Kingdom (17), and United States (68).

Miroslav Zavoral, *Prague*

Denmark

Peter Bytzer, *Koege*

Ecuador

Carlos Robles-Medranda, *Casilla*

Egypt

Nabil Ali Gad El-Hak, *Mansoura*

Finland

Paulina Salminen, *Turku*

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*
Jean-Francois Rey, *Saint Laurent*
José Sahel, *Marseille*
Nathalie Salles, *Pessac*

Germany

Marcel Binnebösel, *Aachen*
Peter Born, *Munich*
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*
Jochen Wedemeyer, *Hannover*
Uwe Will, *Gera*
Michael Vieth, *Bayreuth*
Stefan von Delius, *Munich*

Greece

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

Hungary

Pal Demeter, *Budapest*
Peter Lakatos, *Budapest*
László Lujber, *Munkacsy*
István Rácz, *Petz Aladár*

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 Martin Quigley, *Cork*

Israel

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

Italy

Paolo Giorgio Arcidiacono, *Milan*
Alberto Arezzo, *Torino*
Gabrio Bassotti, *San Sisto*
Giampaolo Bresci, *Pisa*
Carlo Calabrese, *Bologna*
Salvatore Maria Antonio Campo, *Rome*
Livio Cipolletta, *Naples*
Sandro Contini, *Parma*
Salvatore Cucchiara, *Rome*
Gabriele Curcio, *Palermo*
Paola De Angelis, *Rome*
Luigi Familiari, *Messina*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Naples*
Giovanni B Gasbarrini, *Rome*
Carlo M Girelli, *Brescia*
Mauro Manno, *Baggiovara di Modena*
Di Matteo Francesco Maria, *Rome*
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, *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, *Chiba prefecture*
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, *Maebashi*
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, *Nishinomiya*
Akihiro Mori, *Aichi*
Yoshihiro Moriwaki, *Yokohama*
Naoki Muguruma, *Tokushima*
Koichi Nagata, *Chiba*
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, *Saitama*
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, *Shimonoseki*
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

Oscar T Teramoto-Matsubara, *Chapultepec*

Netherlands

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

New Zealand

Michael PG Schultz, *Dunedin*

Norway

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

Pakistan

Lubna Kamani, *Karachi*
Syed HA Shah, *Karachi*

Poland

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

Portugal

Miguel Tavares Coimbra, *Porto*
Marie Isabelle Cremers, *Montijo*
Rui MA da Silva, *Porto*
Mário Dinis-Ribeiro, *Porto*
Pedro Narra Figueiredo, *Coimbra*

Romania

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

Singapore

Zhiwei Huang, *Singapore*
Surendra Kumar Mantoo, *Singapore*

South Africa

Roland N Ndip, *Alice*

South Korea

Young-Tae Bak, *Seoul*
Dong Kyung Chang, *Seoul*
Young-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*
Si-Young Song, *Seoul*
Jaekyu Sung, *Daejeon*

Spain

Jose Francisco Noguera Aguilar, *Palma*
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 FPC Martinez, *Murcia*
Enrique Pérez-Cuadrado Martínez, *Murcia*
Adolfo Parra-Blanco, *Asturias*
Luis Rabago, *Madrid*
Eduardo Redondo-Cerezo, *Granada*
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*

Switzerland

Valérie Pittet, *Bugnon*

Thailand

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

Turkey

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

United Arab Emirates

Margit Gabriele Muller, *Abu Dhabi*

United Kingdom

Basil Jaser Ammori, *Manchester*
Simon Hamish Charles Anderson, *London*
Federico Carpi, *London*
Adam Donald Farmer, *London*
Annette Fritscher-Ravens, *London*
Gianpiero Gravante, *Bristol*
Abdulzahra Hussain, *Orpington*
Vassilis Kodogiannis, *London*
Seamus Joseph Murphy, *Newry*
Perminder Phull, *Aberdeen*
Krish Ragunath, *Nottingham*
Jayesh Sagar, *Brighton*
Reena Sidhu, *Sheffield*
Adrian Stanley, *Glasgow*
Hu Zhang, *Cambridge*

United States

Maher-Aref Abbas, *Los Angeles*
Douglas G Adler, *Salt Lake*
Deepak Agrawal, *Dallas*
Mohammad Al-Haddad, *Indianapolis*
Jamie S Barkin, *Miami Beach*
Pedro W Baron, *Loma Linda*
James Stephen Barthel, *Tampa*
Neil Bhattacharyya, *Boston*
Juliane Bingener, *Rochester*
Cheri Lee Canon, *Birmingham*
Sherman M Chamberlain, *Augusta*
Edward John Ciaccio, *New York*
Lawrence Bruce Cohen, *New York*
Paul G Curcillo II, *Philadelphia*
Kiron M Daskiron, *New Brunswick*

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 5 Number 8 August 16, 2013

World Journal of Gastrointestinal Endoscopy
Volume 5 Number 8 August 16, 2013

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381891
Fax: +86-10-85381893

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F, Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
August 16, 2013

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.v5.i8.359

World J Gastrointest Endosc 2013 August 16; 5(8): 359-365
ISSN 1948-5190 (online)

EDITORIAL

Air embolism complicating gastrointestinal endoscopy: A systematic review

Suman Donepudi, Disaya Chavalitdhamrong, Liping Pu, Peter V Draganov

Suman Donepudi, Disaya Chavalitdhamrong, Liping Pu, Peter V Draganov, Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Florida, Gainesville, FL 32610, United States
Liping Pu, Department of Medicine and Nursing, Suzhou Health College, Suzhou 215009, Jiangsu Province, China
Author contributions: Donepudi S and Chavalitdhamrong D performed the literature review and drafted the manuscript; Pu L performed the literature review; Draganov PV performed critical revision of the manuscript for all intellectual contents.
Correspondence to: Peter V Draganov, MD, Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Florida, Room HD 602, PO Box 100214, Gainesville, FL 32610,
United States. dragapv@medicine.ufl.edu
Telephone: +1-352-2739474 Fax: +1-352-3923618
Received: May 29, 2013 Revised: July 12, 2013
Accepted: July 17, 2013
Published online: August 16, 2013

Abstract

Gastrointestinal endoscopy has become an important modality for the diagnosis and treatment of various gastrointestinal disorders. One of its major advantages is that it is minimally invasive and has an excellent safety record. Nevertheless, some complications do occur, and endoscopists are well aware and prepared to deal with the commonly recognized ones including bleeding, perforation, infection, and adverse effects from the sedative medications. Air embolism is a very rare endoscopic complication but possesses the potential to be severe and fatal. It can present with cardiopulmonary instability and neurologic symptoms. The diagnosis may be difficult because of its clinical presentation, which can overlap with sedation-related cardiopulmonary problems or neurologic symptoms possibly attributed to an ischemic or hemorrhagic central nervous system event. Increased awareness is essential for prompt recognition of the air embolism, which can allow potentially life-saving therapy to be provided. Therefore, we wanted to review the risk factors, the clinical presentation, and the therapy of an air embolism from the perspective of the practicing endoscopist.

Key words: Air embolism; Endoscopy; Endoscopic retrograde cholangiopancreatography; Complications; Therapy

Core tip: Air embolism at the time of endoscopy can cause cardiovascular, pulmonary, and neurologi cal symptoms. Symptom onset during the position change from prone to supine is characteristic and should trigger immediate suspicion for air embolism. Potentially lifesaving therapeutic measures should be promptly initiated, including placing the patient in Trendelenburg and left lateral decubitus position, high-flow oxygen, volume expansion and urgent hyperbaric oxygenation therapy.

Donepudi S, Chavalitdhamrong D, Pu L, Draganov PV. Air embolism complicating gastrointestinal endoscopy: A systematic review. *World J Gastrointest Endosc* 2013; 5(8): 359-365 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/359.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.359

INTRODUCTION

Air embolism is a consequence of direct communication between a source of air and the vasculature and a pressure gradient favoring the passage of air into the circulation. The effect of an air embolus depends upon both the rate and the volume of air introduced into the circulation. A venous air embolism occurs when air enters the systemic venous circulation. An arterial air embolism results from introduction of air into the arterial system and can produce ischemia of any organ. An air embolism

is an uncommon but potentially catastrophic event. Many cases are subclinical with no adverse outcome. However, severe cases are characterized by hemodynamic collapse and/or acute vascular insufficiency of specific organs, such as the brain or the spinal cord. Symptoms may be nonspecific, and therefore, a high index of clinical suspicion for a possible air embolism is required to prompt investigations and initiate appropriate therapy.

RESEARCH

We conducted a systematic review by searching the PubMed database on reported air embolisms complicating all endoscopic procedures. Medical subject headings "endoscopy, complications, air embolism, cerebrovascular accident, cardiovascular abnormalities, esophagogastroduodenoscopy (EGD), enteroscopy, colonoscopy, sigmoidoscopy, endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP)" were used in the title, the abstract, or the index term fields. Manual searches were then conducted using the reference lists from identified articles.

RISK FACTORS FOR AIR EMBOLISM

Air embolism is most commonly associated with an ERCP, but it can result from any endoscopic procedure including an EGD, an enteroscopy, an EUS, a colonoscopy, and a sigmoidoscopy.

Risk factors for an air embolism that have been reported are previous interventions or surgeries of the bile duct system, transhepatic portosystemic shunt[1-3], blunt or penetrating trauma to the liver[4], inflammation of the digestive system, post-surgical gastrointestinal fistula[5-7], and particular interventional techniques.

The inflammatory conditions associated with an increased risk for an air embolism include inflammation of the bile duct or surrounding veins (pylephlebitis), hepatic abscesses, inflammatory bowel diseases, necrotizing enterocolitis, and mesenteric ischemia[2,7,8]. In addition, gastrointestinal tumors and biliary atresia have been described as risk factors[9,10].

Interventional techniques include cholangioscopy, biliary sphincterotomy, metal stent placement, liver biopsy, insufflation of air with high pressure, excessive amount and/or increased rate of air infusion, procedural site located higher than the level of the heart, and the use of nitrous oxide (N_2O)[3,11-18].

MECHANISMS AND CLINICAL SIGNS AND SYMPTOMS

A number of potential mechanisms for air entry into the venous system have been described. These include intramural dissection of insufflated air into the portal vein, transection of duodenal vein radicles, biliary-venous fistulas/shunts, portocaval collaterals, air flow directly into the hepatic veins or inferior vena cava, retrograde flow into cerebral veins *via* superior vena cava[7], inability of the pulmonary circulation to filter out gas emboli[19,20], or entry into the vertebral venous plexus[21]. Rapid entry or large volumes of air entering the systemic venous circulation causes a substantial strain on the right ventricle, especially if this results in a significant rise in pulmonary artery pressures. This increase in pulmonary artery pressure can lead to right ventricular outflow obstruction and further compromise pulmonary venous return to the left heart. Consequently, the diminished pulmonary venous return will lead to decreased left ventricular preload with resultant decreased cardiac output, and eventually, systemic cardiovascular collapse.

Importantly, a venous air embolism can be limited to the portal venous system or can evolve into a systemic air embolism through intracardiac shunts, intrapulmonary right to left shunts, retrograde flow into cerebral veins *via* the superior vena cava, or air passage into the left atrium *via* the pulmonary veins[18,22]. The most common cause of an intracardiac shunt is a patent foramen ovale[11,23]. Atrial septal defect, arterio-venous shunts, and intrapulmonary shunts are also reported mechanisms[24-26].

The systemic air embolism can cause cardiovascular, pulmonary, and neurological symptoms[15]. Cardiovascular signs, symptoms, and findings include arrhythmia, hypotension, myocardial ischemia, right heart failure, cardiovascular collapse, and cardiac arrest. Pulmonary signs, symptoms, and findings include acute dyspnea, tachypnea, breathlessness, rales, wheezing, decrease in end tidal carbon dioxide concentration, hypoxia, cyanosis, and respiratory failure. Neurological signs, symptoms, and findings include eye deviation, dilated pupil(s), failure to regain consciousness after anesthesia, hypertonicity, altered mental status, loss of consciousness, hemiparesis, cerebral hypoperfusion, cerebral edema, and coma.

In the case of an ERCP-related air embolism, typically the symptoms appear or get significantly worse when the patient is repositioned from prone to supine position at the end of the procedure. This patient deterioration with position change should immediately raise a red flag and trigger suspicion for an air embolism as the underlying cause of the patient symptoms.

REPORTED CASES OF AIR EMBOLISM

We were able to identify 41 cases of air embolism in the published literature following various endoscopic procedures.

Air embolism cases following EGD and intraoperative small bowel endoscopy

The first case of air embolism following an EGD was reported by Lowdon *et al*[18] in 1988. A 5-wk old infant with biliary atresia status post Kasai procedure (hepatoportojejunostomy) died during endoscopy, and the autopsy revealed air in both the right atrium and right ventricle and in the large hepatic vein in the area of the porta hepatis. The patient was also found to have a patent fora-

men ovale and air in the coronary arteries. The authors proposed that air under pressure dissected across the diseased hepatic tissue into the large hepatic vein lying just below the denuded liver surface. This combined with her patent foramen ovale resulted in the systemic embolism.

Christl *et al*[5] described the first incident of a cerebral air embolism following endoscopy in a patient with a duodenal ulcer and a duodenocaval fistula. It was believed that the air emboli exceeding the absorptive rate of the pulmonary capillary bed might be the cause in this patient, especially with the total amount of air entering the inferior vena cava.

A case report by Katzgraber *et al*[14] identified an embolism risk when air insufflation occurs in the presence of damaged vessels. The patient, whom had a history of a perforated gastric ulcer surgically treated 13 years prior, underwent an upper endoscopy for the evaluation of epigastric pain. High-volume air insufflation was noted during the procedure. As the study was continued, the patient suddenly went into cardiac arrest and resuscitation was unsuccessful. On forensics, the right gastric vein was found to be eroded most likely due to his history of multiple ulcerations. The presence of this lesion in combination with the amount of insufflation required allowed air to enter the venous supply, and eventually, enter the heart causing death.

McAree *et al*[27] reported a cerebral air embolism in a patient being evaluated for metastatic adenocarcinoma of an unknown origin. Abdominal computed tomography (CT) scan showed ascites and a thickened cecal wall; cytology study of the ascites determined the presence of an adenocarcinoma. Soon after, the patient began vomiting blood and an EGD showed erosive esophagitis. As the procedure was ending, the patient became unresponsive and displayed neurological symptoms. An emergency cerebral CT confirmed air in the brain, specifically the right frontotemporal area. The esophagitis mucosal breakdown is to be considered as the leading cause of the embolism.

Meier *et al*[28] reported a patient with an air embolism during an EGD. The patient had a history of a pancreaticoduodenectomy for pancreatic adenocarcinoma and a percutaneous transhepatic cholangiography (PTC) for recent ascending cholangitis. An EGD was done due to the patient developing melena. As the scope was maneuvered towards the hepaticojejunostomy site, the patient's condition became unstable; unfortunately, the patient was unable to be successfully resuscitated and passed away. The investigators believed the PTC catheter may have created a fistula between the vasculature and the biliary tract. This abnormality allowed the air to enter the venous supply, specifically the hepatic veins and inferior vena cava, upon air insufflation during endoscopy.

Pandurangadu *et al*[24] reported about an incident of a cerebral embolism in 2010. The patient received an outpatient EGD, which required an esophageal biopsy and ablation of duodenal arteriovenous malformations. Shortly after the EGD procedure, he presented to the emergency room with neurological symptoms of sudden onset lethargy and left-sided weakness. CT scan of the brain showed multiple gas emboli in two areas, the right frontal lobe and frontoparietal region. A transesophageal echocardiogram (TEE) was also done, which ruled out a patent foramen ovale. Therefore, the study proposed the most likely cause of the embolism was the duodenal arteriovenous malformations.

Additionally in 2010, a case reported by Park *et al*[23] described a paradoxical air embolism during an intraoperative small bowel endoscopy. An adolescent female, with a history of a Kasai operation for biliary atresia, presented with gastrointestinal bleeding. The plan was for an exploratory laparotomy and intraoperative endoscopy for further evaluation. It must also be noted she had a previous exploratory laparotomy three months prior for hematochezia, which was unremarkable with the exception of some bluish edema on the small bowel wall. All preoperative protocols were performed, including an abdominal CT scan; the scan revealed a highly, irregular liver architecture showing massive fibrosis. As the endoscopy procedure ensued, excessive air insufflation was needed to facilitate visualization. An ulcerative lesion was found near the site of the previous Kasai procedure. The patient thereafter became unstable systemically, and immediate stabilization methods were started. TEE confirmed air bubbles entered the heart and the systemic vasculature. In this case, there were multiple risk factors present. The high amount of air insufflation administered and the ulcerative lesion are two of the immediate possibilities. However, two other risk factors can be added. Hopkins *et al*[29] found that 47% of patients with chronic liver disease possess an intrapulmonary right to left shunt. The other possibility is the patient's history of biliary atresia. A previous study showed that 18 of 88 biliary atresia patients, a total of 9.1%, between the ages of 8 mo and 16 years old possessed an intrapulmonary shunt; this shunt can cause fatal complications in previously operated biliary atresia patients[9].

Reported air embolism cases following colonoscopy and sigmoidoscopy

Chorost *et al*[21] reported on a case of a routine screening colonoscopy. Three days after the procedure, the patient presented with severe, lower back pain. After a CT scan of the abdomen, it became evident there was air anterior to the lumbar vertebrae. Batson[30], in 1940, suggested that an increase in intraabdominal pressure could allow venous effluent from the pelvis to enter into unimpeded valveless venous channels, such as in this example, the vertebrae. Therefore in this case, it was proposed the combination of the high intraabdominal pressure along with the low intraluminal pressure system of the vertebral venous system provided an optimum pressure gradient for air to seep, causing an air embolism.

Mittnacht *et al*[31] reported the only sigmoidoscopy case known to be complicated by an air embolism. The patient had a history of long-standing Crohn's disease and 2 years status post left partial colectomy with de-

Table 1 Reported cases on air embolism complicated endoscopic retrograde cholangiopancreatography

Case	Ref.	Age/sex	Risk factor(s)	Diagnosis	Outcome
1	Bisceglia *et al*[7]	78/male	Surgical gastroduodenal resection	Pulmonary air embolism	Dead
2	Rabe *et al*[12]	87/male	Metal stent placement	Cerebral air embolism	Survived
3	Rabe *et al*[12]	54/male	Billroth II operation, Metal stent placement	Cardiac air embolism	Dead
4	Jow *et al*[38]	65/male	Biliary duct stones/inflammation	Cardiac air embolism	Dead
5	Maccarone *et al*[1]	45/male	Percutaneous transhepatic biliary drainage	Cerebral air embolism	Survived
6	Siddiqui *et al*[37]	43/female	Biliary sphincterotomy, liver biopsy	Venous air embolism	Dead
7	Nayagam *et al*[39]	57/male	-	Cerebral air embolism	Dead
8	Kennedy *et al*[8]	63/female	Biliary sphincterotomy	Venous air embolism	Dead
9	Stabile *et al*[6]	65/male	Biliary sphincterotomy, PTC	Cerebral air embolism	Dead
10	Mohammedi *et al*[4]	27/male	Biliary sphincterotomy, blunt hepatic trauma	Cardiac air embolism	Survived
11	Romberg[40]	53/male	Biliary duct stones	Cardiac air embolism	Survived
12	Rangappa *et al*[41]	50/female	Biliary duct stones	Cerebral air embolism	Dead
13	Bechi *et al*[33]	79/female	Biliary sphincterotomy	Cerebral air embolism	Survived
14	Goins *et al*[16]	72/female	Cholangiocarcinoma	Cerebral air embolism	Survived
15	Cha *et al*[42]	50/female	Biliary duct stones, liver abscesses, choledochoduodenostomy	Cardiac air embolism	Dead
16	Di Pisa *et al*[13]	8/male	Splenomesenteric portal shunt	Venous air embolism	Survived
17	Giuly *et al*[43]	60/female	Biliary sphincterotomy, choledochal varices	Venous air embolism	Survived
18	van Boxel *et al*[44]	82/male	-	Cerebral air embolism	Survived
19	Tan *et al*[45]	82/female	Metal stent placement	Cerebral air embolism	Dead
20	Nern *et al*[46]	58/female	Cholangiocarcinoma	Cerebral air embolism	Dead
21	Simmons[47]	Not available	Biliary sphincterotomy	Venous air embolism	Survived
22	Merine *et al*[48]	39/female	Biliary sphincterotomy	Venous air embolism	Survived
23	Barthet *et al*[49]	31/male	Biliary sphincterotomy	Venous air embolism	Survived
24	Efthymiou *et al*[11]	62/female	Cholangioscopy	Cerebral air embolism	Survived
25	Our case[50]	66/male	Metal stent placement	Cerebral air embolism	Dead
26	Our case[50]	51/female	Status post Whipple's operation	Spinal air embolism	Survived

PTC: Percutaneous transhepatic cholangiography.

scending colostomy, which was complicated by poor wound healing and fistula formations. The patient required the sigmoidoscopy before a revision of her previous abdominal bowel surgery. During the procedure, the patient went into cardiac arrest as a result of an air embolism. The history of Crohn's disease, which led to inflamed and deteriorated mucosa, was proposed to allow air entry. Also proposed, there was possible injury to hemorrhoidal veins during the biopsy of the sigmoid. An additional risk was the patient being in Trendelenburg position, allowing for the surgery site to be above the heart.

Reported air embolism cases following EUS

Pfaffenbach *et al*[32] reported about a patient with severe upper abdominal pain requiring an EUS for evaluation of a pancreatic head lesion. EUS-guided fine needle aspiration was performed. Hepatic portal venous gas was found on a follow up abdominal ultrasonography.

Reported air embolism cases following ERCP

Most described cases of endoscopy-related air embolism have been related to an ERCP. We recently reported two air embolism cases following an ERCP, one with an intracranial air embolism and one with a spinal air embolism. To date, a total of 26 cases of systemic air embolism complicating ERCP have been reported (Table 1). Described risk factors for an air embolism following an ERCP are previous interventions or surgeries of the bile duct system, transhepatic portosystemic shunts, percutaneous transhepatic biliary drains, blunt or penetrating trauma to the liver, sphincterotomy, metal stent placement, the inflammation of the bile duct or surrounding veins, hepatic abscesses or tumors, liver biopsy, and insufflation of air with high pressure. Cholangioscopy with air insufflation directly into the bile duct appears to be a particularly strong risk factor for an air embolism. Reported clinical presentations are cardiovascular, pulmonary, and neurological symptoms. Again, we want to emphasize the onset of symptoms or symptom escalation with change of patient position from prone to supine should immediately trigger suspicion for an air embolism.

DIAGNOSIS

The diagnosis of an air embolism is often difficult and is complicated by the fact that air may be rapidly absorbed from the circulation while diagnostic tests are being arranged. Exclusion of other life-threatening processes is generally required.

Transthoracic and transesophageal echocardiography have been used to document the presence of air and may show evidence of acute right ventricular dilation and pulmonary artery hypertension consistent with air embolism. An echocardiography also aids in the diagnosis of cardiac anomalies, assessment of volume status, and cardiac contractility; this allows exclusion of other causes of hypotension, dyspnea, and aiding in further patient management. End-tidal CO_2 monitoring may show a fall in end-tidal CO_2; however, this finding is nonspecific and also

occurs with pulmonary embolism, massive blood loss, circulatory arrest, and disconnection from the anesthesia circuit. The pulmonary artery catheter may show a rise in pulmonary artery pressure in venous air embolism, but this is a nonspecific finding. Ventilation-perfusion scan abnormalities may be seen in the setting of a massive air embolism, but this is also a nonspecific finding and the perfusion defects resolve rapidly. The chest CT can detect air with higher sensitivity for massive air emboli. A pulmonary angiography could also be useful but may be normal often times in patients who have suffered an air embolism because of rapid resorption of air.

MANAGEMENT

The most crucial step in patient management is to maintain a high index of suspicion for an air embolism. An air embolism should be included in the differential diagnosis of procedural or periprocedural cardiopulmonary instability and neurologic symptoms, particularly in patients with recognized risk factors. Since the clinical presentation of an air embolism can significantly overlap with sedation-related problems and ischemic or hemorrhagic cerebrovascular events, some simple maneuvers to decrease the impact of a potential air embolism should be promptly initiated while the definitive diagnosis is established. These maneuvers include: (1) immediately stop the procedure if at all possible; (2) administer high flow 100% oxygen, which can reduce air bubbles expansion; (3) initiate high volume normal saline infusion; (4) place the patient in Trendelenburg (feet higher than the head) and left lateral decubitus position in order to minimize air migration to the brain and to force-out air from the right ventricular outflow tract[33], thereby increasing venous return[23]; and (5) if N_2O is being used, it must be discontinued because of its ability to rapidly diffuse into the trapped air bubbles, causing an additive effect on the embolism[23].

After these initial stabilizing measures are implemented, which should take no more than a few minutes, a decision has to be made regarding the type of evaluation needed to secure the diagnosis. This is a crucial branching point in the management of these patients. Since cerebrovascular accident is most commonly suspected in patients with neurologic symptoms, arrangements for an urgent head CT scan are typically made. If the underlying problem is an air embolism, the patient being sent for a CT scan can have some serious, adverse consequences, because it will delay the diagnosis and the application of specific targeted therapy. Therefore if an air embolism is suspected, a bedside echocardiogram should be promptly performed to quickly secure the diagnosis with visualization of air within the right heart. This can have immediate therapeutic implications. An air aspiration *via* a central venous catheter can be done, and arrangements for urgent hyperbaric oxygenation therapy can be carried out. Hyperbaric oxygenation therapy may reduce air bubble size, accelerate nitrogen reabsorption, and increase the oxygen content of arterial blood; this potentially reduces the ischemia. In the event of circulatory collapse, cardiopulmonary resuscitation (CPR) should be initiated in order to maintain the cardiac output. CPR may also serve to break large air bubbles into smaller ones and force air out of the right ventricle into the pulmonary vessels.

PROPHYLACTIC MEASURES TO DECREASE THE RISK OF AIR EMBOLISM

Using CO_2 for insufflation instead of air can eliminate the risk of an air embolism, because CO_2 can be easily absorbed[34]. The use of CO_2 for insufflation during gastrointestinal endoscopy has been shown superiority than using room air by multiple randomized controlled trials and a meta-analysis[35,36]. It was associated with a decreased postprocedural pain, flatus, and bowel distension. CO_2 insufflation also appears to be safe in patients without severe underlying pulmonary disease. This finding supports the use of CO_2 in most cases if available. In our unit, we perform all endoscopies with CO_2; if CO_2 is not available for routine use, we believe it must be used in all cholangioscopy cases or when other risk factors are present.

Another option for patients at risk is to use a precordial Doppler probe monitor during the procedure; it can quickly detect air within the heart and pulmonary vasculature before clinical symptoms may appear[37].

CONCLUSION

In summary, endoscopists should be aware of the signs and symptoms of an air embolism. In patients with risk factors, prophylactic measures can be applied. A high index of suspicion for an air embolism should be maintained, because prompt recognition can allow timely administration of specific, potential life-saving therapy.

REFERENCES

1 **Maccarone G**, Shakoor T, Ellis B. Air embolism after percutaneous transhepatic biliary drainage and subsequent endoscopic retrograde cholangiopancreatography (ERCP). *Endoscopy* 2011; **43** Suppl 2 UCTN: E399 [PMID: 22275020 DOI: 10.1055/s-0030-1256943]

2 **Finsterer J**, Stöllberger C, Bastovansky A. Cardiac and cerebral air embolism from endoscopic retrograde cholangio-pancreatography. *Eur J Gastroenterol Hepatol* 2010; **22**: 1157-1162 [PMID: 20555267 DOI: 10.1097/MEG.0b013e32833c5459]

3 **Green BT**, Tendler DA. Cerebral air embolism during upper endoscopy: case report and review. *Gastrointest Endosc* 2005; **61**: 620-623 [PMID: 15812425]

4 **Mohammedi I**, Ber C, Peguet O, Ould-Aoudia T, Duperret S, Petit P. Cardiac air embolism after endoscopic retrograde cholangiopancreatography in a patient with blunt hepatic trauma. *J Trauma* 2002; **53**: 1170-1172 [PMID: 12478046]

5 **Christl SU**, Scheppach W, Peters U, Kirchner T. Cerebral air embolism after gastroduodenoscopy: complication of a duodenocaval fistula. *Gastrointest Endosc* 1994; **40**: 376-378 [PMID: 8056250]

6 **Stabile L**, Cigada M, Stillittano D, Morandi E, Zaffroni M,

Rossi G, Lapichino G. Fatal cerebral air embolism after endoscopic retrograde cholangiopancreatography. *Acta Anaesthesiol Scand* 2006; **50**: 648-649 [PMID: 16643257]
7 **Bisceglia M**, Simeone A, Forlano R, Andriulli A, Pilotto A. Fatal systemic venous air embolism during endoscopic retrograde cholangiopancreatography. *Adv Anat Pathol* 2009; **16**: 255-262 [PMID: 19546613 DOI: 10.1097/PAP.0b013e3181aab793]
8 **Kennedy C**, Larvin M, Linsell J. Fatal hepatic air embolism following ERCP. *Gastrointest Endosc* 1997; **45**: 187-188 [PMID: 9041008]
9 **Sasaki T**, Hasegawa T, Kimura T, Okada A, Mushiake S, Matsushita T. Development of intrapulmonary arteriovenous shunting in postoperative biliary atresia: evaluation by contrast-enhanced echocardiography. *J Pediatr Surg* 2000; **35**: 1647-1650 [PMID: 11083444]
10 **Lamparter S**, Goecke W, Koehler HH. Hepatic portal venous gas after upper endoscopy in a patient with a gastrointestinal stromal tumor. *J Clin Ultrasound* 2009; **37**: 401-402 [PMID: 19475552 DOI: 10.1002/jcu.20598]
11 **Efthymiou M**, Raftopoulos S, Antonio Chirinos J, May GR. Air embolism complicated by left hemiparesis after direct cholangioscopy with an intraductal balloon anchoring system. *Gastrointest Endosc* 2012; **75**: 221-223 [PMID: 21470606 DOI: 10.1016/j.gie.2011.01.038]
12 **Rabe C**, Balta Z, Wüllner U, Heller J, Hammerstingl C, Tiemann K, Sommer T, Schepke M, Fischer HP, Sauerbruch T. Biliary metal stents and air embolism: a note of caution. *Endoscopy* 2006; **38**: 648-650 [PMID: 16586241]
13 **Di Pisa M**, Chiaramonte G, Arcadipane A, Burgio G, Traina M. Air embolism during endoscopic retrograde cholangiopancreatography in a pediatric patient. *Minerva Anestesiol* 2011; **77**: 90-92 [PMID: 21150852]
14 **Katzgraber F**, Glenewinkel F, Fischler S, Rittner C. Mechanism of fatal air embolism after gastrointestinal endoscopy. *Int J Legal Med* 1998; **111**: 154-156 [PMID: 9587799]
15 **Mirski MA**, Lele AV, Fitzsimmons L, Toung TJ. Diagnosis and treatment of vascular air embolism. *Anesthesiology* 2007; **106**: 164-177 [PMID: 17197859]
16 **Goins KM**, May JM, Hucklenbruch C, Littlewood KE, Groves DS. Unexpected cardiovascular collapse from massive air embolism during endoscopic retrograde cholangiopancreatography. *Acta Anaesthesiol Scand* 2010; **54**: 385-388 [PMID: 19878099 DOI: 10.1111/j.1399-6576.2009.02144.x]
17 **Mammoto T**, Hayashi Y, Ohnishi Y, Kuro M. Incidence of venous and paradoxical air embolism in neurosurgical patients in the sitting position: detection by transesophageal echocardiography. *Acta Anaesthesiol Scand* 1998; **42**: 643-647 [PMID: 9689268]
18 **Lowdon JD**, Tidmore TL. Fatal air embolism after gastrointestinal endoscopy. *Anesthesiology* 1988; **69**: 622-623 [PMID: 3177925]
19 **Butler BD**, Hills BA. Transpulmonary passage of venous air emboli. *J Appl Physiol* 1985; **59**: 543-547 [PMID: 4030608]
20 **Thackray NM**, Murphy PM, McLean RF, deLacy JL. Venous air embolism accompanied by echocardiographic evidence of transpulmonary air passage. *Crit Care Med* 1996; **24**: 359-361 [PMID: 8605815]
21 **Chorost MI**, Wu JT, Webb H, Ghosh BC. Vertebral venous air embolism: an unusual complication following colonoscopy: report of a case. *Dis Colon Rectum* 2003; **46**: 1138-1140 [PMID: 12907914]
22 **Desmond PV**, MacMahon RA. Fatal air embolism following endoscopy of a hepatic portoenterostomy. *Endoscopy* 1990; **22**: 236 [PMID: 2242745]
23 **Park YH**, Kim HJ, Kim JT, Kim HS, Kim CS, Kim SD. Prolonged paradoxical air embolism during intraoperative intestinal endoscopy confirmed by transesophageal echocardiography -A case report-. *Korean J Anesthesiol* 2010; **58**: 560-564 [PMID: 20589182 DOI: 10.4097/kjae.2010.58.6.560]
24 **Pandurangadu AV**, Paul JA, Barawi M, Irvin CB. A case report of cerebral air embolism after esophagogastroduodenoscopy: diagnosis and management in the emergency department. *J Emerg Med* 2012; **43**: 976-979 [PMID: 21236613 DOI: 10.1016/j.jemermed.2010.11.031]
25 **Gottdiener JS**, Papademetriou V, Notargiacomo A, Park WY, Cutler DJ. Incidence and cardiac effects of systemic venous air embolism. Echocardiographic evidence of arterial embolization via noncardiac shunt. *Arch Intern Med* 1988; **148**: 795-800 [PMID: 3355298]
26 **Butler BD**, Bryan-Brown C, Hills BA. Paradoxical air embolism: transcapillary route. *Crit Care Med* 1983; **11**: 837 [PMID: 6617227]
27 **McAree BJ**, Gilliland R, Campbell DM, Lucas JW, Dickey W. Cerebral air embolism complicating esophagogastroduodenoscopy (EGD). *Endoscopy* 2008; **40** Suppl 2: E191-E192 [PMID: 18709611 DOI: 10.1055/s-2007-995728]
28 **Meier CB**, Moser AJ, Sanders MK. Fatal venous air embolism during upper endoscopy in a patient with percutaneous transhepatic cholangiography (PTC) catheter. *Endoscopy* 2010; **42** Suppl 2: E111 [PMID: 20306397 DOI: 10.1055/s-0029-1243942]
29 **Hopkins WE**, Waggoner AD, Barzilai B. Frequency and significance of intrapulmonary right-to-left shunting in end-stage hepatic disease. *Am J Cardiol* 1992; **70**: 516-519 [PMID: 1642191]
30 **Batson OV**. The function of the vertebral veins and their role in the spread of metastases. 1940. *Clin Orthop Relat Res* 1995; (**312**): 4-9 [PMID: 7634616]
31 **Mittnacht AJ**, Sampson I, Bauer J, Reich DL. Air embolism during sigmoidoscopy confirmed by transesophageal echocardiography. *J Cardiothorac Vasc Anesth* 2006; **20**: 387-389 [PMID: 16750742]
32 **Pfaffenbach B**, Wegener M, Böhmeke T. Hepatic portal venous gas after transgastric EUS-guided fine-needle aspiration of an accessory spleen. *Gastrointest Endosc* 1996; **43**: 515-518 [PMID: 8726771]
33 **Bechi A**, Nucera MP, Olivotto I, Manetti R, Fabbri LP. Complete neurological recovery after systemic air embolism during endoscopic retrograde cholangiopancreatography. *Minerva Anestesiol* 2012; **78**: 622-625 [PMID: 22240610]
34 **Muley SS**, Saini SS, Dash HH, Bithal PK. End tidal carbon dioxide monitoring for detection of venous air embolism. *Indian J Med Res* 1990; **92**: 362-366 [PMID: 2125580]
35 **Wang WL**, Wu ZH, Sun Q, Wei JF, Chen XF, Zhou DK, Zhou L, Xie HY, Zheng SS. Meta-analysis: the use of carbon dioxide insufflation vs. room air insufflation for gastrointestinal endoscopy. *Aliment Pharmacol Ther* 2012; **35**: 1145-1154 [PMID: 22452652 DOI: 10.1111/j.1365-2036.2012.05078.x]
36 **Dellon ES**, Hawk JS, Grimm IS, Shaheen NJ. The use of carbon dioxide for insufflation during GI endoscopy: a systematic review. *Gastrointest Endosc* 2009; **69**: 843-849 [PMID: 19152906 DOI: 10.1016/j.gie.2008.05.067]
37 **Siddiqui J**, Jaffe PE, Aziz K, Forouhar F, Sheppard R, Covault J, Bonkovsky HL. Fatal air and bile embolism after percutaneous liver biopsy and ERCP. *Gastrointest Endosc* 2005; **61**: 153-157 [PMID: 15672079]
38 **Jow AZ**, Wan D. Complication of cardiac air embolism during ERCP and EUS-assisted cyst-gastrostomy for pancreatic pseudocyst. *Gastrointest Endosc* 2012; **75**: 220-221 [PMID: 21492848 DOI: 10.1016/j.gie.2011.01.047]
39 **Nayagam J**, Ho KM, Liang J. Fatal systemic air embolism during endoscopic retrograde cholangio-pancreatography. *Anaesth Intensive Care* 2004; **32**: 260-264 [PMID: 15957727]
40 **Romberg C**. Systemic air embolism after ERCP: a case report and review of the literature (with video). *Gastrointest Endosc* 2009; **70**: 1043-1045 [PMID: 19577747 DOI: 10.1016/j.gie.2009.03.028]
41 **Rangappa P**, Uhde B, Byard RW, Wurm A, Thomas PD. Fatal cerebral arterial gas embolism after endoscopic retrograde

cholangiopancreatography. *Indian J Crit Care Med* 2009; **13**: 108-112 [PMID: 19881196 DOI: 10.4103/0972-5229.56061]
42 **Cha ST**, Kwon CI, Seon HG, Ko KH, Hong SP, Hwang SG, Park PW, Rim KS. Fatal biliary-systemic air embolism during endoscopic retrograde cholangiopancreatography: a case with multifocal liver abscesses and choledochoduodenostomy. *Yonsei Med J* 2010; **51**: 287-290 [PMID: 20191026 DOI: 10.3349/ymj.2010.51.2.287]
43 **Giuly E**, Pesenti C, Pernoud N, Bories E, Francon D. [Air embolism: an unusual complication of endoscopic retrograde cholangiopancreatography]. *Ann Fr Anesth Reanim* 2005; **24**: 1400-1403 [PMID: 16226421]
44 **van Boxel GI**, Hommers CE, Dash I, Goodman AJ, Green J, Orme RM. Myocardial and cerebral infarction due to massive air embolism following endoscopic retrograde cholangiopancreatography (ERCP). *Endoscopy* 2010; **42** Suppl 2: E80-E81 [PMID: 20195976 DOI: 10.1055/s-0029-1243826]
45 **Tan BK**, Saunier CF, Cotton F, Gueugniaud PY, Piriou V. [Thoracoabdominal CT scan: a useful tool for the diagnosis of air embolism during an endoscopic retrograde cholangiopancreatography]. *Ann Fr Anesth Reanim* 2008; **27**: 240-243 [PMID: 18313255 DOI: 10.1016/j.annfar.2007.12.015]
46 **Nern C**, Bellut D, Husain N, Pangalu A, Schwarz U, Valavanis A. Fatal cerebral venous air embolism during endoscopic retrograde cholangiopancreatography-case report and review of the literature. *Clin Neuroradiol* 2012; **22**: 371-374 [PMID: 22689221 DOI: 10.1007/s00062-012-0155-0]
47 **Simmons TC**. Hepatic portal venous gas due to endoscopic sphincterotomy. *Am J Gastroenterol* 1988; **83**: 326-328 [PMID: 3344739]
48 **Merine D**, Fishman EK. Uncomplicated portal venous gas associated with duodenal perforation following ERCP: CT features. *J Comput Assist Tomogr* 1989; **13**: 138-139 [PMID: 2910933]
49 **Barthet M**, Membrini P, Bernard JP, Sahel J. Hepatic portal venous gas after endoscopic biliary sphincterotomy. *Gastrointest Endosc* 1994; **40**: 261-263 [PMID: 8013847]
50 **Chavalitdhamrong D**, Draganov PV. Acute stroke due to air embolism complicating ERCP. *Endoscopy* 2013; **45** Suppl 2 UCTN: E177-E178 [PMID: 23801290 DOI: 10.1055/s-0032-1326643]

P- Reviewers De Palma GD, Lachter J **S- Editor** Gou SX
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.v5.i8.366

World J Gastrointest Endosc 2013 August 16; 5(8): 366-368
ISSN 1948-5190 (online)

FIELD OF VISION

Fetal radiation exposure: Is monitoring really needed?

Milena Di Leo, Paolo Giorgio Arcidiacono

Milena Di Leo, Paolo Giorgio Arcidiacono, Endoscopy Unit, Gastroenterology and Gastrointestinal Endoscopy Unit, Vita Salute San Raffaele University, San Raffaele Scientific Institute, 20132 Milano, Italy
Author contributions: Di Leo M, Arcidiacono PG contributed to conception and design, acquisition and interpretation of data, drafting the article and final approval of the version to be published.
Correspondence to: Paolo Giorgio Arcidiacono, MD, FASGE, Chief Endoscopy Unit, Gastroenterology and Gastrointestinal Endoscopy Unit, Vita Salute San Raffaele University, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy. arcidiacono.paologiorgio@hsr.it
Telephone: +39-2-26436306 Fax: +39-2-26435609
Received: February 17, 2013 Revised: April 10, 2013
Accepted: May 8, 2013
Published online: August 16, 2013

Abstract

The effect of fetal radiation during endoscopic retrograde cholangiopancreatography (ERCP) on pregnant women is a very interesting topic. Smith *et al* recently estimated the fetal radiation exposure in pregnant women undergoing ERCPs using thermoluminescent dosimeters (TLDs). The authors concluded that TLDs are unnecessary during ERCP with modified techniques. We believe that an extreme caution is needed in clinical practice before drawing such conclusions when they are not strongly supported by enough experimental evidence. Therefore, we recommend that fetal radiation exposure be monitored in clinical practice by using dosimeters, bearing in mind that all relevant techniques to control and minimize the exposure must be applied.

Key words: Endoscopic retrograde cholangiopancreatography; Pregnancy; Fetal radiation exposure; Thermoluminescent dosimeters; Post-endoscopic retrograde cholangio-pancreatography pancreatitis

Core tip: The effects of endoscopic retrograde cholangiopancreatography (ERCP) on pregnant women, addressed in the recent article by Smith *et al*, is an interesting topic. Despite the large sample of patients investigated by the authors, strong experimental evidence on this topic is still lacking. ERCP should be performed only with a therapeutic purpose and by experienced ERCP endoscopists, preferably during the second trimester of pregnancy.

Di Leo M, Arcidiacono PG. Fetal radiation exposure: Is monitoring really needed? *World J Gastrointest Endosc* 2013; 5(8): 366-368 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/366.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.366

COMMENTARY ON HOT TOPICS

The effects of endoscopic retrograde cholangiopancreatography (ERCP) on pregnant women, addressed in the recent article by Smith *et al*[1], is an interesting topic. It is estimated that 3%-12% of pregnancies are complicated by gallstone disease. In pregnant women weight increase and hormonal changes are responsible for an increase in the prevalence of cholelithiasis or gallbladder sludge. Uncomplicated cholelithiasis should preferably be treated before planning the pregnancy or during the postpartum phase. Fortunately, a pregnancy does not increase the frequency or the severity of complicated gallstone disease. However, when pancreatobiliary disease comes in an acute form, such as acute pancreatitis or cholangitis, there are increased rates of the morbidity and mortality for both the mother and the fetus[2-4]. Since 1990, ERCP has been used in biliary stone disease during pregnancy, although this technique could increase the risk of maternal complications (such as bleeding, perforation, pancreatitis), as in non-pregnant women. Moreover, fetal teratogenicity or tumorigenesis is an additional risk factor for pregnant patients. For these reasons, ERCP is

nowadays only used for therapeutic purposes.

The irradiation risk for the fetus depends on both deterministic and stochastic effects. Deterministic effects are dose-correlated, can affect the growth and development of the fetus, and are most probable between the second and fifteenth week of gestation. According to the consensus statements from the relevant major national organizations, in particular the American Congress of Obstetricians and Gynecologists, the risk of malignancy, miscarriage, or major malformations is negligible in fetuses exposed to 50 mGy or less[5]. The risk of developing cancer following irradiation, although characterized by a small probability, is a stochastic effect and does not have any threshold level. In fact, the probability of stochastic effects shows a monotonic increase as a function of the absorbed dose and follows a "no-threshold" model. According to this model, the carcinogenesis risk has a linear dependence with the radiation doses, and even the smallest dose can potentially increase the risk of cancer occurrence[6].

Numerous studies have addressed the estimation of the radiation exposure levels for the fetus. Cappell[7] performed a comprehensive analysis of 46 previous studies including 296 pregnant women. He observed that the rate of complications after therapeutic ERCP is similar for both pregnant and not-pregnant patients. Cappell identified the most common maternal complications to be pancreatitis, with a rate of 6.4% (only one case was severe and no cases required surgical intervention), and post-sphincterotomy bleeding with an incidence of 1%. Among the 254 cases examined in the Cappell's review the most common fetal complications were: (1) prematurely born infants with a low birth weight (4.3%); (2) late spontaneous abortion (1.2%); (3) infant death right after the birth (0.8%); and (4) voluntary abortion (0.4%).

It is important to mention that the teratogenic effects of radiation on the fetus have a stochastic nature and are essentially unknown. The reason for this may be related to the lack of follow-up after birth in most of the studies on ERCP in pregnancy, potentially underestimating eventual complications. To the best of our knowledge, only Gupta *et al*[8] performed a long term follow up, which revealed that after a median time of 6 years all the babies were healthy.

The aim of the article by Smith *et al*[1] was to estimate the fetal radiation exposure in pregnant women undergoing ERCPs using thermoluminescent dosimeters (TLDs). This is the largest prospective study of ERCP during pregnancy ever published: 35 patients were subjected to ERCP performed by expert endoscopists. In order to minimize the amount of maternal and fetal exposure, the authors suggest performing a modified ERCP technique where colangiography is used only to detect the presence and position of stones after blind common bile duct cannulation and sphincterotomy. Complications occurred in 6 patients (17%): 2 post-sphincterotomy bleeding (5.7%), 2 post-ERCP pancreatitis (5.7%), 1 fatal acute respiratory distress syndrome (2.8%), 1 cholecystitis (2.8%). Four of these patients were carrying a term-fetus, while only two were pre-term, and no data were available regarding the outcome of the uncomplicated pregnancies. In this paper, the authors reported that the fetal irradiation, supposedly due to ERCP, was less than 0.2 mGy in 88.6% of the patient population, concluding that TLDs are actually unnecessary during ERCP with modified techniques since the radiation exposure of the fetus was well below the threshold established by the International Commission of Radiological Protections (10 mGy)[9].

However, this very strong statement it seems not to be strongly supported by sufficient experimental evidence. We strongly disagree with the authors as we believe that extreme caution should always be advocated before drawing such conclusions in clinical practice. We will now critically address all the unclear points and inconsistencies present in the paper. Firstly, we wish to repeat the main message of the paper as reported by the authors themselves: "for a routine ERCP with modified techniques, estimating the fetal radiation exposure from the fluoroscopy time and measuring it with the use of TLDS is unnecessary". This is in apparent contradiction with the statement which appears in the following paragraph of their manuscript: "The threshold may be exceeded in complicated long-lasting ERCPs and in these complicated long-lasting ERCPs, dosimeters may be used to estimate the fetal radiation exposure". In these situations a clear decision cannot be taken, since there are no objective clinical and imaging parameters that can be evaluated prior to ERCP, which are able to predict the duration of the procedure and its difficulty. Furthermore, continued monitoring offers a quality benchmark or an opportunity to keep doses "as low as reasonably attainable".

An additional weak point of the paper is the lack of a proper discussion of age and physical issues. The authors affirmed that the 10% of the dose recorded by TLDs on the upper back could considered to be the fetal dose. However, different gestation ages and different physical and demographic features of the mother could dramatically influence these parameters, considerably modifying their value.

We suggest using a more empirical approach to the problem. In order to verify the real need for radiation dose monitoring, a mathematic model correlating the estimated fetal exposure with physical observables associated with the treatment of the patient should be developed and tested. These parameters could include fluoroscopy exposure time, the procedure time, the gestation age, maternal features, and could vary in number according to the complexity of the model. In this framework, we suggest that entrance skin exposure of the mother could be used as the input variable in an appropriate algorithm able to derive the absolute value of the fetal exposure. This approach would have the advantage of being selective and specific to each patient.

Despite the findings from Smith *et al*[1] and any pos-

sible analytical model, many studies have shown that repeated exposures to low levels of ionizing radiation can cause cancer. In fact, stochastic effects of radiation do not exhibit any threshold dose. For this reason, ESGE Guidelines[10] recommend that the kerma-area product should be monitored, and its cumulative value should be recorded for every ERCP.

In conclusion, we have discussed disease occurrence, radiation risks and fetal exposure during ERCP on pregnant women. In particular we closely evaluated the results obtained by Smith *et al*[1] who estimated the fetal radiation exposure in pregnant women undergoing ERCPs using TLDs, and claimed that TLDs are unnecessary when ERCP is performed with modified techniques. Despite the large sample of patients investigated by these authors, strong experimental evidence is still lacking on this topic. Therefore, until other prospective studies show that TLD monitoring is not necessary, fetal radiation exposure should be always monitored in clinical practice by dosimeters, bearing in mind that all relevant techniques to control and minimize exposure should be applied. Moreover, ERCP should be performed only with a therapeutic purpose and by experienced ERCP endoscopists, preferably during the second trimester of pregnancy.

REFERENCES

1 **Smith I**, Gaidhane M, Goode A, Kahaleh M. Safety of endoscopic retrograde cholangiopancreatography in pregnancy: Fluoroscopy time and fetal exposure, does it matter? *World J Gastrointest Endosc* 2013; **5**: 148-153 [PMID: 23596536 DOI: 10.4253/wjge.v5.i4.148]

2 **Menees S**, Elta G. Endoscopic retrograde cholangiopancreatography during pregnancy. *Gastrointest Endosc Clin N Am* 2006; **16**: 41-57 [PMID: 16546022 DOI: 10.1016/j.giec.2006.01.004]

3 **Shelton J**, Linder JD, Rivera-Alsina ME, Tarnasky PR. Commitment, confirmation, and clearance: new techniques for nonradiation ERCP during pregnancy (with videos). *Gastrointest Endosc* 2008; **67**: 364-368 [PMID: 18226705 DOI: 10.1016/j.gie.2007.09.036]

4 **Tham TC**, Vandervoort J, Wong RC, Montes H, Roston AD, Slivka A, Ferrari AP, Lichtenstein DR, Van Dam J, Nawfel RD, Soetikno R, Carr-Locke DL. Safety of ERCP during pregnancy. *Am J Gastroenterol* 2003; **98**: 308-311 [PMID: 12591046 DOI: 10.1111/j.1572-0241.2003.07261.x]

5 **ACOG Committee Opinion**. Number 299, September 2004 (replaces No. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. *Obstet Gynecol* 2004; **104**: 647-651 [PMID: 15339791]

6 **Doll R**, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 1997; **70**: 130-139 [PMID: 9135438]

7 **Cappell MS**. Risks versus benefits of gastrointestinal endoscopy during pregnancy. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 610-634 [PMID: 21970872 DOI: 10.1038/nrgastro.2011.162]

8 **Gupta R**, Tandan M, Lakhtakia S, Santosh D, Rao GV, Reddy DN. Safety of therapeutic ERCP in pregnancy - an Indian experience. *Indian J Gastroenterol* 2005; **24**: 161-163 [PMID: 16204904]

9 **Pregnancy and medical radiation**. *Ann ICRP* 2000; **30**: iii-viii, 1-43 [PMID: 11108925]

10 **Dumonceau JM**, Garcia-Fernandez FJ, Verdun FR, Carinou E, Donadille L, Damilakis J, Mouzas I, Paraskeva K, Ruiz-Lopez N, Struelens L, Tsapaki V, Vanhavere F, Valatas V, Sans-Merce M. Radiation protection in digestive endoscopy: European Society of Digestive Endoscopy (ESGE) guideline. *Endoscopy* 2012; **44**: 408-421 [PMID: 22438152 DOI: 10.1055/s-0031-1291791]

P- Reviewers Anastasian ZH, Mercuri M
S- Editor Gou SX **L- Editor** Hughes D **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i8.369

World J Gastrointest Endosc 2013 August 16; 5(8): 369-378
ISSN 1948-5190 (online)

REVIEW

Training in endoscopic submucosal dissection

Roxana M Coman, Takuji Gotoda, Peter V Draganov

Roxana M Coman, Peter V Draganov, Division of Gastroenterology, Hepatology and Nutrition, University of Florida, Gainesville, Gainesville, FL 32610, United States
Takuji Gotoda, Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo 160-0023, Japan
Author contributions: Coman RM did the literature search and wrote the first draft of the manuscript; Gotoda T contributed new articles to the literature search and provided critical review of the article; Draganov PV provided the concept of the article, contributed new articles to the literature search and provided critical review.
Correspondence to: Dr. Peter V Draganov, Division of Gastroenterology, Hepatology and Nutrition, University of Florida, 1600 SW Archer Rd., Room HD 602, PO Box 100214, Gainesville, FL 32610, United States. dragapv@medicine.ufl.edu
Telephone: +1-352-3922877 Fax: +1-352-3923618
Received: March 28, 2013 Revised: April 26, 2013
Accepted: June 18, 2013
Published online: August 16, 2013

Abstract

Endoscopic submucosal dissection (ESD) represents an important advancement in the therapy of early neoplastic gastrointestinal lesions by providing higher *en-bloc* curative resection rate with lower recurrence compared to endoscopic mucosal resection (EMR) and by sparing the involved organ and protecting patient's quality of life. Despite these advantages ESD is associated with long procedure times and a higher rate of complications, making ESD a challenging procedure which requires advanced endoscopic skills. Thus, there has been a recognized need for structured training system for ESD to enhance trainee experience and, to reduce the risks of complications and inadequate treatment. ESD has a very flat learning curve. However, we do not have uniformly accepted benchmarks for competency. Nevertheless, it appears that, in Japan, more than 30 supervised gastric ESD procedures are required to achieve technical proficiency and minimize complications. A number of training algorithms have been proposed in Japan with the aim to standardize ESD training. These algorithms cannot be directly applied in the West due to substantial differences including the availability of highly qualified mentors, the type of pathology seen, choice of devices, and trainee's background. We propose a training algorithm for Western physicians which integrates both hands-on training courses, animal model work as well as visits to expert centers. No specific preceptor training programs have been yet developed but there is a consensus that these programs are important for permeation of ESD worldwide.

Key words: Endoscopic submucosal dissection; Training; Learning curve; Early gastrointestinal cancer; Endoscopic mucosal resection

Core tip: Endoscopic submucosal dissection (ESD) is a complex procedure associated with high complication rate. In Japan, training in ESD follows the traditional mentor/apprentice approach but significant variability in training approaches exists. We review the learning curves for ESD and describe the training algorithm proposed in Japan aiming to standardize training, and its applicability in the West. We highlight the challenges for ESD dissemination in the West, describing both the consensus and the diverging opinions between Asian and Western training models. Finally, we emphasize the need for structured training system to enhance trainee experience and, most importantly, to reduce the risks of complications and inadequate treatment.

Coman RM, Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; 5(8): 369-378 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/369.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.369

INTRODUCTION

Endoscopic submucosal dissection (ESD) was developed in Japan in the late 1990s as an advanced, minimally invasive technique for endoscopic removal of early gastric cancers[1-5]. *En-bloc* resection with standard endoscopic mucosal resection (EMR) techniques is limited to lesions less than 2 cm in diameter, while ESD yields a higher complete resection regardless of size. EMR remains the typical approach in Western countries to treat dysplastic lesions and early cancers[6-9] while in Asia, ESD has become the preferred therapeutic modality of superficial tumors in both the upper and lower gastrointestinal tract[3]. It is even considered that it brought about a renaissance of therapeutic endoscopy[10] as it is able to offer organ-sparing cure in patient with early gastrointestinal (GI) cancers[11].

ESD has been a significant advancement in therapeutic endoscopy with its major advantages being the ability to achieve a higher *en-bloc* resection rate, accurate histological evaluation and lower cancer recurrence rates compared to EMR[3,12-15]. In addition, ESD enables *en-bloc* removal of previously unresectable lesions, such as large mucosal tumors, tumors with scars and submucosal fibrosis, or recurrent tumors after EMR[16,17]. Finally, as opposed to surgery, ESD preserves the structural integrity of the GI tract therefore protecting patient's quality of life.

Despite its obvious advantages, ESD is one of the most complex endoscopic techniques, with several technical difficulties to overcome and potentially high complication rates, especially in the beginning of the learning curve[18-20]. The most frequent complications are bleeding and perforation. Bleeding during the procedure is very common but only rarely can be significant to the extent which requires the procedure to be stopped[21]. Compared to conventional EMR, the rate of perforation with ESD is higher, at about 1%-4% and it might require emergent surgical treatment but most of the time, perforations can be successfully managed conservatively[9,21,22].

In Japan, where there is a high incidence of the gastric cancer, a mass screening program with photofluorography, double-contrast radiography, chromoendoscopy, and endoscopy has been conducted since 1960[23-28]. Thus, a large proportion of Japanese gastric cancers are detected at an early stage, with a better overall survival rate[29,30]. ESD is routinely performed for resection of these early cancers in most centers in Japan including local branch hospitals. On the other hand, in the West ESD is still largely not available and is done only in a handful of centers by few advanced therapeutic endoscopy enthusiasts. Although ESD is largely not available in Europe and the United States, over the last 2-3 years there has been significant interest in ESD live demonstrations and hands-on seminars. There is a number of reasons for this slow dissemination of ESD in the West, including the complexity of the procedure, long procedure time, device availability, increased utilization of endoscopic resources, higher complication rates and, in the United States, lack of dedicated reimbursement code. However, the main obstacle for the wide availability of ESD in the West has been and remains the very flat learning curve and lack of training resources[31]. As ESD, with its advantages and challenges, has permeated deeper in the gastroenterology community, it became obvious that more endoscopists will be interested in acquiring this technique. It has been anticipated that the widespread adaptation of ESD for the treatment of pre- and early GI cancers will require major shifts in training and practice culture[32]. Therefore, we wanted to review the current state of training in ESD and emphasize the need for a structured training system in order to enhance trainee experience and, most importantly, to reduce the risks of procedural complications and inadequate treatment.

ESD LEARNING CURVE

It has been showed that when prior knowledge of advanced resection techniques is limited and no supervision by an expert in ESD is available, there is a learning curve in which not only the *en-bloc* resection rate and procedure duration improve with increasing experience but, more importantly, the perforation rate decreases too[33].

Learning curve for gastric ESD

Several reports have analyzed the learning curve for ESD in the stomach. Gotoda *et al*[34] found that experience of at least 30 cases is required for a beginner to gain early proficiency in this technique[34]. Choi *et al*[33] investigated the learning curve for ESD and reported an increase in the *en-bloc* resection rate from 45% to 85% after experience of 40 cases. They concluded that trainees need to perform 20-40 procedures to be able to use the technique effectively, although their method consisted of mucosal incision and snaring rather than standard ESD. From their data, which included 383 ESD procedures for gastric epithelial neoplasms performed over a 5-year period, Kakushima *et al*[11] estimated that a trainee could begin to treat lesions in the lower part of the stomach independently after performing about 30 supervised ESD procedures. In a more recent study, two of the three operators could not achieve a sufficient self-completion rate for submucosal dissection after 30 cases, which suggests that more extensive experience is required before the trainees can be considered proficient[35]. However, in this study, the trainees performed the ESD under the supervision of an experienced endoscopist and their training did not include hands-on training on *ex-vivo* animal models or living animals, which might have improved the learning curve. A study conducted by the same group in 2012 showed that the trainees required approximately 40 and 80 cases for successful removal of guideline-indication lesions and expanded-indication lesions by ESD. The procedural outcomes of ESD performed by preceptees who had experience in over 80 cases were similar to those by expert endoscopists. Thus,

these findings suggest that the amount of training for achieving proficiency in ESD can be the performance of as many as 80 procedures[36]. Tsuji *et al*[37] concluded that the training system at their institution (which included training in animal models) enabled trainees to perform gastric ESD without decline in clinical outcomes, although 30 procedures were not enough for them to perform all gastric ESD independently without expert supervision, as expert assistance was still needed in a remaining 20% of ESDs. The keys to improving the learning curve were considered to be: good hemostasis technique and a sufficient level of submucosal dissection skill. Oda *et al*[38] used procedure time as an indicator of ESD proficiency and determined that 30 cases were necessary to acquire the basic technical skills for successfully performing ESD in the lower third of the stomach. In their estimation, performing at least 40 ESD would be the minimum learning curve point before starting to perform ESD in the middle and upper thirds of the stomach.

Learning curve for extra-gastric ESD

Recent studies showed that high cure rates are achievable using ESD for appropriate lesions in the esophagus and colorectum with no increase in complication rates, when the procedure is done by experienced endoscopist[39-42]. In a meta-analysis including 14 studies, Puli *et al*[43] concluded that ESD is the best minimally invasive endoscopic technique, and an important alternative to surgery, in the treatment of large (> 2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. In a match-control study comparing ESD with EMR for treatment of early-stage colorectal tumors, Kobayashi *et al*[9] showed that colonic ESD achieved a high *en-bloc* resection rate and a low recurrence rate in short term. Most of the learning curve studies and training strategies have been developed for gastric ESD. However, the increased use of ESD in the colon and esophagus created a demand to further study and ESD skill acquisition in extra-gastric sites[9,44-51]. In Japan, endoscopists typically first experience ESD in the stomach because of the high incidence of gastric neoplasms and the relative safety of ESD in this location[36]. These conditions allow for opportunities to acquire sufficient experience in performing ESD. However, esophageal and colonic ESD presents the significant hurdle of technical difficulty and risk of severe complications even among Japanese endoscopists, who generally have greater experience in ESD than endoscopists in other countries.

Some experts consider that ESD in extra-gastric locations should not be attempted unless the endoscopist has experience in performing gastric ESD. Dinis-Ribeiro *et al*[52] suggested that only after performing 20-40 ESDs in the distal stomach, should lesions located in proximal sites in the stomach, esophagus, and colon be tried. Hotta *et al*[53] reported on the learning curve for colonic ESD, and they concluded that performance of approximately 40 procedures was sufficient to acquire the skill to avoid causing perforations during the ESD procedure, and approximately 80 procedures must be carried out to acquire adequate skill to successfully remove large colorectal tumors. Sakamoto *et al*[54] reported that trainees can perform colorectal ESD safely and independently after preparatory training and experience with more than 30 cases. In these two latter studies, the operators had performed 20 upper GI ESD before starting colorectal ESD.

A small number of analyses conducted in an earlier Japanese multicenter study indicated a higher complication rate during colorectal ESDs and that standardization of the colorectal ESD procedure would be difficult[55]. Despite greater risks of postoperative complications, particularly, more and more endoscopists are making an effort to study this new technique in terms of its capability of larger neoplasms resection, higher *en-bloc* resection rate and lower local recurrence rate of neoplasms in comparison with other endoscopic treatments. Ohata *et al*[56] proposed a 7-step training system for learning colorectal ESD, which is very similar to the training algorithms used for gastric ESD, but with the emphasis on technical differences imposed by performing the procedure in a narrower space with thinner wall. One of the mandatory enrolment criteria was performance of at least 30 gastric ESDs. The results suggested that trainees with relatively little prior experience with gastric ESD (*i.e.*, 30 procedures) could reach a stable level of technical competency in colorectal ESD after an average of 30 cases of the latter procedure. The study found that, regardless of the gastric ESD experience, the mean procedure time of each trainee became less than 80 min after performing more than 30 cases. Trainees with experience in many (*i.e.*, 200) gastric ESDs could perform colorectal ESD skillfully from the initial period of training onward[56].

What have we learned about ESD learning curves

Despite significant efforts to evaluate the learning curve of acquiring ESD skills no definitive conclusions can be reached due to the differences among studies as far as the type of lesions included, type of ESD devices used, degree of supervision, type of training system, trainee exposure to animal models, definition of outcomes and in the case of colonic ESD the degree of prior experience with gastric ESD. Therefore, in Japan, although ESD training varies among institutions, skills are still acquired in the traditional time honored apprenticeship model of training in endoscopy "see one, do one, teach one". There has been a recognized need for structured training system for ESD in order to enhance trainee experience and, most importantly, to reduce the risks of procedural complications and inadequate treatment[11].

ESD TRAINING SYSTEMS

At present there is no universally accepted algorithm for training in ESD. Nevertheless, it appears that there is a consensus on some key points. Given the complexities

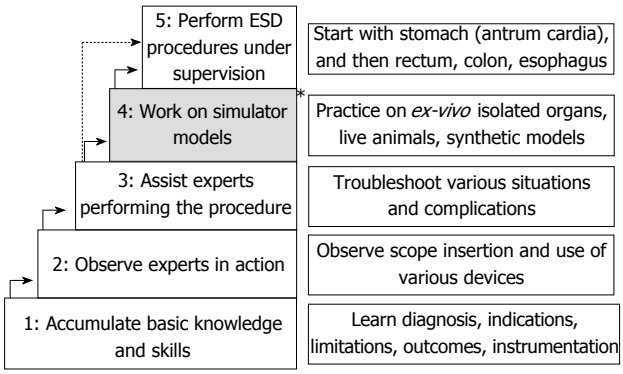


Figure 1 Japanese model for a structured endoscopic submucosal dissection training. The * indicates the 4th step (practice on *ex-vivo* and live animal models) which is not employed in all Japanese training algorithm. ESD: Endoscopic submucosal dissection.

of this technique, the training program must contain a solid cognitive-based preparation, and hands-on patient-based training. Also, the minimal requirements and final attainments for trainees at each level must be established prior to starting the training[37].

As expected, most well-implemented training programs/algorithms are in Japan. These algorithms typically include two major stages of training: pre-procedural, theoretic preparation and hands-on training[32,35-38]. The first stage has two phases: phase 1-accumulation of basic knowledge and phase 2-observe experts in action. The second stage includes phase 3-assist experts performing the procedure, phase 4-working on simulator models, such as *ex-vivo* and *in-vivo* animal model, or synthetic models of organ of interest, and phase 5-perform ESD procedures under supervision (Figure 1).

Recently, several training algorithms have been proposed. One of the earliest proposed training algorithms by Yamamoto *et al*[35] in 2009 puts emphasis on the initial pre-procedural phase of the training. Thus, the endoscopists who intend to learn ESD must attend pre- and post-treatment conferences, and take part in actual ESD procedures as an assistant for at least 1 year before beginning doing the procedure themselves. In addition to gastroenterologists, surgeons and pathologists are included in these conferences, and thus the trainee learns how to diagnose the extent and depth of the tumor, establish the optimum treatment strategy, and manage the patients appropriately according to the histopathological findings in resected specimens. By assisting experienced endoscopists, trainees acquire the skills needed to troubleshoot various situations. Moreover, obtaining expertise in hemostasis before starting ESD is highly recommended since most of the difficulties surrounding the procedure were related to uncontrollable hemorrhage[35]. The same group expanded the requirements of the pre-procedural training to master detailed preoperative examination by magnifying endoscopy with narrowband imaging, preoperative marking using ink and endo-clips, hemostasis of second-look endoscopy after ESD[36]. Similar approach is proposed by Kaltenbach *et al*[32], where the trainees are assisted in developing crucial diagnostic skills to select appropriate lesions and specific management strategy for ESD cases. The next step is for trainees to observe expert endoscopists in action as they perform various ESD procedures[38].

ESD is a technically demanding procedure requiring a high level of endoscopic skill. Consequently, in the second stage of the training, the trainees start by assisting experts in performing ESD procedure. Next, the trainees are exposed to animal models to enhance their technical skills. Hands-on experience with ESD in isolated pig stomach or live pigs facilitates familiarity with the tools and techniques of the procedure. Trainees can appreciate the differences in technique depending on lesion size and location. After gaining familiarity with the tools and technique, trainees typically start performing ESD in patients by removing small gastric lesions in the antrum or body under the close supervision of an experienced endoscopist, who both offers advice and can complete the procedure if necessary[32,38]. Yamamoto *et al*[35] propose a system where the trainees do not use animal models but start as assistants in live patient cases and then continue with performing ESD on patients under expert supervision. For this reason, they recommend that in this "supervision-only" training algorithm, one should start with small lesions in the lower third of the stomach. These lesions are relatively easy and less time-consuming to remove, so the trainees have the opportunity to learn the entire ESD procedure. After this, it is easier to move on to larger lesions, because the procedure for large lesions consists of repeating certain basic steps[35].

In summary, in Japan, a consensus exists on the following issues: (1) need of solid cognitive background regarding lesion evaluation, indications, contraindications and technical aspects of ESD; (2) need for observation of ESD as done by experts; (3) need to assist experts and operate the ESD devices; (4) need for hands-on training in humans under direct expert supervision; and (5) starting hands-on training with easier lesions and progressing to more difficult ones. Importantly, in Japan there is a number of areas where diverging opinions exist. These include: (1) need for simulation-based training; (2) need to use live animal models; (3) need to acquire a predetermined number of ESD cases in the stomach before moving to esophagus and colorectum; and (4) specific milestones for competency that the trainee has to meet before starting to practice ESD independently.

ESD TRAINING IN THE WEST

Unfortunately, the extensive Japanese experience in ESD training cannot be directly applied in the West due to a number of substantial differences. At present, in the West, there is only a handful of highly qualified experts in ESD. Therefore, doing ESD under direct expert supervision is not feasible in most cases. Importantly, the type of pathology seen in the West is different than the

one in Japan. Specifically, there are very few cases of early gastric cancer and therefore no opportunity for the trainee to start their training in locations that are considered easier, such as the gastric antrum[35,57,58]. In addition, the choice of devices, endoscopes and ancillary equipment for ESD available in the West is different compared with the one available in Japan[59]. Likewise, the technical expertise and backgrounds of endoscopists embarking on ESD in the West differs significantly than their Eastern counterparts. At present, in Japan, the typical trainee learning ESD is a GI fellow. On the other hand, in the West, physicians embarking on ESD typically are more mature and otherwise well experienced therapeutic endoscopists. Furthermore, in Japan, physicians learning and performing ESD tend to focus their practice exclusively on ESD as opposed to the endoscopists in the West who tend to incorporate ESD into a developed advanced therapeutic endoscopy practice that typically includes endoscopic retrograde cholangiopancreatography (ERCP) and/or endoscopic ultrasound (EUS). In addition, even if ESD is considered more economical and less invasive, in the West laparoscopic surgery and transanal resection for colorectal lesions are more established techniques[59]. It has been well recognized that the specific circumstances in the West call for tailored approach in ESD training.

In the West, opportunities to pursue ESD training using the Japanese training algorithm have been limited by the low rates of early gastric cancer and thus the inability to enter the ESD learning curve at the relatively safest location[19,32]. To master the techniques of ESD, particularly in areas with a low incidence of early GI cancers, it was recommended to formulate a standardized protocol for training following the Japanese training model. The role of adequate training is, of course, to influence the spread of this technique, to set standards for training and certification, to promote quality management, and to limit complications inherent to early learning[31]. Several studies published good results after successful ESD procedures performed in humans in several Western countries[52,60-62].

In 2008, a panel of experts gathered in Rotterdam ("Experts meet experts," Rotterdam, The Netherlands, 11-12 February 2008) to discuss indications, training, and the wider use of ESD. The minimum training requirements were also defined: knowledge in indications and instruments, exposure to experts (currently mostly in Japan), hands-on experience in a model of isolated pig stomach and in live pigs, and management of complications. The experts did not reach a consensus on a minimum case load, or whether the technique should be restricted to expert centers. Dr. Jelle Haringsma proposed a structured training algorithm with the following steps: (1) acquire basic knowledge, defined as knowledge about the types of disease treated with this approach, instrumentation, operation of the electrosurgical unit, and familiarity with indications, limitations, risks, and outcomes of ESD; (2) see experts at work, namely in Japan; (3) assist in procedures; (4) training on animal models-isolated pig stomach and live pigs. In animal models, a minimum of 30 resections reaching a resection speed of 30 min for a lesion with maximum diameter of 5 cm, and management of complications, were suggested as aims of training; (5) perform procedures on patients; and (6) continue training. Emphasis is also put on a training continuum with books, DVDs, journals, conferences, live demonstrations (master classes and courses), and visits to expert centers.

As outlined earlier, in Japan, one area of diverging opinions is the value of practice in explanted or live animal models. Kakushima *et al*[11] noticed that there does not seem to be any differences in the perforation rates when performing ESD between trainees and experts when the former are supervised by the latter. As a result, training on animal models is not routinely accepted practice in Japan. While training in animal models may not be needed in Japanese institutions where supervision by experts is easily available, these models can be a valuable resource when training in the West. Models could allow endoscopists to ascend the learning curve in a relatively short time, especially when training in low volume centers or/and without direct expert supervision[32,37,63,64]. Two prospective studies were aimed in determining the results, efficacy, and safety of ESD performed in pigs by an endoscopist at the beginning of the learning curve prior to its application in humans. The strategy proposed was to start training in ESD on animal models in the absence of experts to supervise the procedures and ensure the patients' safety. The studies showed that training in pigs could be started without such previous learning, and may augment the acquisition of skills in low-volume centers. However, ESD involves maneuvers that traditionally have not been used during flexible endoscopy, which would be difficult to master by oneself[64,65].

The harvested porcine organs are ready-to-use and inexpensive means of becoming proficient in these techniques. Multiple large resections in the esophagus and stomach may be practiced before using a live porcine model. However, one of the main perceived disadvantages is that the *ex-vivo* animal models do not help in acquiring the skills of hemostasis and approaching a deep enough level of the submucosal layer, because bleeding does not occur[32].

The live pig model simulates a more realistic endoscopy setting and provides the opportunity to respond to and treat potential complications including bleeding and perforation[19]. However, some of the differences between pig and human stomach, such infrequent bleeding and lack of fibrosis in the pig stomach might make the procedure less challenging than in humans. Another potential disadvantage is that live animal models are expensive and not all institutions or hospitals are equipped for their usage.

Animal models could be used not only for training in gastric ESD but also for esophageal and colonic ESD[66-69]. Tanaka *et al*[67] developed an original training

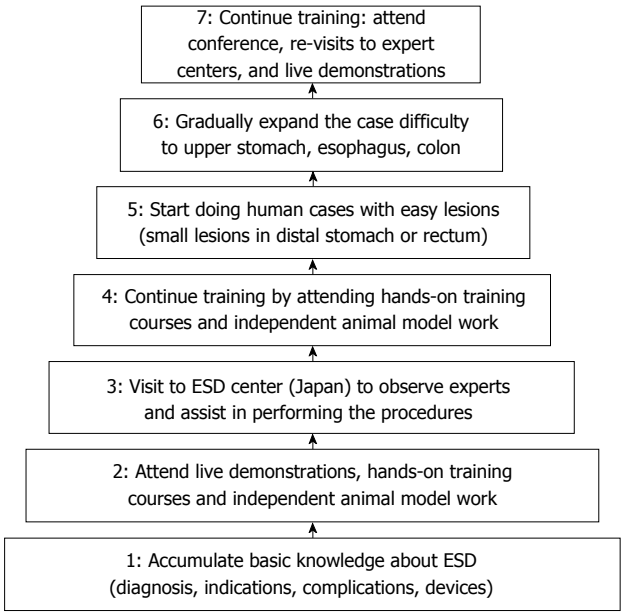


Figure 2 Proposed training algorithm for Western physicians, which integrates hands-on training courses, animal model work and visit to expert centers. ESD: Endoscopic submucosal dissection.

model for esophageal ESD using isolated pig esophagus and assessed this *ex-vivo* model in endoscopists with experience in gastric ESD. The operation time and number of muscularis propria layer injuries decreased gradually as endoscopists gained training experience, while the mean number of muscularis propria layer injuries significantly decreased for all of the endoscopists in the latter period compared with the former period.

While it has been demonstrated that certain skills can be acquired during self-guided animal model training, learning from experts appears crucial to achieve the ability to perform ESD safely in humans[64]. Therefore observing experts and performing ESD under expert supervision in addition to practicing on animal model appears a necessary step while training in the West[31,70-72]. Since, at this time most highly experienced endoscopists performing ESD are in Japan, a visit to a specialized center in Japan most likely will remain, for some time, an essential component of ESD training in the West. Other possible strategies would be to organize training courses (with animal and/or human training) under the supervision of experts, or to attempt ESD procedures supervised by means of a videoconference. However, the impact of these methods on ESD performance has yet to be determined[64]. Such, Western and Asian centers should collaborate closely in terms of training, exchange of data, and initiation of international multicenter trials[60].

We propose a training algorithm for Western physicians which integrates both hands-on training courses, animal model work as well as visit to expert centers (Figure 2). The initial step of the training can be accomplished through independent effort, using printed and video materials to learn about the procedure, indication and diagnosis. We believe that at this stage a dedicated effort to acquire detailed knowledge of the principles of electrosurgery is an essential step. Modern electrosurgical generators provide menus of predetermined settings for most routine procedures (*e.g.*, polypectomy, sphincterotomy, *etc.*). On the other hand, no such preset menus exist for ESD. Settings can vary dramatically based on stage of the procedure, type of instrument and lesion location. In addition, multiple other variables can significantly contribute to the final tissue effect. These include the surface area of the device electrode in contact with the tissue, the speed of movement of the electrode, the pressure applied with the electrode, the presence of coagulated tissue debris sticking to the electrode and the target tissue itself (fibrotic versus high water content). Importantly, the most significant factor remains the endoscopist's ESD technique. Therefore, a thorough understanding of the various modulated currents and their relation to ESD technique is essential to allow individualized choice of electrosurgical unit settings. Then, the endoscopists should attend live presentations and enroll in hands-on training courses to learn about the use of various devices and to practice on animal or synthetic models. After accumulation of this theoretical and practical fund of knowledge, we recommend a visit to an expert center. Most of these centers are currently located in Japan. However, with more endoscopists learning this technique, we anticipate that new training centers will open throughout the world. We are aware that not all endoscopists can spend long periods of time outside their practice, but we encourage at least 3 to 4 wk visit to a high volume ESD center in Japan. During this time, the trainees will assist experts in performing procedures, thus reaching the necessary diagnostic and therapeutic skill level. Upon return, the trainees should practice their newly acquired skills continuing training on simulator models. The next step is to start performing ESD on human patients. We advocate to start with lesions located in the distal stomach or rectum, as these are easier to remove and have a lower complication rate. During the initial human cases, expert supervision by means of videoconference is encouraged if direct supervision is not possible. Review of the endoscopy images prior to the ESD by an expert can provide the valuable opportunity to outline a specific procedure strategy which is an essential part of successful ESD. Then, gradually, the endoscopists can expand to cases of increasing difficulty such as treating larger lesions, or lesions located in the cardia, fundus, colon or esophagus. Finally, as in any other field, we recommend continuous training, with attending/presenting at conferences, re-visiting expert centers, reviewing literature and participating in courses and live demonstrations.

TRAINING PROGRAMS FOR TRAINERS

This is a relatively new but important concept, as the training program for trainers is highly demanded for permeation of ESD worldwide and it is also necessary for trainers to be evaluated and rewarded. Endoscopists in Asian as well as Western countries are waiting for Japanese endoscopists to assist them more or less,

in different ways according to the background of each country[73]. To assess the prerequisites for preceptorship, Goda *et al*[74] used a questionnaire survey to Japanese experts in representative teaching hospitals regarding their training method of gastric and esophageal ESD. This study indicated many requirements for the preceptor: having quite a high level of diagnostic ability, and proficient ESD techniques in the colorectum as well as the stomach and esophagus. It is also necessary that they are a regular staff with a certified qualification.

In a previous report, most Japanese experts set the level of expertise at 50-100 cases of gastric ESD in order to become proficient in gastric ESD. In a more recent study, Yamamoto *et al*[36] agreed with previous finding, showing that the minimal amount of training for achieving preceptorship in ESD is performance of at least 80 of the procedures.

Thus, so far, it appears that, to reach preceptorship level, the endoscopists need both a certain level of expertise, defined in number of procedures performed and a certification of their skills by an authorized body such as Gastroenterological or Endoscopy Societies. However, no specific preceptor training programs have been yet developed but there is a consensus that these programs are important for spreading ESD worldwide[73].

CONCLUSION

ESD represents an evolutionary step in therapeutic endoscopy. Using new skills, devices, and disposables, ESD achieves high rates of *en-bloc* curative resection rates for early GI cancers. However, the learning process for this advanced endoscopic procedure requires a lengthy training period and considerable experience to be proficient. A well-structured training program, safe, effective and easily reproducible is essential for the trainee, because the outcome of ESD is highly dependent on the experience of the endoscopist. It is also recommended that the training program should be tailored around needs based on culture and/or country since the incidence of disease and working environment may be different.

In Western countries, training in ESD is challenging given the lack of training in early gastric cancer lesions, assumed to be a relatively safer location to enter the learning curve. Currently, esophageal and colonic ESD are getting wider acceptance in the West where there is an effective screening process for Barrett's and colon cancer with a large number of these lesions been detected in an early stage. We are proposing a training algorithm that will employ local resources to start the training in ESD and consolidate the knowledge and skill by learning from experts in Japanese centers.

Despite of all obstacles, ESD applications are continuing to grow in the West. Close collaboration between Western and Asian countries will be helpful to improve ESD technique for various sites and to benefit patients who are suffering from early gastric, esophageal or colorectal cancer.

REFERENCES

1 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645]

2 **Ohkuwa M**, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221-226 [PMID: 11293753 DOI: 10.1055/s-2001-12805]

3 **Tanaka M**, Ono H, Hasuike N, Takizawa K. Endoscopic submucosal dissection of early gastric cancer. *Digestion* 2008; **77** Suppl 1: 23-28 [PMID: 18204258 DOI: 10.1159/000111484]

4 **Gotoda T**, Jung HY. Endoscopic resection (endoscopic mucosal resection/ endoscopic submucosal dissection) for early gastric cancer. *Dig Endosc* 2013; **25** Suppl 1: 55-63 [PMID: 23362925 DOI: 10.1111/den.12003]

5 **Kato M**, Nishida T, Tsutsui S, Komori M, Michida T, Yamamoto K, Kawai N, Kitamura S, Zushi S, Nishihara A, Nakanishi F, Kinoshita K, Yamada T, Iijima H, Tsujii M, Hayashi N. Endoscopic submucosal dissection as a treatment for gastric noninvasive neoplasia: a multicenter study by Osaka University ESD Study Group. *J Gastroenterol* 2011; **46**: 325-331 [PMID: 21107615 DOI: 10.1007/s00535-010-0350-1]

6 **Watanabe K**, Ogata S, Kawazoe S, Watanabe K, Koyama T, Kajiwara T, Shimoda Y, Takase Y, Irie K, Mizuguchi M, Tsunada S, Iwakiri R, Fujimoto K. Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest Endosc* 2006; **63**: 776-782 [PMID: 16650537 DOI: 10.1016/j.gie.2005.08.049]

7 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kanao H, Kawamura T, Yoshida S, Yoshihara M, Chayama K. Endoscopic submucosal dissection for residual/local recurrence of early gastric cancer after endoscopic mucosal resection. *Endoscopy* 2006; **38**: 996-1000 [PMID: 17058164 DOI: 10.1055/s-2006-944780]

8 **Saito Y**, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2010; **72**: 1217-1225 [PMID: 21030017 DOI: 10.1016/j.gie.2010.08.004]

9 **Kobayashi N**, Yoshitake N, Hirahara Y, Konishi J, Saito Y, Matsuda T, Ishikawa T, Sekiguchi R, Fujimori T. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. *J Gastroenterol Hepatol* 2012; **27**: 728-733 [PMID: 22004124 DOI: 10.1111/j.1440-1746.2011.06942.x]

10 **Kwon CI**. Endoscopic Submucosal Dissection (ESD) Training and Performing ESD with Accurate and Safe Techniques. *Clin Endosc* 2012; **45**: 347-349 [PMID: 23251880 DOI: 10.5946/ce.2012.45.4.347]

11 **Kakushima N**, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. *Endoscopy* 2006; **38**: 991-995 [PMID: 17058163 DOI: 10.1055/s-2006-944808]

12 **Uraoka T**, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection in Japan and Western countries. *Dig Endosc* 2012; **24** Suppl 1: 80-83 [PMID: 22533758 DOI: 10.1111/j.1443-1661.2012.01279.x]

13 **Toyokawa T**, Fujita I, Morikawa T, Okamoto A, Miyasaka R, Watanabe K, Horii J, Gobaru M, Terao M, Murakami T, Tomoda J. Clinical outcomes of ESD for early gastric neoplasms in elderly patients. *Eur J Clin Invest* 2011; **41**: 474-478 [PMID: 21128933 DOI: 10.1111/j.1365-2362.2010.02428.x]

14 **Cao Y**, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis

of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; **41**: 751-757 [PMID: 19693750 DOI: 10.1055/s-0029-1215053]
15 **Isomoto H**, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut* 2009; **58**: 331-336 [PMID: 19001058 DOI: 10.1136/gut.2008.165381]
16 **Takeuchi Y**, Uedo N, Iishi H, Yamamoto S, Yamamoto S, Yamada T, Higashino K, Ishihara R, Tatsuta M, Ishiguro S. Endoscopic submucosal dissection with insulated-tip knife for large mucosal early gastric cancer: a feasibility study (with videos). *Gastrointest Endosc* 2007; **66**: 186-193 [PMID: 17591498 DOI: 10.1016/j.gie.2007.03.1059]
17 **Yokoi C**, Gotoda T, Hamanaka H, Oda I. Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006; **64**: 212-218 [PMID: 16860071 DOI: 10.1016/j.gie.2005.10.038]
18 **Oda I**, Suzuki H, Nonaka S, Yoshinaga S. Complications of gastric endoscopic submucosal dissection. *Dig Endosc* 2013; **25** Suppl 1: 71-78 [PMID: 23368986 DOI: 10.1111/j.1443-1661.2012.01376.x]
19 **Berr F**, Ponchon T, Neureiter D, Kiesslich T, Haringsma J, Kaehler GF, Schmoll F, Messmann H, Yahagi N, Oyama T. Experimental endoscopic submucosal dissection training in a porcine model: learning experience of skilled Western endoscopists. *Dig Endosc* 2011; **23**: 281-289 [PMID: 21951087 DOI: 10.1111/j.1443-1661.2011.01129.x]
20 **Toyonaga T**, Man-i M, East JE, Nishino E, Ono W, Hirooka T, Ueda C, Iwata Y, Sugiyama T, Dozaiku T, Hirooka T, Fujita T, Inokuchi H, Azuma T. 1,635 Endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. *Surg Endosc* 2013; **27**: 1000-1008 [PMID: 23052530 DOI: 10.1007/s00464-012-2555-2]
21 **Oda I**, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, Bhandari P, Emura F, Saito D, Ono H. Endoscopic Submucosal Dissection for Early Gastric Cancer: Technical Feasibility, Operation Time and Complications from a Large Consecutive Series. *Digestive Endosc* 2005; **17**: 54-58 [DOI: 10.1111/j.1443-1661.2005.00459.x]
22 **Sugimoto T**, Okamoto M, Mitsuno Y, Kondo S, Ogura K, Ohmae T, Mizuno H, Yoshida S, Isomura Y, Yamaji Y, Kawabe T, Omata M, Koike K. Endoscopic submucosal dissection is an effective and safe therapy for early gastric neoplasms: a multicenter feasible study. *J Clin Gastroenterol* 2012; **46**: 124-129 [PMID: 21959325 DOI: 10.1097/MCG.0b013e31822f3988]
23 **Hamashima C**, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008; **38**: 259-267 [PMID: 18344316 DOI: 10.1093/jjco/hyn017]
24 **Katai H**, Sano T. Early gastric cancer: concepts, diagnosis, and management. *Int J Clin Oncol* 2005; **10**: 375-383 [PMID: 16369740 DOI: 10.1007/s10147-005-0534-5]
25 **Sugano K**, Sato K, Yao K. New diagnostic approaches for early detection of gastric cancer. *Dig Dis* 2004; **22**: 327-333 [PMID: 15812155 DOI: 10.1159/000083594]
26 **Toyoizumi H**, Kaise M, Arakawa H, Yonezawa J, Yoshida Y, Kato M, Yoshimura N, Goda K-i, Tajiri H. Ultrathin endoscopy versus high-resolution endoscopy for diagnosing superficial gastric neoplasia. *Gastrointestinal Endosc* 2009; **70**: 240-245 [DOI: 10.1016/j.gie.2008.10.064]
27 **Dinis-Ribeiro M**. Chromoendoscopy for early diagnosis of gastric cancer. *Eur J Gastroenterol Hepatol* 2006; **18**: 831-838 [PMID: 16825898 DOI: 10.1097/00042737-200608000-00005]
28 **Yao K**, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. *Endoscopy* 2009; **41**: 462-467 [PMID: 19418401 DOI: 10.1055/s-0029-1214594]
29 **Yada T**, Yokoi C, Uemura N. The current state of diagnosis and treatment for early gastric cancer. *Diagn Ther Endosc* 2013; **2013**: 241320 [PMID: 23533320 DOI: 10.1155/2013/241320]
30 **Sano T**, Okuyama Y, Kobori O, Shimizu T, Morioka Y. Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig Dis Sci* 1990; **35**: 1340-1344 [PMID: 2226095 DOI: 10.1007/bf01536738]
31 **Deprez PH**, Bergman JJ, Meisner S, Ponchon T, Repici A, Dinis-Ribeiro M, Haringsma J. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. *Endoscopy* 2010; **42**: 853-858 [PMID: 20623442 DOI: 10.1055/s-0030-1255563]
32 **Kaltenbach T**, Soetikno R, Kusano C, Gotoda T. Development of expertise in endoscopic mucosal resection and endoscopic submucosal dissection. *Techniques in Gastrointestinal Endosc* 2011; **13**: 100-104 [DOI: 10.1016/j.tgie.2011.01.013]
33 **Choi IJ**, Kim CG, Chang HJ, Kim SG, Kook MC, Bae JM. The learning curve for EMR with circumferential mucosal incision in treating intramucosal gastric neoplasm. *Gastrointest Endosc* 2005; **62**: 860-865 [PMID: 16301026 DOI: 10.1016/j.gie.2005.04.033]
34 **Gotoda T**, Friedland S, Hamanaka H, Soetikno R. A learning curve for advanced endoscopic resection. *Gastrointest Endosc* 2005; **62**: 866-867 [PMID: 16301027 DOI: 10.1016/j.gie.2005.07.055]
35 **Yamamoto S**, Uedo N, Ishihara R, Kajimoto N, Ogiyama H, Fukushima Y, Yamamoto S, Takeuchi Y, Higashino K, Iishi H, Tatsuta M. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* 2009; **41**: 923-928 [PMID: 19802773 DOI: 10.1055/s-0029-1215129]
36 **Yamamoto Y**, Fujisaki J, Ishiyama A, Hirasawa T, Igarashi M. Current status of training for endoscopic submucosal dissection for gastric epithelial neoplasm at Cancer Institute Hospital, Japanese Foundation for Cancer Research, a famous Japanese hospital. *Dig Endosc* 2012; **24** Suppl 1: 148-153 [PMID: 22533772 DOI: 10.1111/j.1443-1661.2012.01278.x]
37 **Tsuji Y**, Ohata K, Sekiguchi M, Ito T, Chiba H, Gunji T, Yamamichi N, Fujishiro M, Matsuhashi N, Koike K. An effective training system for endoscopic submucosal dissection of gastric neoplasm. *Endoscopy* 2011; **43**: 1033-1038 [PMID: 22135195 DOI: 10.1055/s-0031-1291383]
38 **Oda I**, Odagaki T, Suzuki H, Nonaka S, Yoshinaga S. Learning curve for endoscopic submucosal dissection of early gastric cancer based on trainee experience. *Dig Endosc* 2012; **24** Suppl 1: 129-132 [PMID: 22533768 DOI: 10.1111/j.1443-1661.2012.01265.x]
39 **Hurlstone DP**, Atkinson R, Sanders DS, Thomson M, Cross SS, Brown S. Achieving R0 resection in the colorectum using endoscopic submucosal dissection. *Br J Surg* 2007; **94**: 1536-1542 [PMID: 17948864 DOI: 10.1002/bjs.5720]
40 **Honda K**, Akiho H. Endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. *World J Gastrointest Pathophysiol* 2012; **3**: 44-50 [PMID: 22532931 DOI: 10.4291/wjgp.v3.i2.44]
41 **Tamegai Y**, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E, Liu Y, Uemura N, Saito K. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418-422 [PMID: 17516348 DOI: 10.1055/s-2007-966427]
42 **Zhou PH**, Yao LQ, Qin XY. Endoscopic submucosal dissection for colorectal epithelial neoplasm. *Surg Endosc* 2009; **23**: 1546-1551 [PMID: 19263116 DOI: 10.1007/s00464-009-0395-5]
43 **Puli SR**, Kakugawa Y, Saito Y, Antillon D, Gotoda T, Antillon MR. Successful complete cure en-bloc resection of large nonpedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. *Ann Surg Oncol* 2009; **16**: 2147-2151 [PMID: 19479308 DOI: 10.1245/

s10434-009-0520-7]
44 **Kobayashi N**, Saito Y, Uraoka T, Matsuda T, Suzuki H, Fujii T. Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2009; **24**: 1387-1392 [PMID: 19702907 DOI: 10.1111/j.1440-1746.2009.05893.x]
45 **Fujishiro M**, Kodashima S, Goto O, Ono S, Niimi K, Yamamichi N, Oka M, Ichinose M, Omata M. Endoscopic submucosal dissection for esophageal squamous cell neoplasms. *Dig Endosc* 2009; **21**: 109-115 [PMID: 19691785 DOI: 10.1111/j.1443-1661.2009.00837.x]
46 **Uraoka T**, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592-1597 [PMID: 16682427 DOI: 10.1136/gut.2005.087452]
47 **Uraoka T**, Kawahara Y, Kato J, Saito Y, Yamamoto K. Endoscopic submucosal dissection in the colorectum: present status and future prospects. *Dig Endosc* 2009; **21** Suppl 1: S13-S16 [PMID: 19691725 DOI: 10.1111/j.1443-1661.2009.00863.x]
48 **Saito Y**, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg Endosc* 2010; **24**: 343-352 [PMID: 19517168 DOI: 10.1007/s00464-009-0562-8]
49 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002]
50 **Iacopini F**, Bella A, Costamagna G, Gotoda T, Saito Y, Elisei W, Grossi C, Rigato P, Scozzarro A. Stepwise training in rectal and colonic endoscopic submucosal dissection with differentiated learning curves. *Gastrointest Endosc* 2012; **76**: 1188-1196 [PMID: 23062760 DOI: 10.1016/j.gie.2012.08.024]
51 **Repici A**, Hassan C, De Paula Pessoa D, Pagano N, Arezzo A, Zullo A, Lorenzetti R, Marmo R. Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review. *Endoscopy* 2012; **44**: 137-150 [PMID: 22271024 DOI: 10.1055/s-0031-1291448]
52 **Dinis-Ribeiro M**, Pimentel-Nunes P, Afonso M, Costa N, Lopes C, Moreira-Dias L. A European case series of endoscopic submucosal dissection for gastric superficial lesions. *Gastrointest Endosc* 2009; **69**: 350-355 [PMID: 19185696 DOI: 10.1016/j.gie.2008.08.035]
53 **Hotta K**, Oyama T, Shinohara T, Miyata Y, Takahashi A, Kitamura Y, Tomori A. Learning curve for endoscopic submucosal dissection of large colorectal tumors. *Dig Endosc* 2010; **22**: 302-306 [PMID: 21175483 DOI: 10.1111/j.1443-1661.2010.01005.x]
54 **Sakamoto T**, Saito Y, Fukunaga S, Nakajima T, Matsuda T. Learning curve associated with colorectal endoscopic submucosal dissection for endoscopists experienced in gastric endoscopic submucosal dissection. *Dis Colon Rectum* 2011; **54**: 1307-1312 [PMID: 21904147 DOI: 10.1097/DCR.0b013e3182282ab0]
55 **Taku K**, Sano Y, Fu KI, Saito Y, Matsuda T, Uraoka T, Yoshino T, Yamaguchi Y, Fujita M, Hattori S, Ishikawa T, Saito D, Fujii T, Kaneko E, Yoshida S. Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. *J Gastroenterol Hepatol* 2007; **22**: 1409-1414 [PMID: 17593224 DOI: 10.1111/j.1440-1746.2007.05022.x]
56 **Ohata K**, Ito T, Chiba H, Tsuji Y, Matsuhashi N. Effective training system in colorectal endoscopic submucosal dissection. *Dig Endosc* 2012; **24** Suppl 1: 84-89 [PMID: 22533759 DOI: 10.1111/j.1443-1661.2012.01272.x]
57 **Bergman JJ**. How to justify endoscopic submucosal dissection in the Western world. *Endoscopy* 2009; **41**: 988-990 [PMID: 19866397 DOI: 10.1055/s-0029-1215247]
58 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]
59 **Conlin A**, Kaltenbach T, Kusano C, Matsuda T, Oda I, Gotoda T. Endoscopic resection of gastrointestinal lesions: advancement in the application of endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2010; **25**: 1348-1357 [PMID: 20659223 DOI: 10.1111/j.1440-1746.2010.06402.x]
60 **Neuhaus H**, Costamagna G, Devière J, Fockens P, Ponchon T, Rösch T. Endoscopic submucosal dissection (ESD) of early neoplastic gastric lesions using a new double-channel endoscope (the "R-scope"). *Endoscopy* 2006; **38**: 1016-1023 [PMID: 17058167 DOI: 10.1055/s-2006-944830]
61 **Probst A**, Pommer B, Golger D, Anthuber M, Arnholdt H, Messmann H. Endoscopic submucosal dissection in gastric neoplasia - experience from a European center. *Endoscopy* 2010; **42**: 1037-1044 [PMID: 20972955 DOI: 10.1055/s-0030-1255668]
62 **Coda S**, Trentino P, Antonellis F, Porowska B, Gossetti F, Ruberto F, Pugliese F, D'Amati G, Negro P, Gotoda T. A Western single-center experience with endoscopic submucosal dissection for early gastrointestinal cancers. *Gastric Cancer* 2010; **13**: 258-263 [PMID: 21128062 DOI: 10.1007/s10120-010-0544-5]
63 **Vázquez-Sequeiros E**, de Miquel DB, Olcina JR, Martín JA, García M, Lucas DJ, Garrido E, González C, Blanco AP, Arnau MR, Buenadicha A, Vicente VM, de Argila CM, Milicua JM. Training model for teaching endoscopic submucosal dissection of gastric tumors. *Rev Esp Enferm Dig* 2009; **101**: 546-552 [PMID: 19785494]
64 **Parra-Blanco A**, Arnau MR, Nicolás-Pérez D, Gimeno-García AZ, González N, Díaz-Acosta JA, Jiménez A, Quintero E. Endoscopic submucosal dissection training with pig models in a Western country. *World J Gastroenterol* 2010; **16**: 2895-2900 [PMID: 20556835]
65 **Teoh AY**, Chiu PW, Wong SK, Sung JJ, Lau JY, Ng EK. Difficulties and outcomes in starting endoscopic submucosal dissection. *Surg Endosc* 2010; **24**: 1049-1054 [PMID: 19911227 DOI: 10.1007/s00464-009-0724-8]
66 **Hon SS**, Ng SS, Lee JF, Li JC, Lo AW. In vitro porcine training model for colonic endoscopic submucosal dissection: an inexpensive and safe way to acquire a complex endoscopic technique. *Surg Endosc* 2010; **24**: 2439-2443 [PMID: 20333407 DOI: 10.1007/s00464-010-0982-5]
67 **Tanaka S**, Morita Y, Fujita T, Wakahara C, Ikeda A, Toyonaga T, Azuma T. Ex vivo pig training model for esophageal endoscopic submucosal dissection (ESD) for endoscopists with experience in gastric ESD. *Surg Endosc* 2012; **26**: 1579-1586 [PMID: 22223113 DOI: 10.1007/s00464-011-2074-6]
68 **Tanimoto MA**, Torres-Villalobos G, Fujita R, Santillan-Doherty P, Albores-Saavedra J, Gutierrez G, Martin-del-Campo LA, Bravo-Reyna C, Villanueva O, Villalobos JJ, Uribe M, Valdovinos MA. Endoscopic submucosal dissection in dogs in a World Gastroenterology Organisation training center. *World J Gastroenterol* 2010; **16**: 1759-1764 [PMID: 20380009 DOI: 10.3748/wjg.v16.i14.1759]
69 **Tanimoto MA**, Torres-Villalobos G, Fujita R, Santillan-Doherty P, Albores-Saavedra J, Chable-Montero F, Martin-del-Campo LA, Vasquez L, Bravo-Reyna C, Villanueva O, Villalobos JJ, Uribe M, Valdovinos MA. Learning Curve in a Western Training Center of the Circumferential En Bloc Esophageal Endoscopic Submucosal Dissection in an In Vivo Animal Model. *Diagnostic and Therapeutic Endosc* 2011; **2011**: 1-8 [DOI: 10.1155/2011/847831]
70 **Kim EY**, Jeon SW, Kim GH. Chicken soup for teaching and learning ESD. *World J Gastroenterol* 2011; **17**: 2618-2622 [PMID: 21677829 DOI: 10.3748/wjg.v17.i21.2618]
71 **Othman MO**, Wallace MB. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in 2011, a Western perspective. *Clin Res Hepatol Gastroenterol* 2011; **35**: 288-294 [PMID: 21458402 DOI: 10.1016/j.clinre.2011.02.006]
72 **Matsui N**, Akahoshi K, Nakamura K, Ihara E, Kita H. Endoscopic submucosal dissection for removal of superficial gas-

trointestinal neoplasms: A technical review. *World J Gastrointest Endosc* 2012; **4**: 123-136 [PMID: 22523613 DOI: 10.4253/wjge.v4.i4.123]

73 **Fujishiro M**, Jung HY, Goda K, Hirasawa K, Kakushima N, Lee IL, Morita Y, Oda I, Takeuchi M, Yamamoto Y, Zhou PH, Uedo N. Desirable training and roles of Japanese endoscopists towards the further penetration of endoscopic submucosal dissection in Asia. *Dig Endosc* 2012; **24** Suppl 1: 121-123 [PMID: 22533766 DOI: 10.1111/j.1443-1661.2012.01254.x]

74 **Goda K**, Fujishiro M, Hirasawa K, Kakushima N, Morita Y, Oda I, Takeuchi M, Yamamoto Y, Uedo N. How to teach and learn endoscopic submucosal dissection for upper gastrointestinal neoplasm in Japan. *Dig Endosc* 2012; **24** Suppl 1: 136-142 [PMID: 22533770 DOI: 10.1111/j.1443-1661.2012.01274.x]

P- Reviewers Albulescu R, Fujishiro M
S- Editor Wen LL **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.v5.i8.379

World J Gastrointest Endosc 2013 August 16; 5(8): 379-390
ISSN 1948-5190 (online)

REVIEW

Endoscopic approach to achalasia

Michaela Müller, Alexander J Eckardt, Till Wehrmann

Michaela Müller, Alexander J Eckardt, Till Wehrmann, Department of Gastroenterology, German Diagnostic Clinic, D-65191 Wiesbaden, Germany
Author contributions: All authors contributed equally to the preparation, writing, and editing of this article; all authors read and approved the final manuscript; the authors did not receive any financial support and have no competing interests.
Correspondence to: Till Wehrmann, MD, PhD, Department of Gastroenterology, German Diagnostic Clinic, Aukammallee 33, D-65191 Wiesbaden,
Germany. till.wehrmann@dkd-wiesbaden.de
Telephone: +49-611-577212 Fax: +49-611-577460
Received: February 17, 2013 Revised: March 19, 2013
Accepted: May 8, 2013
Published online: August 16, 2013

Abstract

Achalasia is a primary esophageal motor disorder. The etiology is still unknown and therefore all treatment options are strictly palliative with the intention to weaken the lower esophageal sphincter (LES). Current established endoscopic therapeutic options include pneumatic dilation (PD) or botulinum toxin injection. Both treatment approaches have an excellent symptomatic short term effect, and lead to a reduction of LES pressure. However, the long term success of botulinum toxin (BT) injection is poor with symptom recurrence in more than 50% of the patients after 12 mo and in nearly 100% of the patients after 24 mo, which commonly requires repeat injections. In contrast, after a single PD 40%-60% of the patients remain asymptomatic for ≥ 10 years. Repeated on demand PD might become necessary and long term remission can be achieved with this approach in up to 90% of these patients. The main positive predictors for a symptomatic response to PD are an age > 40 years, a LES-pressure reduction to < 15 mmHg and/or an improved radiological esophageal clearance post-PD. However PD has a significant risk for esophageal perforation, which occurs in about 2%-3% of cases. In randomized, controlled studies BT injection was inferior to PD and surgical cardiomyotomy, whereas the efficacy of PD, in patients > 40 years, was nearly equivalent to surgery. A new promising technique might be peroral endoscopic myotomy, although long term results are needed and practicability as well as safety issues must be considered. Treatment with a temporary self expanding stent has been reported with favorable outcomes, but the data are all from one study group and must be confirmed by others before definite recommendations can be made. In addition to its use as a therapeutic tool, endoscopy also plays an important role in the diagnosis and surveillance of patients with achalasia.

Key words: Achalasia; Pneumatic dilation; Botulinum toxin injection; Per oral endoscopic myotomy; Dysphagia; Laparoscopic cardiomyotomy

Core tip: Upper gastrointestinal-endoscopy is an important part in the diagnostic algorithm of achalasia. Although it does not have a high sensitivity in detection of early stage achalasia, it is essential to rule out pseudoachalasia. This updated review included the newest data on treatment and surveillance of achalasia patients with special emphasis on the new treatment option of per oral endoscopic myotomy, including all fulltext publications until January, 2013.

Müller M, Eckardt AJ, Wehrmann T. Endoscopic approach to achalasia. *World J Gastrointest Endosc* 2013; 5(8): 379-390 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/379.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.379

INTRODUCTION

Idiopathic achalasia is a rare primary esophageal motor disorder of unknown etiology, with an estimated incidence of 1 case per 100000 of the general population[1]. It represents a neurodegenerative disorder, in which neurons of the myenteric plexus become destroyed.

Although major strides have been made in understanding the pathogenesis, including a probable autoimmune mediated destruction of inhibitory neurons caused by an unknown insult in genetically predisposed patients, the definite pathophysiology is still unknown[2].

Achalasia is characterized by a loss of function of the lower esophageal sphincter and the esophageal peristalsis. The classical features are incomplete relaxation of a frequently hypertensive lower esophageal sphincter (LES) and a lack of peristalsis in the tubular esophagus, which causes symptoms such as dysphagia, regurgitation, weight loss and chest pain.

The diagnosis of achalasia is suspected clinically on the basis of the symptoms mentioned above and confirmed by diagnostic tests, such as barium swallow, and esophageal manometry. However, an endoscopic examination is always necessary to distinguish primary achalasia from the secondary form, in cases of possible malignancy[3].

Since the underlying defect cannot be reversed, the treatment of achalasia remains palliative. Therefore, the aim of all current therapies is the improvement of the esophageal food passage by reducing the distal esophageal obstruction. Such improvement will lead to symptomatic relief of dysphagia, regurgitation, as well as weight gain.

This goal can be achieved by pharmacologic therapy, by endoscopic treatment with pneumatic dilatation (PD) or botulinum toxin (BT) injection, or by surgery. Recently, new therapy options such as stent implantation or peroral endoscopic myotomy (POEM) have been reported[4,5]. However, the efficacy of these treatment options varies and the recommendation for the best therapy is still controversial. Although pneumatic dilation and Heller myotomy seemed to be the most effective treatments for achalasia[6], the choice of treatment modality depends on multiple factors, such as patients' characteristics, clinical presentation, local expertise and patients preference[7].

In addition, surveillance strategies remain a matter of debate. Despite an increased risk for malignancy there are no existing guidelines for surveillance of cancer or other complications such as esophagitis, peptic strictures or megaesophagus[8,9].

This review will provide an evidence-based approach for the use of endoscopic options for the diagnosis, treatment and surveillance of achalasia.

DIAGNOSTIC USE OF ENDOSCOPY

Endoscopy is one of the primary tools in the diagnosis of achalasia as the leading symptom of the disease is dysphagia. Esophago-gastroscopy, esophageal barium swallow and esophageal manometry are the standard diagnostic procedures in suspected achalasia. Although an endoscopic diagnosis can only be made in about 1/3 of all patients with achalasia, its sensitivity increases with progressive stages of disease[10]. Typically the resistance at the gastroesophageal junction is increased, but still relatively easy to pass with the endoscope. In advanced stages of achalasia the esophagus is dilated and contains retention of food or secretions[11]. The esophageal mucosa usually appears normal, although sometimes inflammation or ulceration caused by retained food can be demonstrated. The endoscopic examination is especially important to rule out other possible causes for the symptoms. These include esophageal and gastric tumors as well as stenosis caused by scarring or inflammatory conditions or by aberrant vascular patterns (*e.g.*, dysphagia lusoria). Especially the esophagogastric junction, as well as the gastric cardia and the fundus, should be examined carefully for evidence of neoplasm, because gastric adenocarcinoma is the most common neoplasm associated with pseudoachalasia[12].

Furthermore, esophago-gastroscopy might be important for the detection and treatment of complications that can be a result of the disease itself such as megaesophagus or carcinoma, or of successful treatment for example reflux esophagitis or peptic stricture[13].

ENDOSCOPIC TREATMENT

The treatment options remain strictly palliative; therefore the primary goal of all therapies is the improvement of the esophageal food passage by reducing the distal esophageal obstruction. Such improvement will lead to symptomatic relief of dysphagia, regurgitation, as well as weight gain. Endoscopic treatments include mechanical rupture of the smooth muscle fibers of the LES and relaxation of the hypertensive lower esophageal sphincter by injection of botulinum toxin, an inhibitor of acetylcholine release from nerve endings[14] as well as novel reported endoscopic therapies such as stent placement, and POEM respectively[4,5].

ENDOSCOPIC INJECTION OF BT

Strictly speaking, botulinum toxin injection into the LES is a pharmacologic treatment, but it requires upper endoscopy for its application.

Botulinum toxin is a neurotoxin that leads to a blockade of the release of acetylcholine from vesicles of excitatory motor neurons. Therefore, it counteracts the loss of inhibitory input to the LES and helps to restore the LES to a lower resting pressure[15].

Botulinum neurotoxins are divided into seven subgroups, identified by the letters A-G. In clinical practice subtype A is most frequently used[16].

The application of BT is performed by prograde or retrograde injection into the LES using a standard sclerotherapy needle. The most common approach is the injection of 20-25 units BT-A diluted in 1 mL of saline, in each of the 4 lower esophageal sphincter quadrants approximately 1 cm above the Z-line into the bulging muscle (Figure 1)[17]. Whether the use of endoscopic ultrasound or manometry to identify the LES can achieve better clinical results has not been definitively estab-

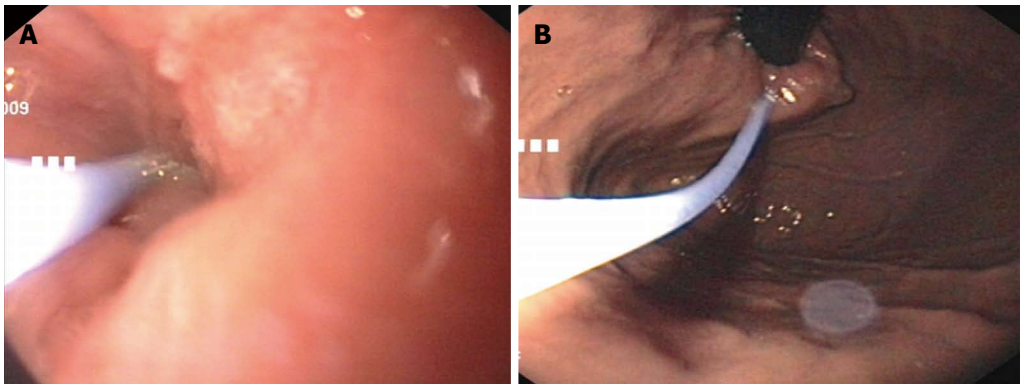


Figure 1 Endoscopic images of botulinum toxin injection. Injection with the standard sclerotherapy needle deep intramuscular in the region of the cardia. A: Prograde injection with an endoscopic view of the distal esophagus; B: Retrograde injection with a retroflexed view of the cardia.

Table 1 Efficacy of botulinum toxin injection in the treatment of achalasia

Ref.	*n*	BT-dose U	Initial symptomatic response	Injection rate	Long-term symptomatic response	Follow up (mo)
Wehrmann *et al*[19]	20	100	80%	2.5	70%	24
Annese *et al*[20]	36	100	90%	0	78%	6
Pasricha *et al*[28]	31	80	90%	1.6	68%	12
Fishman *et al*[31]	60	80	70%	1.3	36%	12
Annese *et al*[32]	38	100	82%	1	68%	24
Gordon *et al*[100]	16	80	75%	1.25	58%	7
Cuillière *et al*[101]	55	80	85%	1.2	60%	6
Vaezi *et al*[102]	22	100	64%	1.1	32%	12

BT: Botulinum toxin.

lished[18,19]. Botulinum toxin diffuses into the surrounding tissue of up to 10 mm, therefore absolute precision might not be necessary[18]. In two studies, instead of BT-A (Allergan Inc., Irvine, CA, United States), Dysport (Ipsen, Milan, Italy) was used at doses of 200-240 U and was equally effective[20]. BT injection is a safe method no more demanding than a routine endoscopy with no major complications. The most common side effect is retrosternal pain in up to 25% of patients[15]. It is an outpatient procedure and the patients can go home after they recover from sedation. The patients are allowed to drink in the recovery room and to eat soft foods later in the day. Symptomatic improvement occurs gradually and usually peaks 1-3 d later, although this may be delayed even further in the occasional patient[21].

The first clinical studies were conducted in the 1990th, after preliminary studies in piglets[22-24]. In these initial studies, patients were treated with endoscopic injection of botulinum toxin in comparison to placebo injection of saline with symptomatic improvement as well as a remarked reduction of the LES pressure after BT injection were demonstrated[25]. However, the clinical effect of botulinum neurotoxins is reversible, because of the regeneration of the presynaptic membrane[26]. Therefore, the efficacy of a single BT injection has been found to vary from 3 mo to 3 years. In numerous placebo-controlled trials, significant improvement of symptoms has been shown in approximately 75% (70%-90%) of the patients[27] (Table 1). Although, after 12 and 24 mo symptoms recurred in more than 50% and in nearly 100% of the patients, respectively[28-30]. Therefore, repeat injections are commonly required and nearly 75% of the initially responsive patients will respond to a second BT treatment. However, patients who failed to respond to initial BT injection respond to a second injection in less than 20%[31]. Furthermore, it is known that increasing the dose to 200 U BT does not improve the success rate whereas two injections of 100 U of BT 30 d apart seemed to be the most effective therapeutic schedule[32].

However, the long-term safety and efficacy are less certain[20]. It is known that repeated BT injections may lead to decreased effects due to the development of inhibitory antibodies[15] and there is some evidence that injection of BT into the LES is associated with increased difficulty of performing esophagomyotomy[33].

The long-term success of BT injection into the LES in patients with achalasia was highest in elderly patients (> 55 years), in patients with vigorous achalasia and those with an LES pressure not exceeding the upper normal level by 50% or more prior to treatment[34,35]. In fact, several investigators have speculated that the better long-term response to BT injections seen in the elderly might be explained by diminished nerve regeneration[36].

In summary, the advantages of this method are that it is simple, effective and relatively inexpensive, with no major side effects and excellent short-term results. Unfortunately this result only lasts for 6-9 mo on average in most patients and only half of them benefit for more than 1

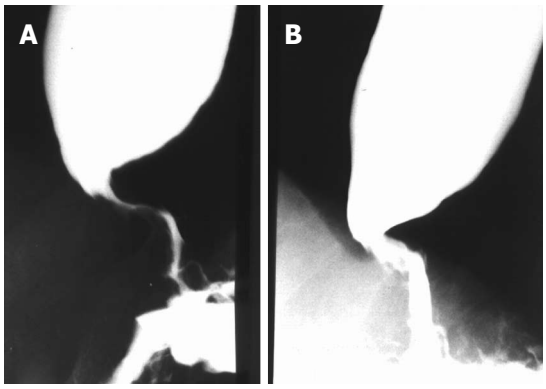


Figure 2 Radiologic image of the esophagus of an elderly patient. A: Before Botox injection; B: After Botox injection, with a decrease of the diameter in the area of the lower esophageal sphincter.

year[37]. Because of its less invasive nature compared with other therapeutic alternatives Botox injection may be the preferred approach in the treatment of some patients with achalasia, such as elderly patients (Figure 2) or patients with multiple medical problems who are poor candidates for more invasive procedures as well as those unwilling to have either surgery or pneumatic dilatation[38]. Furthermore, BT injection might be a useful therapy in patients with atypical achalasia, or complex achalasia in whom it is unclear whether more invasive procedures such as pneumatic dilation or surgical myotomy are the correct therapy[39].

DILATION OF THE LES

Theoretically, there are two possible modalities used to dilate the LES in patients with achalasia: bougienage and pneumatic balloon dilation.

Although bougienage is a technique known to be highly effective in peptic or anastomotic strictures, it provides only temporary and incomplete symptom relief in patients with achalasia[40,41]. Therefore, the more forceful stretching of the LES with pneumatic balloon dilation that weakens the LES by tearing its muscle fibers is the preferred approach.

PD

Pneumatic dilatation has been a well established and proven treatment for achalasia for decades and is currently considered the most effective nonsurgical treatment option for achalasia[42].

Since the first description of treating achalasia with whale bone by Sir Thomas Willis in 1674, the aim of the procedure has principally remained the same. That is to rupture the hypertensive smooth muscle of the LES. In the past different kinds of balloons such as Witzel or Mosher balloons, with a remarkable variation in the methods of dilatation were used for the forceful dilation[43,44]. The procedure has become more standardized with the development of the so called Rigiflex balloon System (Boston Scientific Corporation, MA, United States), a low compliance polyethylene balloon available in 3 diameters (3.0, 3.5, and 4.0 cm) (Figure 3A). It is fixed on a flexible catheter that can be placed over an endoscopically placed guidewire with subsequent fluoroscopic monitoring of the balloon position across the LES. The rapid inflation of the balloon with air leads to stretching of the LES muscle fibers, resulting in at least partial rupture. In order to avoid radiation exposures, some centers monitor balloon position by direct endoscopic observation[45]. A pressure of up to 10-12 psi (average 7 psi) is used to inflate the balloon for 1-2 min until the waist of the balloon, which lies in the region of the LES, is completely elapsed (Figure 3B). The dilation protocols and follow-up varies among different investigators in the United States and Europe[13]. Some authors have used single dilation[46], others performed serial graded dilations on consecutive days or a few weeks apart with balloon sizes ranging from 3 to 4 cm[47-50] and a few European centers perform serial progressive dilations over several days, until the manometrically measured LES pressure is below 10-15 mmHg[51].

However, in the past numerous comparative studies found no significant different symptomatic response rates for the use of different balloon systems, or different length of inflation or peak pressures respectively, although previous studies could show that the use of a Rigiflex dilator and multiple dilations during the initial treatment might improve efficacy[13,43].

The technique of graded balloon dilation starting with 3.0-cm Rigiflex balloon as the initial dilator and progressing to 3.5-cm and 4.0-cm balloon in absence of response to previous balloon size seems to be the safest approach[52]. Following dilation, radiologic esophagograms with water-soluble contrast agents are frequently performed to rule out serious complications; whereas others do not recommend a routine esophagogram in the absence of symptoms suggestive of a perforation, such as chest pain often with radiation to the back or to the shoulder, followed in one third of patients by vomiting and shortness of breath[53].

Transmural perforation, mostly located just above the cardia along the left side of the esophagus where there is an anatomic area of weakness. The perforation rate reported in different studies ranges between 0%-5% with a mean range of 2%-3% (Table 2). In the review of Katzka *et al*[43] in which 29 studies of pneumatic dilation in achalasia were evaluated the overall perforation rate was 2% of which only 1% required surgery.

The mortality rate (5%-6%) after transmural perforation due to pneumatic dilation is usually caused by the development of mediastinitis or bleeding into the mediastinum[54]. In general, conservative treatment with fluid resuscitation, gastric decompression, and antibiotics, best combined with an immediate endoscopic closure of the perforation, is a possible option[43,52]. Complications following pneumatic dilation, if recognized and treated promptly, were not associated with adverse, long-term sequelae[50]. Multiple dilations, the use of inflation pressures

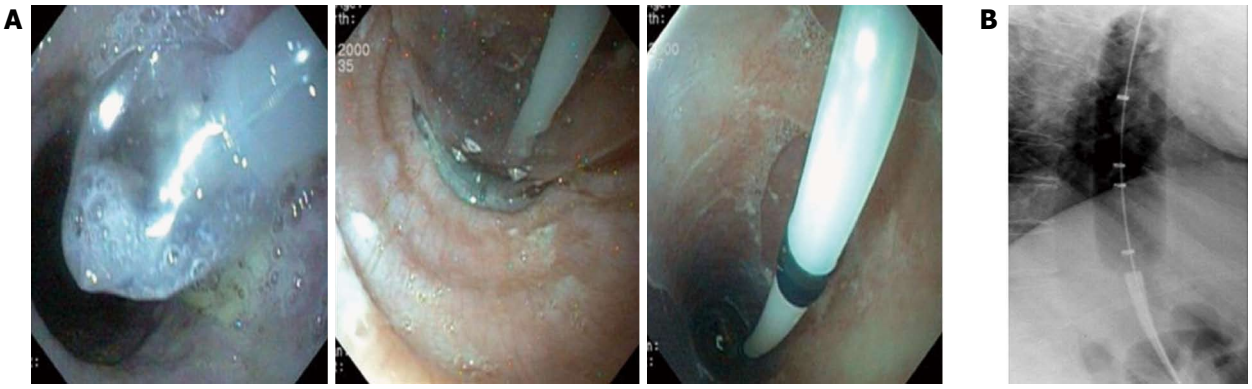


Figure 3 Pneumatic dilation with a rigiflex balloon. A: Endoscopic image; B: Radiologic images. The waist of the balloon lies in the region of the lower esophageal sphincter.

Table 2 Initial efficacy of pneumatic dilation in the treatment of achalasia

Ref.	Dilator-system	*n*	Symptomatic response	Perforation rate
Chuah *et al*[52]	Rigiflex	32	91%	3%
Eckardt *et al*[61]	Brown-McHardy	54	78%	2%
Wehrmann *et al*[62]	Rigiflex	40	88%	3%
Csendes *et al*[73]	Mosher	39	65%	5%
Stark *et al*[103]	Brown-McHardy	10	100%	0%
Parkman *et al*[104]	Brown-McHardy	123	88%	2%
Coccia *et al*[105]	Rider-Moeller	16	75%	0%
Bourgeois *et al*[106]	Rider-Moeller	53	80%	4%
Gelfand *et al*[107]	Rigiflex	24	83%	0%
Vaezi *et al*[108]	Rigiflex	20	75%	5%
Rai *et al*[109]	Rigiflex	56	89%	0%

> or = 11 psi or a large balloon (4 cm) at initial dilation as well as older age (> 65 years) seemed to be risk factors for esophageal perforation[55]. Although suspected by early observations, a hiatus hernia, a diverticulum of the esophagus and vigorous achalasia do not increase this risk[56]. Other minor complications include esophageal mucosal tears, bleeding, intramural hematomas, aspiration and diverticula at the cardia[50,56]. Post procedural fever usually resolves spontaneously without the use of antibiotics, and in approximately 15% of patients severe but self- limited chest pain occurs[50,55].

Furthermore, some patients will develop reflux when measured by 24-h esophageal pH monitoring. Although severe complications of gastro esophageal reflux disease such as peptic stricture, or Barrett esophagus are rare, 15%-45% of the patients will complain of heartburn responding to proton pump inhibitor treatment[57,58].

The only absolute contraindication for pneumatic dilatation is poor cardiopulmonary status or other comorbid illness preventing surgery, if a transmural perforation might occur[17].

Outcome of PD

Initial success rates are high with up to 85% of patients reporting symptom improvement after one month. Table 2 summarizes the results of several studies according to the short-term symptomatic success rate of PD.

A recently published review of 21 studies using Rigiflex balloons demonstrated that the initial success rates depends on the balloon size, with larger balloons showing better outcomes. Success rates of 74%, 80% and 90% were achieved when using balloon sizes of 30, 35 and 40 mm, respectively[45].

However, a decline in success rates over time was consistently found. For example, researchers achieved success rates of 74% at 6 mo, 68% at 12 mo and 58% after 36 or more months. If patients are observed for more than 10 years, only 40%-60% will remain asymptomatic after a single PD. Therefore, repeated on demand PD might be necessary and long term remission can be achieved with this approach in up to 90% of the patients[47,50,58].

Nevertheless, it must be considered that the patients with frequent PD are exposed to potentially serious complications such as esophageal perforation, intramural hematoma or aspiration and the uncertain durability of symptom free intervals between dilations[59,60]. Therefore, it is important to predict which patient is less likely to respond or will have an early recurrence of symptoms. In fact, patients older than 40 years generally have better outcomes following dilation than those who are younger[61,62]. Further positive predictive factors are a LES-pressure of < 15 mmHg or a LES pressure reduction of more than 50% in comparison to the pre-dilation LES pressure[63,64]. By contrast, a wide esophagus, the use of small balloon sizes, an incomplete obliteration of the balloon waist during the procedure, a failed response to one or two dilations, type I or III patterns of achalasia in high resolution manometry, poor esophageal clearance on a timed barium swallow and younger male patients have been shown to predict a poor treatment response[63,65-67].

A recently published study reported a new predictor of treatment success by measuring the distensibility of the esophagogastric junction with an endoscopic functional luminal imaging probe (EndoFLIP®). Even when LES pressure was low, esophagogastric junction distensibility could be reduced, which was associated with

impaired emptying and recurrent symptoms[68]. Although it must be considered that even if LES pressure is not an optimal predictor, it still remains a valuable measure in clinical practice.

In summary, PD is safer than commonly thought and very effective even in the long term, although multiple dilations will be needed over a lifetime in most patients. The technique of graded balloon dilation starting with 3.0 cm Rigiflex balloon as the initial dilator and progressing to 3.5 and 4.0 cm balloon in absence of response to previous balloon size seems to be the safest approach[69]. Patients not responding to three serial dilations are less likely to respond to repeated dilations and should be offered surgery.

Comparative trials between various treatment modalities

The review of six randomized controlled trials comparing PD to BT injection in patients with primary achalasia demonstrated no significant difference in symptomatic remission and the mean esophageal pressure within 4 wk of the initial intervention. However, in the long term (> 6 mo) PD was more effective[30]. The combination of both treatments does not improve the outcome[35].

In summary, BT injection has similar efficacy as pneumatic dilatation in achieving an initial improvement in dysphagia. It can also be effective in some patients with tortuous megaesophagus and vigorous achalasia, but serial injections are required to sustain relief and its long term efficacy is inferior to PD[70]. Furthermore, serial BT injection is more costly than PD dilation, if the life-expectancy is > 2 years[71].

The role of PD in comparison to surgical myotomy is less clear. The difficulty in comparing both therapies is due to the lack of prospective randomized studies with a long follow up (> 5 years) in a large population and the lack of standardized technique of balloon dilation.

In the past years meta-analyses have favored surgery as the best treatment to achieve long-term success[42,72]. However, these analyses mostly included retrospective studies of different sizes and quality and did not include approaches with on demand repeat dilations. In fact, a repeated dilation was the negative endpoint in some of the studies.

Until recently, only one randomized study existed. The study by Csendes *et al*[73], in which conventional cardiomyotomy plus Dor fundoplication was compared with the pneumatic dilation using the so-called "Mosher Bag", reported symptomatic response rates 5 years after treatment of 95%, and 65% in the surgical and PD group, respectively. However, the technique used for the pneumatic dilation was possibly suboptimal and a later published long-term follow-up of the same patient group showed that the results of the surgery were less favorable after more than 15 years of observation, with only 75% of patients being in sustained remission.

Last year, the results of a European multicenter study were published[74]. In one study arm, patients were treated (n = 94) with PD, starting with a 30 mm Rigiflex balloon, followed 1 to 3 wk later by dilation with the use of a 35-mm balloon. All patients thus underwent at least two dilations. If the Eckardt score 4 wk later was greater than 3, a third dilation was performed, with the use of a 40-mm balloon. The other group (n = 104) received a laparoscopic Heller cardiomyotomy with antireflux technique (LHM). Both treatments had comparable therapeutic success at 2 years, with 86% of the patients achieving symptomatic relief with PD and LHM, respectively. Furthermore, there was no significant difference in the LES pressure or esophageal emptying, as assessed by the height of barium-contrast column in both groups. Although age was not an overall predictor for therapeutic success for treatment, similar to previous investigations, an inferior symptomatic response of PD in patients with age < 40 years was observed.

The rate of complications as well as the frequency of induction of gastroesophageal reflux was similar in both groups. This data suggests that PD and LHM have equal efficacy, given that PD is performed with at least two dilations.

Not surprisingly, the only study comparing BT injections with laparoscopic cardiomyotomy showed an inferiority of BT. The 1-year remission rate was 53% in the BT group and 90% in the myotomy group and 2 years later only 34% of the patients treated with BT and 88% of the operated patients were in clinical remission[75].

NEW ENDOSCOPIC THERAPEUTIC APPROACHES

POEM

POEM is a new endoscopic treatment for achalasia. Ortega *et al*[76] first reported an endoscopic myotomy in the treatment of achalasia using a needle knife to cut the inner circular muscle fibers of the LES by cutting directly through the mucosa during endoscopy.

After this small study with excellent results the method fell into oblivion, until Pasricha *et al*[77] reported a technique of endoscopic submucosal method on a pig model. Afterwards Inoue *et al*[78] described a clinical application of the modified Pasricha technique as POEM. This approach involves endoscopic dissection of the esophageal submucosal space (under CO_2 insufflation) to gain access to LES muscle fibers. The semicircumferent dissection starts approximately 6-13 cm proximal to the esophagogastric junction and is extended 2 cm into the stomach. Circular muscle bundles are then dissected, leaving the longitudinal muscle layer intact. Inoue *et al*[78] could show a significant improvement of dysphagia and reduction of LES pressure after this intervention, although the mean postinterventional LES pressure was still high at 20 mmHg. Most recently, several centers are using the POEM technique and reported excellent short term results and no "serious" complications, although pneumomediastinitis, C-reactive protein elevation are common and long term results are required[78-80]. A short overview of the results to date is given by Table 3.

Table 3 Results of peroral endoscopic myotomy for the treatment of patients

Ref.	*n*	Mean age (yr)	Myotomy length (cm)	Follow-up (mo)	Symptomatic response (Eckardt score before/after POEM)	LES-tone (before/after POEM, mmHg)
Inoue *et al*[5]	17	41	8	5	10/1.3	52/20
von Renteln *et al*[80]	16	45	12	3	8.8/1.1	27/12
Swanström *et al*[110]	5	64	7	1	Not quantified	Not measured
Costamagna *et al*[111]	11	32	10	1	7.1/1.1	45/17
Chiu *et al*[112]	16	48	11	6	5.5/0	44/30

Only full text publications are considered. LES: Lower esophageal sphincter; POEM: Peroral endoscopic myotomy.

The procedure is promoted as less invasive than surgical myotomy, but it still requires general anesthesia and is not less time consuming than a laparoscopic approach. It is a sophisticated and demanding technique even for experienced endoscopists and so far has shown suboptimal results for lowering LES pressure compared in comparison to the published results with surgery. Furthermore revisional surgery might be more difficult because the space between the submucosal and muscular layers might become inflamed and scarred[81].

In summary, it is a very interesting approach but long term results as well as a comparison of POEM with other treatment modalities in randomized controlled studies are required and it's use should only be applied in the context of clinical trials.

Stenting

Another novel therapeutic approach is temporary esophageal stenting. Recently, a strategy of using retrievable stents has been successfully applied in the treatment of benign esophageal strictures[82,83]. A few studies, from a single Chinese study group reported a symptomatic benefit with the use of self expanding metal stents in patients with achalasia. In this endoscopic approach a partially covered, self-expanding metal stent (SEMS) with a diameter of 20, 25 or 30 mm was applicated in unsedated patients with achalasia. It was kept in place for 1 wk and then it was removed endoscopically. The best results after 10 years were shown in patients treated with a 30 mm stent. The clinical remission rate was 86%, 27%, 13%, 0%, in 30 mm SEMS, 25 mm SEMS, 20 mm SEMS and PD, respectively[84,85]. In contrast, other study groups could not confirm these results and complications, such as stent migration, chest pain and reflux esophagitis have been reported, with a mortality and morbidity of 33% and 50% respectively[86,87].

Ethanolamine oleate injection

Case reports from southern Europe[88,89] and Iran[90] reported a good response after endoscopic injection of the sclerosing agent ethanolamine oleate in the cardia. As a possible mechanism inflammatory destruction of the LES is discussed. Symptom relief as well as improved esophageal emptying has been demonstrated. However, the reported number of cases is very small and the longest follow up was 17 mo.

USE OF ENDOSCOPY FOR SURVEILLANCE

In patients with achalasia surveillance is important for several reasons. First, treatment success needs to be documented by objective parameters. Second, regular follow-up enables the clinician to detect symptomatic recurrences at an early stage and, third, endoscopic surveillance has the potential for early recognition of late complications, such as esophageal squamous cell cancer, megaesophagus or reflux esophagitis.

Objective evaluation of treatment success at least with a structured symptom orientated questionnaire and esophageal manometry, or better with additional timed barium esophagogram and endoscopy should be performed early (4-12 wk) after the initial intervention. Some centers even perform esophageal manometry intraoperatively or immediately after pneumatic dilation[91,92]. A post-dilation LES resting pressure of < 10-15 mmHg is generally considered to be predictive of a good long-term response[61,62]. However, falsely elevated LES pressure could be measured immediately after disruption of the LES due to associated edema. In the immediate post interventional period endoscopy is less important, but it is useful for further surveillance. Endoscopy might have a role in the detection or prevention of long-term complications. Up to 10% of all patients with long-standing achalasia (more than 10 years after first diagnosis) develop progressive enlargement of the esophagus, which can lead to a sigmoid-shaped esophagus and/or megaesophagus[93] (Figure 4). This complication more frequently develops in patients who remain ineffectively treated for years. If these morphological changes are only recognized at an advanced stage, esophageal resection may be the only remaining therapeutic option[13].

In addition, the risk of esophageal cancer in achalasia patients is estimated to be approximately 30-fold higher than in the general population[8,9]. Especially in male achalasia patients, a substantially greater risk for both squamous cell carcinoma and adenocarcinoma of the esophagus has been shown, whereas the risk in female patients could not be evaluated due to the small numbers[94].

The first prospective evaluation of esophageal cancer risk in a large cohort of achalasia patients with long-term follow-up demonstrated an increased rate of esophageal cancer. The mean age at cancer diagnosis was 71 years,

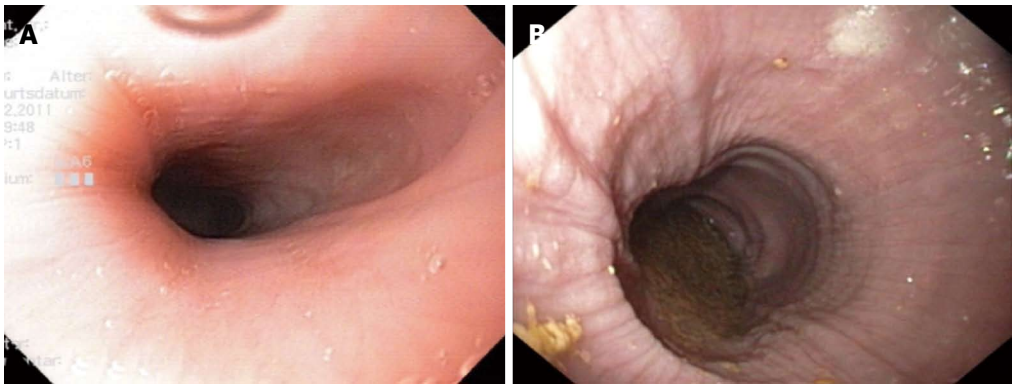


Figure 4 Endoscopic images of patients with achalasia. A: Early achalasia; B: Advanced achalasia with a megaesophagus, hyperplasia of the esophageal epithelium.

after a mean of 11 years (range 2-23 years) following initial diagnosis, and a mean of 24 years (range 10-43 years) after symptom onset. Although, most neoplastic lesions remained undetected until an advanced stage, despite structured endoscopic surveillance, the authors suggested such a surveillance strategy in patients with longstanding achalasia[95].

Even if the latest American Society of Gastrointestinal Endoscopy guidelines correctly state that there are still "insufficient data to support routine endoscopic (cancer) surveillance for patients with achalasia"[96], endoscopic surveillance might be beneficial in particular if one considers that cancer is not the only late complication of this disease. Therefore, most experts favor some form of endoscopic surveillance in patients with achalasia if the disease has been present for more than 10-15 years[97,98]. It could be considered that chromoendoscopy or narrow band imaging might be superior for early detection of neoplastic lesions, but further studies are needed to compare these techniques with standard endoscopy.

Another long-term complication that requires careful attention is the development of clinically significant gastro-esophageal reflux disease (GERD), which occurs in up to 25% of patients with achalasia who are followed up for > 15 years[99]. GERD-related findings range from reflux esophagitis and peptic strictures to Barrett's esophagus, which in rare instances may progress to esophageal adenocarcinoma. In our practice follow-up visits are recommended biannually. The patients undergo structured interviews using a scoring system (Eckardt score) for the symptoms and upper gastrointestinal (GI)-endoscopy to detect reflux-esophagitis or the development of a megaesophagus. If achalasia has been present for more than 10 years the follow-up interval is shortened to annual intervals.

However, further studies are needed to determine whether such surveillance strategies will improve the overall outcome.

CONCLUSION

Upper GI-endoscopy is an important part in the diagnostic algorithm of achalasia. Although it does not have a high sensitivity in detection of early stage achalasia, it is essential to rule out pseudoachalasia.

Treatment remains palliative as the neuronal defect of the disease seems to be irreversible. Therefore, the primary goal of all therapies is the improvement of the esophageal passage by disruption of the LES and the prevention of long-term complications. The most effective endoscopic therapy is graded pneumatic dilation with Rigiflex balloons, whereas the endoscopic injection of Botulinum toxin injection is mostly reserved for old patients or those with major comorbid illnesses preventing surgery. A new promising technique might be POEM although long-term results and comparison of POEM to PD and LHM are needed.

Treatment with a temporary self expanding stent are reported by one group who reported a better long term effect than PD, but the results of PD were poor in this study and the data must be confirmed by others before this method can be recommended. In addition, multiple complications such as stent migration, bleeding and chest pain can occur with this technique.

Most experts favor some form of endoscopic surveillance in patients if achalasia has been present for more than 10-15 years. However, no guidelines exist and further studies are needed to determine whether and which surveillance strategies will improve overall outcome.

REFERENCES

1 **Francis DL**, Katzka DA. Achalasia: update on the disease and its treatment. *Gastroenterology* 2010; **139**: 369-374 [PMID: 20600038 DOI: 10.1053/j.gastro.2010.06.024]
2 **Gockel HR**, Schumacher J, Gockel I, Lang H, Haaf T, Nöthen MM. Achalasia: will genetic studies provide insights? *Hum Genet* 2010; **128**: 353-364 [PMID: 20700745 DOI: 10.1007/s00439-010-0874-8]
3 **Gockel I**, Eckardt VF, Schmitt T, Junginger T. Pseudoachalasia: a case series and analysis of the literature. *Scand J Gastroenterol* 2005; **40**: 378-385 [PMID: 16028431 DOI: 10.1080/00365520510012118]
4 **Zhu YQ**, Cheng YS, Tang GY, Li MH, Zhao JG, Li F. Comparison of temporary stent insertion with pneumatic dilation of the same diameter in the treatment of achalasia patients: a

retrospective study. *J Gastroenterol Hepatol* 2010; **25**: 499-505 [PMID: 20074159 DOI: 10.1111/j.1440-1746.2009.06107.x]
5 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
6 **Eckardt AJ**, Eckardt VF. Achalasia: Should pneumatic dilation be the primary treatment strategy? *Nat Rev Gastroenterol Hepatol* 2010; **7**: 188-190 [PMID: 20376091 DOI: 10.1038/nrgastro.2010.33]
7 **Eckardt AJ**, Eckardt VF. Current clinical approach to achalasia. *World J Gastroenterol* 2009; **15**: 3969-3975 [PMID: 19705490 DOI: 10.3748/wjg.15.3969]
8 **Porschen R**, Molsberger G, Kühn A, Sarbia M, Borchard F. Achalasia-associated squamous cell carcinoma of the esophagus: flow-cytometric and histological evaluation. *Gastroenterology* 1995; **108**: 545-549 [PMID: 7835597 DOI: 10.1016/0016-5085(95)90084-5]
9 **Streitz JM**, Ellis FH, Gibb SP, Heatley GM. Achalasia and squamous cell carcinoma of the esophagus: analysis of 241 patients. *Ann Thorac Surg* 1995; **59**: 1604-1609 [PMID: 7771859]
10 **Howard PJ**, Maher L, Pryde A, Cameron EW, Heading RC. Five year prospective study of the incidence, clinical features, and diagnosis of achalasia in Edinburgh. *Gut* 1992; **33**: 1011-1015 [PMID: 1398223]
11 **Boeckxstaens GE**. Achalasia. *Best Pract Res Clin Gastroenterol* 2007; **21**: 595-608 [PMID: 17643903]
12 **Liu W**, Fackler W, Rice TW, Richter JE, Achkar E, Goldblum JR. The pathogenesis of pseudoachalasia: a clinicopathologic study of 13 cases of a rare entity. *Am J Surg Pathol* 2002; **26**: 784-788 [PMID: 12023584]
13 **Eckardt AJ**, Eckardt VF. Treatment and surveillance strategies in achalasia: an update. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 311-319 [PMID: 21522116 DOI: 10.1038/nrgastro.2011.68]
14 **Dunaway PM**, Wong RK. Achalasia. *Curr Treat Options Gastroenterol* 2001; **4**: 89-100 [PMID: 11177686]
15 **Richter JE**. Achalasia - an update. *J Neurogastroenterol Motil* 2010; **16**: 232-242 [PMID: 20680161 DOI: 10.5056/jnm.2010.16.3.232]
16 **Gui D**, Rossi S, Runfola M, Magalini SC. Review article: botulinum toxin in the therapy of gastrointestinal motility disorders. *Aliment Pharmacol Ther* 2003; **18**: 1-16 [PMID: 12848622]
17 **Classen M**, Tytgat GN, Lightdale CJ, editors. Gastroenterological Endoscopy. 2nd ed. Stuttgart: Georg Thieme Verlag, 2010: 467
18 **Hoffman BJ**, Knapple WL, Bhutani MS, Verne GN, Hawes RH. Treatment of achalasia by injection of botulinum toxin under endoscopic ultrasound guidance. *Gastrointest Endosc* 1997; **45**: 77-79 [PMID: 9013174]
19 **Wehrmann T**, Schmitt T, Dietrich CF, Caspary WF, Seifert H. Manometrically-guided endoscopic injection of botulinum toxin for esophageal achalasia: a pilot trial. *Z Gastroenterol* 2000; **38**: 899-903 [PMID: 11132536]
20 **Annese V**, Bassotti G, Coccia G, D'onofrio V, Gatto G, Repici A, Andriulli A. Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia. The Gismad Achalasia Study Group. *Aliment Pharmacol Ther* 1999; **13**: 1347-1350 [PMID: 10540051]
21 **Dughera L**, Chiaverina M, Cacciotella L, Cisarò F. Management of achalasia. *Clin Exp Gastroenterol* 2011; **4**: 33-41 [PMID: 21694870 DOI: 10.2147/CEG.S11593]
22 **Pasricha PJ**, Ravich WJ, Kalloo AN. Effects of intrasphincteric botulinum toxin on the lower esophageal sphincter in piglets. *Gastroenterology* 1993; **105**: 1045-1049 [PMID: 8405847]
23 **Pasricha PJ**, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Treatment of achalasia with intrasphincteric injection of botulinum toxin. A pilot trial. *Ann Intern Med* 1994; **121**: 590-591 [PMID: 8085691]
24 **Rollan A**, Gonzalez R, Carvajal S, Chianale J. Endoscopic intrasphincteric injection of botulinum toxin for the treatment of achalasia. *J Clin Gastroenterol* 1995; **20**: 189-191 [PMID: 7797823]
25 **Hoogerwerf WA**, Pasricha PJ. Pharmacologic therapy in treating achalasia. *Gastrointest Endosc Clin N Am* 2001; **11**: 311-24, vii [PMID: 11319064]
26 **Ma J**, Shen J, Lee CA, Elsaidi GA, Smith TL, Walker FO, Rushing JT, Tan KH, Koman LA, Smith BP. Gene expression of nAChR, SNAP-25 and GAP-43 in skeletal muscles following botulinum toxin A injection: a study in rats. *J Orthop Res* 2005; **23**: 302-309 [PMID: 15734240]
27 **Richter JE**. Update on the management of achalasia: balloons, surgery and drugs. *Expert Rev Gastroenterol Hepatol* 2008; **2**: 435-445 [PMID: 19072391 DOI: 10.1586/17474124.2.3.435]
28 **Pasricha PJ**, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. *Gastroenterology* 1996; **110**: 1410-1415 [PMID: 8613045]
29 **Allescher HD**, Storr M, Seige M, Gonzales-Donoso R, Ott R, Born P, Frimberger E, Weigert N, Stier A, Kurjak M, Rösch T, Classen M. Treatment of achalasia: botulinum toxin injection vs. pneumatic balloon dilation. A prospective study with long-term follow-Up. *Endoscopy* 2001; **33**: 1007-1017 [PMID: 11740642]
30 **Leyden JE**, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev* 2006; (**4**): CD005046 [PMID: 17054234]
31 **Fishman VM**, Parkman HP, Schiano TD, Hills C, Dabezies MA, Cohen S, Fisher RS, Miller LS. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. *Am J Gastroenterol* 1996; **91**: 1724-1730 [PMID: 8792688]
32 **Annese V**, Bassotti G, Coccia G, Dinelli M, D'Onofrio V, Gatto G, Leandro G, Repici A, Testoni PA, Andriulli A. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. GISMAD Achalasia Study Group. *Gut* 2000; **46**: 597-600 [PMID: 10764700]
33 **Smith CD**, Stival A, Howell DL, Swafford V. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. *Ann Surg* 2006; **243**: 579-84; discussion 584-6 [PMID: 16632991]
34 **D'Onofrio V**, Miletto P, Leandro G, Iaquinto G. Long-term follow-up of achalasia patients treated with botulinum toxin. *Dig Liver Dis* 2002; **34**: 105-110 [PMID: 11926552]
35 **Mikaeli J**, Bishehsari F, Montazeri G, Mahdavinia M, Yaghoobi M, Darvish-Moghadam S, Farrokhi F, Shirani S, Estakhri A, Malekzadeh R. Injection of botulinum toxin before pneumatic dilatation in achalasia treatment: a randomized-controlled trial. *Aliment Pharmacol Ther* 2006; **24**: 983-989 [PMID: 16948810]
36 **Neubrand M**, Scheurlen C, Schepke M, Sauerbruch T. Long-term results and prognostic factors in the treatment of achalasia with botulinum toxin. *Endoscopy* 2002; **34**: 519-523 [PMID: 12170400]
37 **Pasricha PJ**, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; **332**: 774-778 [PMID: 7862180]
38 **Bruley des Varannes S**, Scarpignato C. Current trends in the management of achalasia. *Dig Liver Dis* 2001; **33**: 266-277 [PMID: 11407673]
39 **Katzka DA**, Castell DO. Use of botulinum toxin as a diagnostic/therapeutic trial to help clarify an indication for definitive therapy in patients with achalasia. *Am J Gastroenterol* 1999; **94**: 637-642 [PMID: 10086644]
40 **McJunkin B**, McMillan WO, Duncan HE, Harman KM, White JJ, McJunkin JE. Assessment of dilation methods in

achalasia: large diameter mercury bougienage followed by pneumatic dilation as needed. *Gastrointest Endosc* 1991; **37**: 18-21 [PMID: 2004680]
41 **Mandelstam P**, Dillon M. Role of bougienage in the management of achalasia--need for reappraisal in the light of recent studies. *J Clin Gastroenterol* 1990; **12**: 3-4 [PMID: 2303684]
42 **Wang L**, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. *Dig Dis Sci* 2009; **54**: 2303-2311 [PMID: 19107596 DOI: 10.1007/s10620-008-0637-8]
43 **Katzka DA**, Castell DO. Review article: an analysis of the efficacy, perforation rates and methods used in pneumatic dilation for achalasia. *Aliment Pharmacol Ther* 2011; **34**: 832-839 [PMID: 21848630 DOI: 10.1111/j.1365-2036.2011.04816.x]
44 **Vela MF**, Richter JE, Khandwala F, Blackstone EH, Wachsberger D, Baker ME, Rice TW. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. *Clin Gastroenterol Hepatol* 2006; **4**: 580-587 [PMID: 16630776]
45 **Dobrucali A**, Erzin Y, Tuncer M, Dirican A. Long-term results of graded pneumatic dilatation under endoscopic guidance in patients with primary esophageal achalasia. *World J Gastroenterol* 2004; **10**: 3322-3327 [PMID: 15484309]
46 **Eckardt VF**, Gockel I, Bernhard G. Pneumatic dilation for achalasia: late results of a prospective follow up investigation. *Gut* 2004; **53**: 629-633 [PMID: 15082578]
47 **West RL**, Hirsch DP, Bartelsman JF, de Borst J, Ferwerda G, Tytgat GN, Boeckxstaens GE. Long term results of pneumatic dilation in achalasia followed for more than 5 years. *Am J Gastroenterol* 2002; **97**: 1346-1351 [PMID: 12094848]
48 **Chan KC**, Wong SK, Lee DW, Mui WL, Chan AC, Ng EK, Wu JC, Sung JJ, Chung SC. Short-term and long-term results of endoscopic balloon dilation for achalasia: 12 years' experience. *Endoscopy* 2004; **36**: 690-694 [PMID: 15280973]
49 **Kadakia SC**, Wong RK. Graded pneumatic dilation using Rigiflex achalasia dilators in patients with primary esophageal achalasia. *Am J Gastroenterol* 1993; **88**: 34-38 [PMID: 8420271]
50 **Zerbib F**, Thétiot V, Richy F, Benajah DA, Message L, Lamouliatte H. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. *Am J Gastroenterol* 2006; **101**: 692-697 [PMID: 16635216]
51 **Hulselmans M**, Vanuytsel T, Degreef T, Sifrim D, Coosemans W, Lerut T, Tack J. Long-term outcome of pneumatic dilation in the treatment of achalasia. *Clin Gastroenterol Hepatol* 2010; **8**: 30-35 [PMID: 19782766 DOI: 10.1016/j.cgh.2009.09.020]
52 **Chuah SK**, Hu TH, Wu KL, Hsu PI, Tai WC, Chiu YC, Lee CM, Changchien CS. Clinical remission in endoscope-guided pneumatic dilation for the treatment of esophageal achalasia: 7-year follow-up results of a prospective investigation. *J Gastrointest Surg* 2009; **13**: 862-867 [PMID: 19165550 DOI: 10.1007/s11605-009-0804-z]
53 **Søreide JA**, Viste A. Esophageal perforation: diagnostic work-up and clinical decision-making in the first 24 hours. *Scand J Trauma Resusc Emerg Med* 2011; **19**: 66 [PMID: 22035338 DOI: 10.1186/1757-7241-19-66]
54 **Vanuytsel T**, Lerut T, Coosemans W, Vanbeckevoort D, Blondeau K, Boeckxstaens G, Tack J. Conservative management of esophageal perforations during pneumatic dilation for idiopathic esophageal achalasia. *Clin Gastroenterol Hepatol* 2012; **10**: 142-149 [PMID: 22064041 DOI: 10.1016/j.cgh.2011.10.032]
55 **Nair LA**, Reynolds JC, Parkman HP, Ouyang A, Strom BL, Rosato EF, Cohen S. Complications during pneumatic dilation for achalasia or diffuse esophageal spasm. Analysis of risk factors, early clinical characteristics, and outcome. *Dig Dis Sci* 1993; **38**: 1893-1904 [PMID: 8404411]
56 **Metman EH**, Lagasse JP, d'Alteroche L, Picon L, Scotto B, Barbieux JP. Risk factors for immediate complications after progressive pneumatic dilation for achalasia. *Am J Gastroenterol* 1999; **94**: 1179-1185 [PMID: 10235189]
57 **Kadakia SC**, Wong RK. Pneumatic balloon dilation for esophageal achalasia. *Gastrointest Endosc Clin N Am* 2001; **11**: 325-46, vii [PMID: 11319065]
58 **Karamanolis G**, Sgouros S, Karatzias G, Papadopoulou E, Vasiliadis K, Stefanidis G, Mantides A. Long-term outcome of pneumatic dilation in the treatment of achalasia. *Am J Gastroenterol* 2005; **100**: 270-274 [PMID: 15667481]
59 **Gockel I**, Junginger T, Bernhard G, Eckardt VF. Heller myotomy for failed pneumatic dilation in achalasia: how effective is it? *Ann Surg* 2004; **239**: 371-377 [PMID: 15075654 DOI: 10.1097/01.sla.0000114228.34809.01]
60 **Eckardt VF**, Kanzler G, Westermeier T. Complications and their impact after pneumatic dilation for achalasia: prospective long-term follow-up study. *Gastrointest Endosc* 1997; **45**: 349-353 [PMID: 9165313]
61 **Eckardt VF**, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. *Gastroenterology* 1992; **103**: 1732-1738 [PMID: 1451966]
62 **Wehrmann T**, Jacobi V, Jung M, Lembcke B, Caspary WF. Pneumatic dilation in achalasia with a low-compliance balloon: results of a 5-year prospective evaluation. *Gastrointest Endosc* 1995; **42**: 31-36 [PMID: 7557173]
63 **Ghoshal UC**, Rangan M. A review of factors predicting outcome of pneumatic dilation in patients with achalasia cardia. *J Neurogastroenterol Motil* 2011; **17**: 9-13 [PMID: 21369487 DOI: 10.5056/jnm.2011.17.1.9]
64 **Dağli U**, Kuran S, Savaş N, Ozin Y, Alkim C, Atalay F, Sahin B. Factors predicting outcome of balloon dilatation in achalasia. *Dig Dis Sci* 2009; **54**: 1237-1242 [PMID: 18975085 DOI: 10.1007/s10620-008-0493-6]
65 **Alderliesten J**, Conchillo JM, Leeuwenburgh I, Steyerberg EW, Kuipers EJ. Predictors for outcome of failure of balloon dilatation in patients with achalasia. *Gut* 2011; **60**: 10-16 [PMID: 21068135 DOI: 10.1136/gut.2010.211409]
66 **Pandolfino JE**, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008; **135**: 1526-1533 [PMID: 18722376 DOI: 10.1053/j.gastro.2008.07.022]
67 **Chawda SJ**, Watura R, Adams H, Smith PM. A comparison of barium swallow and erect esophageal transit scintigraphy following balloon dilatation for achalasia. *Dis Esophagus* 1998; **11**: 181-17; discussion 181-17; [PMID: 9844801]
68 **Rohof WO**, Hirsch DP, Kessing BF, Boeckxstaens GE. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. *Gastroenterology* 2012; **143**: 328-335 [PMID: 22562023 DOI: 10.1053/j.gastro.2012.04.048]
69 **Guardino JM**, Vela MF, Connor JT, Richter JE. Pneumatic dilation for the treatment of achalasia in untreated patients and patients with failed Heller myotomy. *J Clin Gastroenterol* 2004; **38**: 855-860 [PMID: 15492600]
70 **Ghoshal UC**, Chaudhuri S, Pal BB, Dhar K, Ray G, Banerjee PK. Randomized controlled trial of intrasphincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. *Dis Esophagus* 2001; **14**: 227-231 [PMID: 11869325]
71 **Panaccione R**, Gregor JC, Reynolds RP, Preiksaitis HG. Intrasphincteric botulinum toxin versus pneumatic dilatation for achalasia: a cost minimization analysis. *Gastrointest Endosc* 1999; **50**: 492-498 [PMID: 10502169]
72 **Campos GM**, Vittinghoff E, Rabl C, Takata M, Gadenstätter M, Lin F, Ciovica R. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 2009; **249**: 45-57 [PMID: 19106675 DOI: 10.1097/SLA.0b013e31818e43ab]
73 **Csendes A**, Braghetto I, Henríquez A, Cortés C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. *Gut* 1989; **30**: 299-304 [PMID: 2651226]

74 **Boeckxstaens GE**, Annese V, des Varannes SB, Chaussade S, Costantini M, Cuttitta A, Elizalde JI, Fumagalli U, Gaudric M, Rohof WO, Smout AJ, Tack J, Zwinderman AH, Zaninotto G, Busch OR. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011; **364**: 1807-1816 [PMID: 21561346 DOI: 10.1056/NEJMoa1010502]

75 **Zaninotto G**, Annese V, Costantini M, Del Genio A, Costantino M, Epifani M, Gatto G, D'onofrio V, Benini L, Contini S, Molena D, Battaglia G, Tardio B, Andriulli A, Ancona E. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Ann Surg* 2004; **239**: 364-370 [PMID: 15075653]

76 **Ortega JA**, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980; **26**: 8-10 [PMID: 7358270]

77 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382]

78 **Inoue H**, Tianle KM, Ikeda H, Hosoya T, Onimaru M, Yoshida A, Minami H, Kudo SE. Peroral endoscopic myotomy for esophageal achalasia: technique, indication, and outcomes. *Thorac Surg Clin* 2011; **21**: 519-525 [PMID: 22040634 DOI: 10.1016/j.thorsurg.2011.08.005]

79 **Stavropoulos SN**, Harris MD, Hida S, Brathwaite C, Demetriou C, Grendell J. Endoscopic submucosal myotomy for the treatment of achalasia (with video). *Gastrointest Endosc* 2010; **72**: 1309-1311 [PMID: 21111876 DOI: 10.1016/j.gie.2010.04.016]

80 **von Renteln D**, Inoue H, Minami H, Werner YB, Pace A, Kersten JF, Much CC, Schachschal G, Mann O, Keller J, Fuchs KH, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: a prospective single center study. *Am J Gastroenterol* 2012; **107**: 411-417 [PMID: 22068665 DOI: 10.1038/ajg.2011.388]

81 **Gutschow CA**, Hölscher AH. Myotomy for esophageal achalasia - laparoscopic versus peroral endoscopic approach. *Endoscopy* 2010; **42**: 318-319 [PMID: 20354941 DOI: 10.1055/s-0029-1244071]

82 **Holm AN**, de la Mora Levy JG, Gostout CJ, Topazian MD, Baron TH. Self-expanding plastic stents in treatment of benign esophageal conditions. *Gastrointest Endosc* 2008; **67**: 20-25 [PMID: 17945227]

83 **Repici A**, Conio M, De Angelis C, Battaglia E, Musso A, Pellicano R, Goss M, Venezia G, Rizzetto M, Saracco G. Temporary placement of an expandable polyester silicone-covered stent for treatment of refractory benign esophageal strictures. *Gastrointest Endosc* 2004; **60**: 513-519 [PMID: 15472671]

84 **Li YD**, Tang GY, Cheng YS, Chen NW, Chen WX, Zhao JG. 13-year follow-up of a prospective comparison of the long-term clinical efficacy of temporary self-expanding metallic stents and pneumatic dilatation for the treatment of achalasia in 120 patients. *AJR Am J Roentgenol* 2010; **195**: 1429-1437 [PMID: 21098206 DOI: 10.2214/AJR.10.4407]

85 **Cheng YS**, Li MH, Chen WX, Chen NW, Zhuang QX, Shang KZ. Selection and evaluation of three interventional procedures for achalasia based on long-term follow-up. *World J Gastroenterol* 2003; **9**: 2370-2373 [PMID: 14562416]

86 **De Palma GD**, lovino P, Masone S, Persico M, Persico G. Self-expanding metal stents for endoscopic treatment of esophageal achalasia unresponsive to conventional treatments. Long-term results in eight patients. *Endoscopy* 2001; **33**: 1027-1030 [PMID: 11740645]

87 **Mukherjee S**, Kaplan DS, Parasher G, Sipple MS. Expandable metal stents in achalasia--is there a role? *Am J Gastroenterol* 2000; **95**: 2185-2188 [PMID: 11007215]

88 **Terruzzi V**, Minoli G. Endoscopic injection of ethanolamine as a treatment for achalasia: a first report. *Gastrointest Endosc* 1997; **45**: 540-542 [PMID: 9199925]

89 **Moretó M**, Ojembarrena E. Treatment of achalasia by injection of botulinum toxin or sclerosants? *Endoscopy* 2000; **32**: 361-362 [PMID: 10774979]

90 **Niknam R**, Mikaeli J, Mehrabi N, Mahmoudi L, Elahi E, Shirani S, Malekzadeh R. Ethanolamine oleate in resistant idiopathic achalasia: a novel therapy. *Eur J Gastroenterol Hepatol* 2011; **23**: 1111-1115 [PMID: 21971376 DOI: 10.1097/MEG.0b013e328349647e]

91 **Mattioli S**, Ruffato A, Lugaresi M, Pilotti V, Aramini B, D'Ovidio F. Long-term results of the Heller-Dor operation with intraoperative manometry for the treatment of esophageal achalasia. *J Thorac Cardiovasc Surg* 2010; **140**: 962-969 [PMID: 20828770 DOI: 10.1016/j.jtcvs.2010.07.053]

92 **Endo S**, Nakajima K, Nishikawa K, Takahashi T, Souma Y, Taniguchi E, Ito T, Nishida T. Laparoscopic Heller-Dor surgery for esophageal achalasia: impact of intraoperative real-time manometric feedback on postoperative outcomes. *Dig Surg* 2009; **26**: 342-348 [PMID: 19816021 DOI: 10.1159/000244512]

93 **Mattioli S**, Di Simone MP, Bassi F, Pilotti V, Felice V, Pastina M, Lazzari A, Gozzetti G. Surgery for esophageal achalasia. long-term results with three different techniques. *Hepatogastroenterology* 1996; **43**: 492-500 [PMID: 8799383]

94 **Zendehdel K**, Nyrén O, Edberg A, Ye W. Risk of esophageal adenocarcinoma in achalasia patients, a retrospective cohort study in Sweden. *Am J Gastroenterol* 2011; **106**: 57-61 [PMID: 21212754 DOI: 10.1038/ajg.2010.449]

95 **Leeuwenburgh I**, Scholten P, Alderliesten J, Tilanus HW, Looman CW, Steijerberg EW, Kuipers EJ. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. *Am J Gastroenterol* 2010; **105**: 2144-2149 [PMID: 20588263 DOI: 10.1038/ajg.2010.263]

96 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580 [PMID: 16564854]

97 **Dunaway PM**, Wong RK. Risk and surveillance intervals for squamous cell carcinoma in achalasia. *Gastrointest Endosc Clin N Am* 2001; **11**: 425-34, ix [PMID: 11319071]

98 **Clemente G**. The choice of fundoplication after myotomy for achalasia. *Arch Surg* 2006; **141**: 612; author reply 612-613 [PMID: 16785367]

99 **Csendes A**, Braghetto I, Burdiles P, Korn O, Csendes P, Henríquez A. Very late results of esophagomyotomy for patients with achalasia: clinical, endoscopic, histologic, manometric, and acid reflux studies in 67 patients for a mean follow-up of 190 months. *Ann Surg* 2006; **243**: 196-203 [PMID: 16432352]

100 **Gordon JM**, Eaker EY. Prospective study of esophageal botulinum toxin injection in high-risk achalasia patients. *Am J Gastroenterol* 1997; **92**: 1812-1817 [PMID: 9382042]

101 **Cuillière C**, Ducrotté P, Zerbib F, Metman EH, de Looze D, Guillemot F, Hudziak H, Lamouliatte H, Grimaud JC, Ropert A, Dapoigny M, Bost R, Lémann M, Bigard MA, Denis P, Auget JL, Galmiche JP, Bruley des Varannes S. Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin. *Gut* 1997; **41**: 87-92 [PMID: 9274478]

102 **Vaezi MF**, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL, Koehler RE, Baker ME. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999; **44**: 231-239 [PMID: 9895383]

103 **Stark GA**, Castell DO, Richter JE, Wu WC. Prospective randomized comparison of Brown-McHardy and microvasive balloon dilators in treatment of achalasia. *Am J Gastroenterol* 1990; **85**: 1322-1326 [PMID: 2220722]

104 **Parkman HP**, Reynolds JC, Ouyang A, Rosato EF, Eisenberg JM, Cohen S. Pneumatic dilatation or esophagomyotomy treatment for idiopathic achalasia: clinical outcomes and cost analysis. *Dig Dis Sci* 1993; **38**: 75-85 [PMID: 8420763]

105 **Coccia G**, Bortolotti M, Michetti P, Dodero M. Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. *Gut* 1991; **32**: 604-606 [PMID: 2060867]
106 **Bourgeois N**, Coffernils M, Buset M, Gelin M, Deltenre M, Panzer JM, Cremer M. Management of dysphagia in suspected esophageal motor disorders. *Dig Dis Sci* 1991; **36**: 268-273 [PMID: 1995259]
107 **Gelfand MD**, Kozarek RA. An experience with polyethylene balloons for pneumatic dilation in achalasia. *Am J Gastroenterol* 1989; **84**: 924-927 [PMID: 2756984]
108 **Vaezi MF**, Baker ME, Richter JE. Assessment of esophageal emptying post-pneumatic dilation: use of the timed barium esophagram. *Am J Gastroenterol* 1999; **94**: 1802-1807 [PMID: 10406238]
109 **Rai RR**, Shende A, Joshi A, Mathur A, Nijhawan S. Rigiflex pneumatic dilation of achalasia without fluoroscopy: a novel office procedure. *Gastrointest Endosc* 2005; **62**: 427-431 [PMID: 16111963]
110 **Swanström LL**, Rieder E, Dunst CM. A stepwise approach and early clinical experience in peroral endoscopic myotomy for the treatment of achalasia and esophageal motility disorders. *J Am Coll Surg* 2011; **213**: 751-756 [PMID: 21996484 DOI: 10.1016/j.jamcollsurg.2011.09.001]
111 **Costamagna G**, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis* 2012; **44**: 827-832 [PMID: 22609465 DOI: 10.1016/j.dld.2012.04.003]
112 **Chiu PW**, Wu JC, Teoh AY, Chan Y, Wong SK, Liu SY, Yung MY, Lam CC, Sung JJ, Chan FK, Lau JY, Ng EK. Peroral endoscopic myotomy for treatment of achalasia: from bench to bedside (with video). *Gastrointest Endosc* 2013; **77**: 29-38 [PMID: 23043852 DOI: 10.1016/j.gie.2012.08.018]

P- Reviewer Holscher AH **S- Editor** Gou SX **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.v5.i8.391

World J Gastrointest Endosc 2013 August 16; 5(8): 391-397
ISSN 1948-5190 (online)

BRIEF ARTICLE

Prevalence and clinical features of colonic diverticulosis in a Middle Eastern population

Nahla Azzam, Abdulrahman M Aljebreen, Othman Alharbi, Majid A Almadi

Nahla Azzam, Abdulrahman M Aljebreen, Othman Alharbi, Majid A Almadi, Division of Gastroenterology, Department of Medicine, King Khalid University Hospital, King Saud University, Riyadh 11461, Saudi Arabia
Majid A Almadi, Division of Gastroenterology, the McGill University Health Center, Montreal General Hospital, McGill University, Montreal, QC H3A 0G4, Canada
Author contributions: Azzam N, Aljebreen AM, Almadi MA and Alharbi O did the conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.
Supported by King Saud University for its funding of this research through the Research Group Project, No. RGP-VPP-279
Correspondence to: Dr. Majid A Almadi, Division of Gastroenterology, Department of Medicine, King Khalid University Hospital, King Saud University, PO Box 2925(59), Riyadh 11461, Saudi Arabia. maalmadi@ksu.edu.sa
Telephone: +966-1-4679167 Fax: +966-1-4671217
Received: March 25, 2013 Revised: July 2, 2013
Accepted: July 9, 2013
Published online: August 16, 2013

Abstract

AIM: To determine the prevalence, location, associations and clinical features of colonic-diverticulosis and its role as a cause of lower-gastroenterology-bleeding.

METHODS: We retrospectively reviewed the medical records of 3649 consecutive patients who underwent a colonoscopy for all indications between 2007 and 2011 at King Khalid University Hospital, Riyadh, Saudi Arabia. The demographic data were collected retrospectively through the hospital's information system, electronic file system, endoscopic e-reports, and manual review of the files by two research assistants. The demographic information included the age, sex, comorbidities and indication for the colonoscopy. The association among colonic polyps, comorbidities and diverticular disease was also measured.

RESULTS: A total of 270 patients out of 3649 were diagnosed with colonic diverticulosis, with a prevalence of 7.4%. The mean age was 60.82 years ± 0.833, (range 12-110). Females comprised 38.89% (95%CI: 33-44.7) of the study population. The major symptoms were rectal bleeding in 33.6%, abdominal pain in 19.3%, constipation in 12.8% and anemia in 6%. Diverticula were predominantly left-sided (sigmoid and descending colon) in 62%, right-sided in 13% and in multiple locations in 25%. There was an association between the presence of diverticulosis and adenomatous polyps (*P*-value < 0.001), hypertension (*P*-value < 0.0001) and diabetes mellitus (*P*-value < 0.0016). Diverticular disease was the second most common cause of lower gastrointestinal bleeding, in 33.6% (95%CI: 27.7-39.4), after internal hemorrhoids, in 44.6% (95%CI: 40.3-48.9). On multivariable logistic regression, hypertension (OR = 2.30; 95%CI: 1.29-4.10), rectal bleeding (OR = 2.57; 95%CI: 1.50-4.38), and per year increment in age (OR = 1.05; 95%CI: 1.03-1.07) were associated with diverticulosis but not with bleeding diverticular disease. Limitations: A small proportion of the patients included had colonoscopies performed as a screening test.

CONCLUSION: Colonic-diverticulosis was found to have a low prevalence, be predominantly left-sided and associated with adenomatous-polyps. Age, hypertension and rectal bleeding predict the presence of diverticular disease.

Key words: Colonic diverticulosis; Diverticular disease; Saudi Arabia; Prevalence; Lower gastrointestinal bleeding; Epidemiology

Core tip: Colonic-diverticulosis is common in Western populations as well as an emerging disease in Eastern populations but prevalence data for Arab populations is scarce. We retrospectively reviewed the medical

records of 3649 consecutive patients who underwent a colonoscopy for all indications. The demographic information included the age, sex, comorbidities and indication for the colonoscopy. The association among colonic polyps, comorbidities and diverticular disease was also measured. Colonic-diverticulosis was found to have a low prevalence among the Saudi population, be predominantly left-sided and associated with adenomatous-polyps. Age, hypertension and rectal bleeding predict the presence of diverticular disease.

Azzam N, Aljebreen AM, Alharbi O, Almadi MA. Prevalence and clinical features of colonic diverticulosis in a Middle Eastern population. *World J Gastrointest Endosc* 2013; 5(8): 391-397 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/391.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.391

INTRODUCTION

Diverticulosis of the colon is a common disease in Western societies[1]. Although the true prevalence of diverticula is unknown, a large observational study of 9086 consecutive patients undergoing colonoscopy found a prevalence of 27%[2], which increased with advancing age. Some studies suggested that the prevalence of diverticula may be as high as 60% in patients older than 80 years of age[3] and has no sex predilection. Most patients with diverticulosis will have clinically quiescent disease; approximately 80% to 85% are believed to remain asymptomatic.

Recent evidence showed a rising prevalence of diverticulosis in Europe, the United States and Canada[4-6]. Although Western populations have predominantly left-sided diverticulosis[7], right-sided diverticulosis is common in Asia. Diverticulosis of the colon is rare in rural Asia and Africa, and its incidence increases with age[8-15]. The prevalence in Southeast Asia ranges from 8% to 22%[8,9], affecting the right side of the colon in most cases (70%-98%) and showing a peak incidence in patients 50 to 60 years of age[10,11]. Studies from China and South Korea have noted a prevalence of 0.5% to 1.7% with a right-side predilection in 75% of the patients[12]. However, an even lower prevalence of diverticulosis was reported in Sub-Saharan Africa, with a slightly younger age (45 to 60 years) with right colon involvement in 62% of the cases[13-15]. Data from the Arab world examining the prevalence and clinical features of colonic diverticulosis are scant. In a retrospective evaluation of 274 consecutive barium enemas performed at a single institute in patients aged 20 to 85 years over a three-year period (1979 to 1981) in Jordan, colonic diverticula were found in 4%[16]. A study from Iran examined the frequency of diverticulosis in 656 barium enemas and found it to be 2.4% in patients older than 50 years[17]. A higher prevalence was reported in Israel, reaching up to 9.5% among Arabs, with a seven-fold increase over a 10-year period[18]. Diverticular disease (DD) refers to symptomatic diverticula that cause complications, including acute diverticulitis, perforations and lower gastroenterointestinal bleeding. Bleeding from colonic diverticula is the most common cause of acute lower gastrointestinal (GI) bleeding[19,20]. Acute lower intestinal bleeding has been reported to occur in up to 3%-5% of colonic diverticula[21,22]. Most cases of diverticular bleeding resolve on their own, and diverticular bleeding stops spontaneously in 70%-80% of cases[23]. Shennak *et al*[24] reported that hemorrhoids were the most common cause of lower GI bleeding in 701 Jordanian patients, followed by polyps and colitis.No data are available from Saudi Arabia, and whether the incidence, prevalence or epidemiology of the disease is similar or differs from that in other populations is not clear. The aim of our study was to investigate the prevalence, location, distribution, clinical features and associations of colonic diverticulosis as well as the factors that contribute to bleeding in Saudi patients with DD.

MATERIALS AND METHODS

Ethics

This study was approved ethically by the Internal Review Board (IRB) (Study No. E-12-818) at King Khalid University Hospital, Riyadh, Saudi Arabia.

Data Collection

A retrospective cohort study was conducted using an endoscopic reporting database of individuals seen at a major tertiary care university hospital (King Khalid University Hospital) in Riyadh, Saudi Arabia. The demographic data of consecutive patients who underwent a complete colonoscopy for all indications between August 2007 and April 2011 were collected retrospectively through the hospital's HIS system, electronic file system, endoscopic e-reports, and a manual review of the files by two research assistants. The demographic features included age, sex, symptoms, indication for colonoscopy, medication history and comorbidities. Patients with a history of any of the following were excluded from this study: colon cancer, colonic resection, incomplete colonoscopy, active colitis, active diverticulitis and inflammatory bowel disease. Colonic diverticulosis was defined as the presence of one or more diverticula, which is a saccular out pouching of the colon. The location of the diverticula was classified as follows: left-sided refers to diverticulosis involving the descending colon and/or sigmoid colon with or without the transverse colon, right-sided refers to diverticulosis involving the caecum and/or ascending colon with or without the transverse colon and hepatic flexure, and multiple locations refers to both right and left colonic involvement. The ethics committee of King Khalid University Hospital approved the study.

Statistical analysis

Descriptive statistics were computed for continuous variables including means, SD and minimum and maximum values. Frequencies and inter-quintile ranges were used

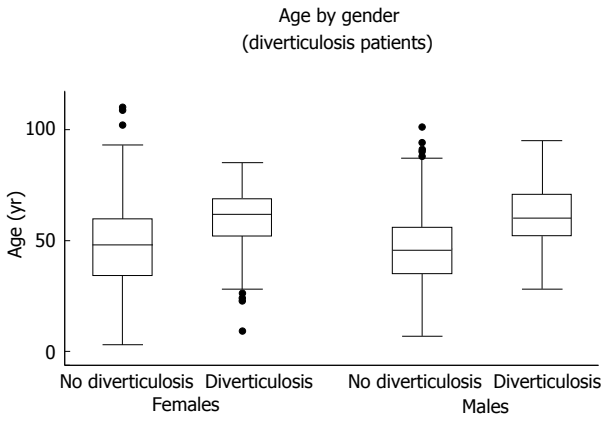


Figure 1 The age distribution of patients stratified by the presences or absence of diverticulosis as well as gender. Source: King Khalid University Hospital.

for categorical variables. The χ^2 test was used for categorical variables, and the *t*-test for continuous variables. Univariable and multivariable logistic regressions were used to examine the association between independent variables and the presence of diverticulosis. The OR and 95%CI were estimated. We used the software STATA 11.2 (StataCorp, TX, United States) in our analysis. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Out of 3649 patients undergoing colonoscopy, 270 patients (7.4%) were diagnosed with colonic diverticulosis. The mean age was 60.82 years ± 0.833 (range 12-110), and the majority were Saudi nationals (92.9%). Females were 38.89% ± 2.97 and males were 61.11% ± 1.51 of the cohort, and there was no gender-specific predilection ($P < 0.218$) (Figure 1). The comorbidities and the indications for the colonoscopy for all patients are presented in Table 1. Diverticulosis was predominantly left-sided (sigmoid and descending colon) in 62%, followed by right-sided in 13% and multiple locations in 25%.

In the patients with diverticulosis, there was a higher history of hypertension (63.88% *vs* 25.92%, *P*-value < 0.01), diabetes (44.44% *vs* 24.32%, *P*-value < 0.01), dyslipidemia (22.22% *vs* 10.77%, *P*-value = 0.03) and a higher history of the use of aspirin (21.33% *vs* 9.23%, *P*-value = 0.01). Furthermore, those with diverticulosis were referred for a colonoscopy more frequently for rectal bleeding (33.60% *vs* 22.08%, *P*-value < 0.01) and were less likely to be referred for surveillance (10.40% *vs* 16.72%, *P*-value < 0.01), diarrhea (2.40% *vs* 9.28%, *P*-value < 0.01), or weight loss (2.00% *vs* 5.79%, *P*-value < 0.01) (Table 1).

The univariable analysis revealed that diverticulosis was associated with a history of hypertension (OR = 5.05; 95%CI: 3.06-8.34), diabetes (OR = 2.49; 95%CI: 1.53-4.05), dyslipidemia (OR = 2.37; 95% CI, 1.31-4.27), and aspirin use (OR = 2.67; 95%CI: 1.48-4.81) and that the diverticulosis patients were more likely to be referred for a colonoscopy for rectal bleeding (OR = 1.79; 95%CI: 1.35-2.35) but less likely to be referred for surveillance (OR = 0.58; 95%CI: 0.38-0.87), diarrhea (OR = 0.24; 95%CI: 0.11-0.55), or weight loss (OR = 0.33; 95%CI: 0.14-0.82) (Table 2).

Table 1 Comorbidities of patients and indications for a colonoscopy for the complete cohort of patients

Variable	Percentage	95%CI
Comorbidities		
Hypertension	63.88%	52.52-75.25
Diabetes	44.44%	32.68-56.20
Dyslipidemia	22.22%	12.38-32.06
Aspirin	10.07%	8.35-11.82
Chronic kidney disease	5.55%	0.10-11.00
Coronary artery disease	4.16%	0.10-9.00
Indication for colonoscopy		
Bleeding per rectum	22.94%	21.50-24.38
Abdominal pain	19.30%	17.94-20.64
Surveillance	16.29%	15.03-17.55
Constipation	9.57%	8.57-10.58
Diarrhea	8.75%	7.79-9.72
Screening	7.57%	6.67-8.48
Weight loss	5.50%	4.72-6.28
Anemia	5.02%	4.27-5.76
Melena	3.13%	2.54-3.73
Anal pain	1.91%	1.45-2.38
Altered bowel habits	1.76%	1.31-2.21
Perianal fistula	1.19%	0.82-1.55
Positive for occult blood	0.52%	0.27-0.76

The multivariable analysis revealed that the only factors associated with the presence of diverticulosis were age (OR = 1.05; 95%CI: 1.03-1.07 per year), hypertension (OR = 2.30; 95%CI: 1.29-4.10), rectal bleeding (OR = 2.57; 95%CI: 1.50-4.38), and the finding of internal hemorrhoids (OR = 1.96; 95%CI: 1.06-3.65) (Table 3). However, none of these variables predicted bleeding in the patients with DD (Table 4).

There was an association between the presence of diverticulosis and adenomatous polyps (OR = 1.76; 95%CI: 1.33-2.33).

Regarding the etiology of the patients presenting with rectal bleeding based on the colonoscopy findings, internal hemorrhoids was the most common cause (44.7%), followed by DD (33.6%), colonic mass (31.5%), polyps (24.8%), and colitis (19.0%) (Table 5).

We found that bleeding as an indication for a colonoscopy was present in 58% of the patients with left-sided DD, 18% with right-sided DD, and 23% with DD in multiple locations.

DISCUSSION

Colonic diverticulosis is a prevalent gastrointestinal disorder in Western populations and less so in Eastern ones[4,25,26]. Ascertaining the true prevalence of diverticulosis in the general population is difficult given that most affected individuals will remain asymptomatic. Our knowledge about the magnitude of the effect and prevalence in Arab populations is limited. The results

Table 2 Comorbidities of patients and indications for a colonoscopy stratified by the presence and absence of diverticulosis as well as the univariable analysis between the presence of diverticulosis and the corresponding variables

Variable	Diverticulosis	No diverticulosis	*P*-value	Univariable analysis	
				OR	95%CI
Comorbidities					
Hypertension	63.88%	25.92%	< 0.01	5.05	3.06-8.34
Diabetes	44.44%	24.32%	< 0.01	2.49	1.53-4.05
Dyslipidemia	22.22%	10.77%	0.03	2.37	1.31-4.27
Aspirin	21.33%	9.23%	0.01	2.67	1.48-4.81
Chronic kidney disease	5.56%	3.12%	0.38	2.91	0.82-10.29
Coronary artery disease	4.16%	1.43%	0.27	1.82	0.62-5.30
Indication for colonoscopy					
Bleeding per rectum	33.60%	22.08%	< 0.01	1.79	1.35-2.35
Abdominal pain	19.30%	15.20%	0.06	0.73	0.51-1.05
Constipation	12.80%	9.31%	0.11	1.43	0.96-2.11
Surveillance	10.40%	16.72%	< 0.01	0.58	0.38-0.87
Screening	6.40%	7.67%	0.43	0.82	0.49-1.39
Anemia	6.00%	4.94%	0.5	1.23	0.71-2.12
Melena	3.13%	4.40%	0.31	1.47	0.78-2.79
Diarrhea	2.40%	9.28%	< 0.01	0.24	0.11-0.55
Altered bowel habits	2.00%	1.74%	0.78	1.15	0.46-2.90
Weight loss	2.00%	5.79%	< 0.01	0.33	0.14-0.82
Anal pain	1.20%	1.97%	0.29	0.6	0.19-1.94
Positive for occult blood	1.20%	0.46%	0.29	2.62	0.75-9.19
Perianal fistula	0.40%	1.25%	0.06	0.32	0.04-2.32

Table 3 Variables associated with the presence of diverticulosis on multivariable analysis

Variable	Multivariable analysis	
	OR	95%CI
Age	1.05	1.03-1.07
Hypertension	2.30	1.29-4.10
Bleeding per rectum	2.57	1.50-4.38
Internal hemorrhoids	1.96	1.06-3.65

Table 4 Factors associated with of bleeding per rectum in those with diverticulosis on univariable analysis, none of the variables were associated with bleeding per rectum on multivariable analysis

Variable	OR	95%CI
Age	1.00	0.97-1.02
Hypertension	0.73	0.27-1.95
Diabetes	1.27	0.48-3.32
Dyslipidemia	1.00	0.32-3.15
Atrial fibrillation	0.44	0.05-3.50
Abdominal Pain	0.19	0.07-0.57
Constipation	0.75	0.33-1.70
Diarrhea	0.39	0.04-3.38
Internal hemorrhoids	2.61	1.48-4.61
Polyps	1.28	0.72-2.29

Table 5 Findings on colonoscopy and possible etiologies for patients referred for bleeding per rectum

Etiology	Percentage	95%CI
Internal hemorrhoids	44.66%	40.36-48.96
Diverticulosis	33.60%	27.73-39.47
Mass	31.45%	26.03-36.87
Polyps	24.76%	21.37-28.15
Colitis	18.97%	14.44-23.49

of this study showed that the prevalence of colonic diverticulosis is 7.4%, which is low compared with Western and Eastern populations and slightly higher compared with data from other countries in the Arab world[16,17].

The mean age of the patients with diverticulosis was 60.82 years, and the majority (92.3%) were older than 50 years of age. The disease was more prevalent with advancing age, which is in agreement with the international data[27].

The distribution pattern of diverticulosis differs between Western and Eastern populations, with sigmoid diverticulea predominating in the Western population and the right colon most commonly affected in Asians[28-30]. Left-sided diverticulosis was found to be more common, which is most likely due to urbanization in the gulf region, with the increased consumption of red meat and a low fiber diet. The study was conducted in one of the largest tertiary care hospitals in Riyadh, the capital of the Kingdom of Saudi Arabia. The caption area of the hospital covers the population inhabiting the northern part of Riyadh, which has an urban inhabitance. Right colonic diverticulosis is thought to be congenital, which differs from the development of sigmoid diverticula, which in turn is thought to be acquired as a result of the raised intraluminal pressure within the colon[31] that is attributable to inadequate dietary fiber intake[32,33].

Colonic neoplasia and colonic diverticulosis have common epidemiological trends and risk factors, such as age and a lack of dietary fiber[34]. However, the association between these diseases remains elusive. In a pro-

spective study, Morini *et al*[35] found an increased risk for sigmoid colon adenomas in Italian patients with DD. In a cross-sectional study in the United States, an increased risk for distal neoplasia was found in women with extensive distal diverticulosis[36]. Such an association was also observed in our study (OR = 1.76; 95%CI: 1.33-2.33), with a predominantly left-sided location for diverticulosis in 62% and for adenomatous polyps in 65% of our cohort.

Studies have shown that NSAID use in patients with complicated DD is nearly double the rate of NSAID use in patients with normal, healthy colons[37]. In addition, multiple studies have demonstrated a clear link between NSAID use and an increased risk of diverticular hemorrhaging. Hypertension was also found to be associated with the risk of DD complicated with a high bleeding risk, which is predominantly due to vascular endothelial injury and atheroma formation that lead to arteriosclerosis and increased pressure within exposed blood vessels, which elevate the risk for bleeding[38,39]. Sakuta *et al*[40] reported the first study that evaluated the prevalence rates of type 2 diabetes and hypertension among the subjects with asymptomatic colonic diverticula and found that type 2 diabetes (21.6% *vs* 14.0%, $P = 0.047$) and hypertension (30.9% *vs* 19.8%, $P = 0.011$) were more prevalent among the subjects with colonic diverticulum than in those without it. The mechanism of the association between diabetes and colonic diverticula is not yet clear. However, low dietary fiber intake is assumed to contribute to the development of colonic diverticula[41-43]. Our data showed similar associations with hypertension, diabetes mellitus, dyslipidemia, the history of aspirin use and colonic diverticulosis , but the only factors that predicted the presence of colonic diverticulosis were age (OR = 1.05; 95%CI: 1.03-1.07 per year), hypertension (OR = 2.40; 95%CI: 1.31-4.39), rectal bleeding (OR = 2.57; 95%CI: 3.06-8.34), and the finding of internal hemorrhoids (OR = 1.96; 95%CI: 1.06-3.65). Surprisingly, these factors were not associated with complicated diverticulosis patients who presented with lower GI bleeding.

Before the era of the colonoscopy, DD was thought to be the most common cause of massive lower GI bleeding[44], as it was often diagnosed by barium enemas in earlier studies. Recently after the introduction of colonoscopy, however, DD was shown to be the second-most common etiology of massive GI bleeding in the elderly after colonic angioma[45]. Our data found that internal hemorrhoids were the most common etiology of rectal bleeding, with DD being second. This result is likely related to the retrospective study design.

Our study may have suffered bias towards symptomatic patients because it was an observational study instead of a population-based study. In addition, because of the limited number of patients with screening colonoscopy as an indication, a definitive conclusion could not be drawn, especially given the lack of previous studies from Saudi Arabia or Gulf countries for comparison. However, this study is the first, to the best of our knowledge, evaluating the prevalence, clinical features, and associations of colonic diverticulosis in Saudi Arabia and may open the door for future research with a larger cohort to elucidate the true prevalence, behavior, risk factors and association of DD in our population.

COMMENTS

Background

Colonic diverticulosis is common in Western populations as well as an emerging disease in Eastern populations but data are scarce about the prevalence among the Arab population with no previous reported studies on the prevalence of diverticular disease.

Research frontiers

Diverticulosis of the colon is a common disease in the Western populations and associated with many gastrointestinal complications that might be life threatening as in case of lower gastrointestinal (GI) bleeding. The prevalence of colonic diverticulosis have been studied thoroughly in Western and Eastern populations, however it was never studied in Arab or among gulf populations. In this study, the authors aimed to look at the prevalence, clinical pictures, and locations of colonic diverticulosis as well as it's role to the patients who presented with lower GI bleeding.

Innovations and breakthroughs

The study demonstrate that the colonic diverticulosis prevalence among Saudi population was low compared to the reported prevalence from the other ethnic population, however colonic diverticula were predominantly at the left side similar to Western populations. Other important issue was being associated with the presence of adenomatous polyps in left side of the colon. It's role in contributions of lower GI bleeding was also studied and found that diverticular disease was the second most common etiology for lower GI bleeding in these cohort.

Applications

Future population based studies to look at the true prevalence of colonic diverticulosis among patients for screening colonoscopy are highly recommended.

Peer review

The manuscript underlies the prevalence, clinical pictures, locations, and association of colonic diverticulosis among Saudi populations which never been studied before and it looks also at the factors that predict the presence of colonic diverticula which might help in patients selection to undergo colonoscopic studies. It is well written manuscript in an important GI topic.

REFERENCES

1 **Campbell WB**, Lee EJ, Van de Sijpe K, Gooding J, Cooper MJ. A 25-year study of emergency surgical admissions. *Ann R Coll Surg Engl* 2002; **84**: 273-277 [PMID: 12215033 DOI: 10.1308/003588402320439739]

2 **Loffeld RJ**, Van Der Putten AB. Diverticular disease of the colon and concomitant abnormalities in patients undergoing endoscopic evaluation of the large bowel. *Colorectal Dis* 2002; **4**: 189-192 [PMID: 12780614 DOI: 10.1046/j.1463-1318.2002.00328.x]

3 **Floch MH**, White JA. Management of diverticular disease is changing. *World J Gastroenterol* 2006; **12**: 3225-3228 [PMID: 16718843]

4 **Etzioni DA**, Mack TM, Beart RW, Kaiser AM. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. *Ann Surg* 2009; **249**: 210-217 [PMID: 19212172 DOI: 10.1097/SLA.0b013e3181952888]

5 **Warner E**, Crighton EJ, Moineddin R, Mamdani M, Upshur R. Fourteen-year study of hospital admissions for diverticular disease in Ontario. *Can J Gastroenterol* 2007; **21**: 97-99 [PMID: 17299613]

6 **Kang JY**, Hoare J, Tinto A, Subramanian S, Ellis C, Majeed A, Melville D, Maxwell JD. Diverticular disease of the colon--on the rise: a study of hospital admissions in England between 1989/1990 and 1999/2000. *Aliment Pharmacol Ther* 2003; **17**: 1189-1195 [PMID: 12752356 DOI: 10.1046/j.1365-2036.2003.01551.x]

7 **Koehler R**. The incidence of colonic diverticulosis in finland and sweden. *Acta Chir Scand* 1963; **126**: 148-155 [PMID: 14059862]

8 **Chan CC**, Lo KK, Chung EC, Lo SS, Hon TY. Colonic diverticulosis in Hong Kong: distribution pattern and clinical significance. *Clin Radiol* 1998; **53**: 842-844 [PMID: 9833789 DOI: 10.1016/S0009-9260(98)80197-9]

9 **Munakata A**, Nakaji S, Takami H, Nakajima H, Iwane S, Tuchida S. Epidemiological evaluation of colonic diverticulosis and dietary fiber in Japan. *Tohoku J Exp Med* 1993; **171**: 145-151 [PMID: 8128483 DOI: 10.1620/tjem.171.145]

10 **Fong SS**, Tan EY, Foo A, Sim R, Cheong DM. The changing trend of diverticular disease in a developing nation. *Colorectal Dis* 2011; **13**: 312-316 [PMID: 19906060 DOI: 10.1111/j.1463-1318.2009.02121.x]

11 **Miura S**, Kodaira S, Shatari T, Nishioka M, Hosoda Y, Hisa TK. Recent trends in diverticulosis of the right colon in Japan: retrospective review in a regional hospital. *Dis Colon Rectum* 2000; **43**: 1383-1389 [PMID: 11052515 DOI: 10.1007/BF02236634]

12 **Pan GZ**, Liu TH, Chen MZ, Chang HC. Diverticular disease of colon in China. A 60-year retrospective study. *Chin Med J (Engl)* 1984; **97**: 391-394 [PMID: 6437755]

13 **Ihekwaba FN**. Diverticular disease of the colon in black Africa. *J R Coll Surg Edinb* 1992; **37**: 107-109 [PMID: 1377244]

14 **Madiba TE**, Mokoena T. Pattern of diverticular disease among Africans. *East Afr Med J* 1994; **71**: 644-646 [PMID: 7821243]

15 **Baako BN**. Diverticular disease of the colon in Accra, Ghana. *Br J Surg* 2001; **88**: 1595 [PMID: 11736970 DOI: 10.1046/j.0007-1323.2001.01917.x]

16 **Fatayer WT**, A-Khalaf MM, Shalan KA, Toukan AU, Daker MR, Arnaout MA. Diverticular disease of the colon in Jordan. *Dis Colon Rectum* 1983; **26**: 247-249 [PMID: 6839895 DOI: 10.1007/BF02562489]

17 **Dabestani A**, Aliabadi P, Shah-Rookh FD, Borhanmanesh FA. Prevalence of colonic diverticular disease in southern Iran. *Dis Colon Rectum* 1981; **24**: 385-387 [PMID: 6266788 DOI: 10.1007/BF02603424]

18 **Levy N**, Stermer E, Simon J. The changing epidemiology of diverticular disease in Israel. *Dis Colon Rectum* 1985; **28**: 416-418 [PMID: 4006637 DOI: 10.1007/BF02560228]

19 **Vernava AM**, Moore BA, Longo WE, Johnson FE. Lower gastrointestinal bleeding. *Dis Colon Rectum* 1997; **40**: 846-858 [PMID: 9221865 DOI: 10.1007/BF02055445]

20 **Zuckerman GR**, Prakash C. Acute lower intestinal bleeding. Part Ⅱ: etiology, therapy, and outcomes. *Gastrointest Endosc* 1999; **49**: 228-238 [PMID: 9925703 DOI: 10.1016/S0016-5107(99)70491-8]

21 **Stollman NH**, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999; **94**: 3110-3121 [PMID: 10566700 DOI: 10.1111/j.1572-0241.1999.01501.x]

22 **McGuire HH**, Haynes BW. Massive hemorrhage for diverticulosis of the colon: guidelines for therapy based on bleeding patterns observed in fifty cases. *Ann Surg* 1972; **175**: 847-855 [PMID: 4537394 DOI: 10.1097/00000658-197206010-00004]

23 **McGuire HH**. Bleeding colonic diverticula. A reappraisal of natural history and management. *Ann Surg* 1994; **220**: 653-656 [PMID: 7979613 DOI: 10.1097/00000658-199411000-00008]

24 **Shennak MM**, Tarawneh MM. Pattern of colonic disease in lower gastrointestinal bleeding in Jordanian patients: a prospective colonoscopic study. *Dis Colon Rectum* 1997; **40**: 208-214 [PMID: 9075759 DOI: 10.1007/BF02054990]

25 **Chia JG**, Wilde CC, Ngoi SS, Goh PM, Ong CL. Trends of diverticular disease of the large bowel in a newly developed country. *Dis Colon Rectum* 1991; **34**: 498-501 [PMID: 1645247 DOI: 10.1007/BF02049937]

26 **Markham NI**, Li AK. Diverticulitis of the right colon--experience from Hong Kong. *Gut* 1992; **33**: 547-549 [PMID: 1582600 DOI: 10.1136/gut.33.4.547]

27 **Parks TG**. Natural history of diverticular disease of the colon. A review of 521 cases. *Br Med J* 1969; **4**: 639-642 [PMID: 5359917 DOI: 10.1136/bmj.4.5684.639]

28 **Lee YS**. Diverticular disease of the large bowel in Singapore. An autopsy survey. *Dis Colon Rectum* 1986; **29**: 330-335 [PMID: 3084185 DOI: 10.1007/BF02554125]

29 **Yap I**, Hoe J. A radiological survey of diverticulosis in Singapore. *Singapore Med J* 1991; **32**: 218-220 [PMID: 1775996]

30 **Arfwidsson S**, Knock NG, Lehmann L, Winberg T. Pathogenesis of multiple diverticula of the sogmoid colon in diverticular disease. *Acta Chir Scand Suppl* 1964; **63**: SUPPL 342: 1-68 [PMID: 14227870]

31 **Beranbaum SL**, Zausner J, Lane B. Diverticular disease of the right colon. *Am J Roentgenol Radium Ther Nucl Med* 1972; **115**: 334-348 [PMID: 5037795 DOI: 10.2214/ajr.115.2.334]

32 **Burkitt DP**, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. *Lancet* 1972; **2**: 1408-1412 [PMID: 4118696 DOI: 10.1016/S0140-6736(72)92974-1]

33 **Gear JS**, Ware A, Fursdon P, Mann JI, Nolan DJ, Brodribb AJ, Vessey MP. Symptomless diverticular disease and intake of dietary fibre. *Lancet* 1979; **1**: 511-514 [PMID: 85104 DOI: 10.1016/S0140-6736(79)90942-5]

34 **Howe GR**, Benito E, Castelleto R, Cornée J, Estève J, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 1992; **84**: 1887-1896 [PMID: 1334153 DOI: 10.1093/jnci/84.24.1887]

35 **Morini S**, Hassan C, Zullo A, De Francesco V, Festa V, Barberani F, Faleo D, Stroffolini T. Diverticular disease as a risk factor for sigmoid colon adenomas. *Dig Liver Dis* 2002; **34**: 635-639 [PMID: 12405250 DOI: 10.1016/S1590-8658(02)80206-7]

36 **Kieff BJ**, Eckert GJ, Imperiale TF. Is diverticulosis associated with colorectal neoplasia? A cross-sectional colonoscopic study. *Am J Gastroenterol* 2004; **99**: 2007-2011 [PMID: 15447764 DOI: 10.1111/j.1572-0241.2004.30332.x]

37 **Ballinger A**. Adverse effects of nonsteroidal anti-inflammatory drugs on the colon. *Curr Gastroenterol Rep* 2008; **10**: 485-489 [PMID: 18799124 DOI: 10.1007/s11894-008-0089-5]

38 **Niikura R**, Nagata N, Akiyama J, Shimbo T, Uemura N. Hypertension and concomitant arteriosclerotic diseases are risk factors for colonic diverticular bleeding: a case-control study. *Int J Colorectal Dis* 2012; **27**: 1137-1143 [PMID: 22354135 DOI: 10.1007/s00384-012-1422-x]

39 **Yamada A**, Sugimoto T, Kondo S, Ohta M, Watabe H, Maeda S, Togo G, Yamaji Y, Ogura K, Okamoto M, Yoshida H, Kawabe T, Kawase T, Omata M. Assessment of the risk factors for colonic diverticular hemorrhage. *Dis Colon Rectum* 2008; **51**: 116-120 [PMID: 18085336 DOI: 10.1007/s10350-007-9137-8]

40 **Sakuta H**, Suzuki T. Prevalence rates of type 2 diabetes and hypertension are elevated among middle-aged Japanese men with colonic diverticulum. *Environ Health Prev Med* 2007; **12**: 97-100 [PMID: 21431826 DOI: 10.1007/BF02898156]

41 **Fung TT**, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, Willett WC. Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr* 2002; **76**: 535-540 [PMID: 12197996]

42 **Liu S**, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC. A prospective study of

whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000; **90**: 1409-1415 [PMID: 10983198 DOI: 10.2105/AJPH.90.9.1409]

43 **Mimura T**, Emanuel A, Kamm MA. Pathophysiology of diverticular disease. *Best Pract Res Clin Gastroenterol* 2002; **16**: 563-576 [PMID: 12406451 DOI: 10.1053/bega.2002.0298]

44 **Jensen DM**, Machicado GA. Diagnosis and treatment of severe hematochezia. The role of urgent colonoscopy after purge. *Gastroenterology* 1988; **95**: 1569-1574 [PMID: 3263294]

45 **Machicado GA**, Jensen DM. Acute and chronic management of lower gastrointestinal bleeding: cost-effective approaches. *Gastroenterologist* 1997; **5**: 189-201 [PMID: 9298374]

P- Reviewers Rustemovic N, Tursi A
S- Editor Wen LL **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.v5.i8.398

World J Gastrointest Endosc 2013 August 16; 5(8): 398-401
ISSN 1948-5190 (online)

CASE REPORT

Conservative management of small bowel perforation in Ehlers-Danlos syndrome type Ⅳ

Satya Allaparthi, Himanshu Verma, David L Burns, Ann M Joyce

Satya Allaparthi, Department of Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States
Himanshu Verma, David L Burns, Ann M Joyce, Department of Gastroenterology, Lahey Clinic, Burlington, MA 01805, United States
Author contributions: Allaparthi S, Verma H, Burns DL and Joyce AM reviewed, designed, edited, and organized the report; Burns DL and Joyce AM served as the attending doctors for the patient; Allaparthi S performed the literature review and wrote the paper.
Correspondence to: Satya Allaparthi, MD, Department of Medicine, Saint Vincent Hospital, 123 Summer Street, Worcester, MA 01608, United States. surgsatya@yahoo.com
Telephone: +1-508-3636208 Fax: +1-508-3639798
Received: April 13, 2013 Revised: May 15, 2013
Accepted: June 5, 2013
Published online: August 16, 2013

Abstract

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders caused by collagen synthesis defects. EDS type Ⅳ, or vascular EDS, is caused by loss-of-function mutations in the type Ⅲ pro-collagen gene (*COL3A1*). Common complications of EDS type IV include gastrointestinal bleeding and bowel perforations, posing diagnostic and therapeutic dilemmas for both surgeons and gastroenterologists. Here, we describe a complicated case of EDS type Ⅳ in a 35-year-old caucasian female who presented with overt gastrointestinal bleeding. The patient had a prior history of spontaneous colonic perforation, and an uncomplicated upper endoscopy was performed. A careful ileoscopy was terminated early due to tachycardia and severe abdominal pain, and a subsequent computed tomography scan confirmed the diagnosis of ileal perforation. The patient was managed conservatively, and demonstrated daily improvement. At the time of hospital discharge, no further episodes of gastrointestinal blood loss had occurred. This case highlights the benefit of conservative management for EDS patients with gastrointestinal hemorrhage. It is recommended that surgical treatment should be reserved for patients who fail conservative treatment or in cases of hemodynamic instability. Finally, this case demonstrates the necessity for a higher threshold of operative or endoscopic interventions in EDS type Ⅳ patients.

Key words: Type-Ⅳ Ehlers-Danlos syndrome; Gastrointestinal hemorrhage; Bowel perforation; Conservative management; Non-operative; *COL3A1*; Connective tissue disorder

Core tip: Gastrointestinal bleeding and bowel perforations are known complications of Ehlers-Danlos syndrome (EDS) type Ⅳ Tissue fragility and hemorrhage tendency pose diagnostic as well as therapeutic dilemmas for both surgeons and gastroenterologists. We performed an upper gastrointestinal endoscopy and ileoscopy in a bleeding patient with history of EDS type Ⅳ. The upper endoscopy procedure was uneventful with minimal air used for luminal distension. A small bowel perforation was found. This case highlights the tissue fragility and serosal tears that can occur upon slight handling. Conservative management proved the best course of action.

Allaparthi S, Verma H, Burns DL, Joyce AM. Conservative management of small bowel perforation in Ehlers-Danlos syndrome type Ⅳ. *World J Gastrointest Endosc* 2013; 5(8): 398-401 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/398.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.398

INTRODUCTION

Ehlers-Danlos syndrome (EDS) comprises of a heterogeneous family of inherited connective tissue disorders

known for its features of fragile, hyperextensible skin, hypermobile joints, and tissue fragility. EDS type Ⅳ, also known as vascular EDS, is an inherited connective tissue disorder caused by loss-of-function mutations of the pro-alpha-1 chains of type Ⅲ pro-collagen (*COL3A1*). Vascular EDS causes severe fragility of connective tissues with increased risk of arterial and gastrointestinal (GI) rupture and complications during surgical and radiological interventions. Spontaneous vascular dissection, GI perforation, or organ rupture are the presenting signs in the majority of adults identified to have EDS type Ⅳ[1-3]. Diagnostic criteria for EDS type Ⅳ includes reduced levels of type Ⅲ collagen protein or identification of the *COL3A1* gene along with two of the following diagnostic criteria: (1) easy bruising; (2) thin skin with visible veins; (3) characteristic facial features (in some individuals); and (4) rupture of arteries, uterus, or intestines[3]. These aberrations in collagen processing correlate with reduced strength of the vascular and hollow organ soft tissue, abnormalities of the large and small bowel architecture including abrupt changes in the caliber of the lamina muscularis, secondary diverticula formation, and strongly reduced expression of collagen 3[4].

We report a complicated clinical course of a 35-year-old female with EDS type Ⅳ and multiple complications (including spontaneous colonic perforation with ileostomy, spontaneous pneumothorax, carotid artery dissection, and multiple orthopedic joint surgeries), who presented with overt GI bleeding.

CASE REPORT

A 35-year-old Caucasian female with history of EDS type-Ⅳ was transferred to our institution for evaluation of overt GI bleeding. She was diagnosed with classical vascular EDS type-Ⅳ at age 16 with easy bruising, thin skin with visible veins, characteristic facial features, and positive family history of EDS in her mother and grandmother. She had a stroke secondary to carotid artery dissection at age 17, ruptured ovarian cyst at 19, postpartum spontaneous sigmoid perforation at 23, spontaneous pneumothorax at 26, and multiple orthopedic surgeries for joint dislocations. The spontaneous colonic perforation at age 23 occurred during labor and required colon resection with resultant ileostomy. She presented to an outside institution with sharp abdominal pain, vomiting, and bright red blood present in the ileostomy pouch. The patient was unable to keep food down and had had several episodes of vomiting over the course of the previous 24 h. She was hemodynamically stable and in no acute distress, but laboratory results revealed hemoglobin of 12 g/dL, which subsequently dropped to 6.1 g/dL, blood urea nitrogen of 60 mg/dL and creatinine of 3.1 mg/dL. An initial abdominal computed tomography (CT) scan was positive for some abdominal distension but no signs of intestinal obstruction or perforation. The subsequent upper endoscopy was normal, and no bleeding site was identified. The patient was then transferred to our institution's medical intensive care unit due to the unknown source of the GI bleeding and to manage the particular complexity of her case.

The gastroenterology team determined that the patient was actively bleeding into her ileostomy pouch. Considering the worsening renal parameters, all further imaging studies were suspended. After weighing the risks and benefits with the patient, in view of her history of EDS and spontaneous bowel perforations, an upper GI endoscopy and possible ileoscopy was planned. The upper endoscopy was performed safely with minimal luminal distension, and no evidence of active bleeding was found. At the time of the upper endoscopy, however, fresh blood emerged from the ileostomy; this issue was addressed by performing an additional ileoscopy using the utmost care and following the same principles as above. However, after the scope was advanced less than 10 cm, the patient developed tachycardia and severe abdominal pain, which prompted early termination of the procedure. Abdominal CT scan revealed free air and extravasation of oral contrast into the peritoneum, confirming the diagnosis of ileal perforation. CT angiography was negative for extravasation of parenteral contrast. Following surgical consultation about the patient's prior abdominal surgical interventions and complexity of the case, and discussion with the patient, a conservative management procedure was designed to address the ileal perforation. The patient was treated with nasogastric suction, antibiotics, and blood transfusions as needed, and total parental nutrition and bowel rest. The patient demonstrated daily improvement and spontaneous resolution of the bleeding. After four days, the patient was able to tolerate oral intake. On day 7 of hospitalization, the patient was discharged in stable condition. Ultimately, no etiology for GI hemorrhage was found.

DISCUSSION

Ehlers-Danlos syndrome is a heterogeneous group of hereditary disorders of connective tissue, whose prevalence is estimated between 1/10000 and 1/25000, with no ethnic predisposition[5]. According to the Villefranche classification, there are 6 clinical types[6], with type Ⅳ, or vascular EDS, accounting for about 5%-10% of cases[7]. The symptoms of each EDS type differs based on the causative gene and inheritance pattern. As a result, the genetic heterogeneity of EDS is very strong. Moreover, each clinical entity of EDS needs to be considered as a different disease that results from different causative gene based on clinical symptoms and family history (Table 1).

Based on Villefranche diagnostic criteria (Table 2)[6], the combination of any two of the major diagnostic criteria should have a high specificity for vascular EDS and further testing is strongly recommended to confirm the diagnosis. The presence of one or more minor criteria supports the diagnosis of vascular EDS but is not sufficient to establish the diagnosis[5]. Vascular EDS is

Table 1 Classification of Ehlers-Danlos syndrome

New classification, Villefranche (1997)	Former classification Berlin (1988)	MIM number[1]	Inheritance	Biochemical defects
Classic	Type Ⅰ	130000	AD	COL5A1
	Type Ⅱ	130010		COL5A2
Hypermobility	Type Ⅲ	130020	AD	Unknown
Vascular	Type Ⅳ	130050	AD	COL3A1
Kyphoscoliosis	Type Ⅵ	225400	AR	Lysyl hydroxylase
Arthrochalasia	ⅦA, ⅦB	130060	AD	COL1A1, COL1A2
Dermatosporaxis	ⅦC	225410	AR	Type I collagen N-peptidase
Others	Ⅴ	305200	XR	
	Ⅷ	130800	AD	
	Ⅹ	225310	AR	
	Ⅺ	147900	AD	

It's adapted from Beighton *et al*[6], Wenstrup *et al*[17] and Steinmann *et al*[18]. [1]The MIM number is a numerical assignment for inherited diseases, genes and functional segments of DNA. AD: Autosomal dominant; AR: Autosomal recessive; XR: X-linked recessive.

Table 2 Vascular Ehlers-Danlos syndrome: Villefranche diagnostic criteria

Major diagnostic criteria	Minor diagnostic criteria
Arterial, digestive or uterine fragility or rupture	Positive family history
Thin, translucent skin	Sudden death in a close relative
Extensive bruising	Acrogeria
Characteristic facial appearance	Hypermobility of small joints
	Tendon and muscle rupture
	Talipes equinovarus (clubfoot)
	Early onset varicose veins
	Spontaneous pneumo or hemothorax

It's adapted from Germain *et al*[5] and Beighton *et al*[6].

an autosomal dominant inherited disease caused by one allele mutation of the *COL3A1* gene, which encodes type Ⅲ procollagen. This mutation results in qualitative and quantitative abnormalities of mature type Ⅲ collagen. Systemic arteries that are rich in type Ⅲ collagen may undergo dissection, aneurysm, or rupture. In addition to vascular complications, ruptures of hollow organs that are rich in type Ⅲ collagen, *i.e.*, intestines and uterus, are also characteristic[8]. Pneumothorax is also a frequent complication, as the pleura also contains a high degree of type Ⅲ collagen. While rare in childhood, EDS type Ⅳ complications occur in approximately 25% of 20-year-old diagnosed with vascular EDS[3]. Further, by age 40, 80% of diagnosed individuals have no less than one complication[9]. The median age of death is estimated to be 50 years, with the most common cause of death being arterial rupture. Pepin *et al*[1] reported that the likelihood of death was greatest after organ rupture (45%) and least after bowel rupture (2%). In view of the multitude of clinical presentations, symptoms, natural history and prognosis, EDS type Ⅳ should be assessed separately within the group of EDS.

Understanding the GI manifestations of EDS type Ⅳ is necessary for both surgeons and gastroenterologists. The two main complications are perforation and bleeding. *In vitro* electromyographic studies of the colonic tissue suggest a possible link between abnormal myogenic activity and colonic perforations[10]. Of the perforations, most occur within the colon, more specifically the rectosigmoid junction. Leake *et al*[11] reported that bleeding into the wall of the gut might precede local necrosis and subsequent perforation. This hypothesis was supported by microscopy findings of submucosal edema in small bowel sections, vascular dilatation with focal hemorrhage, perforation, and organized inflammation in the serosal surface[11].

Our case posed an endoscopic and surgical dilemma due to the complicated history of the patient. There is very limited data available concerning the safety of GI procedures in patients with EDS. Although some reports suggest avoiding elective procedures such as endoscopy, colonoscopy, angiography, nasogastric tube placement, and enema administration due to perforation or dissection[12,13], there are also case reports of performing upper endoscopy and endoscopic retrograde cholangiopancreatiography (ERCP) safely[14,15]. In our patient, who had overt bleeding with significant hemodynamic instability, we believed that potential risk of ileoscopy was justified. Given the fact that our index case was a classical EDS type Ⅳ with complicated surgeries in the past, safety and caution were our paramount concerns. While the rarity of this syndrome precludes an evidence-based approach to management, previous cases served as a guide in the clinical care of this patient. We performed upper GI endoscopy uneventfully and in spite of using minimal air for luminal distension; the patient developed tachycardia and severe abdominal pain during ileoscopy, prompting early termination of the procedure. Abdominal CT scan revealed free air and extravasation of oral contrast into the peritoneum, confirming the diagnosis of ileal perforation. These events and findings served to emphasize the tissue fragility in EDS patients due to the collagen deficiency and the high risk of serosal tears that can occur upon minimal handling, as noted by many operating surgeons. For our patient, conservative care proved to be the best course of action. The overt bleeding was self-limited and the perforation was managed with bowel rest induced by antibiotics and total parental nutrition (Table 3).

In conclusion, our case highlights the clinical dilem-

Table 3 Endoscopic procedures reported in Ehlers-Danlos syndrome patients

Ref.	Age/sex	Procedure	Outcome/treatment
Hawk *et al*[15]	41/F	ERCP Sphincterotomy	No complication Non-pulsatile bleeding (conservative management)
Kahn *et al*[19]	45/F	ERCP	Bile duct rupture (conservative management)
Rana *et al*[20]	33/M	Colonoscopy	Perforation (Surgical intervention)
Baichi *et al*[14]	51/F	Upper endoscopy	No complication
Present case	35/F	Upper endoscopy Ileoscopy	No complication Perforation (conservative management)

F: Female; M: Male; ERCP: Endoscopic retrograde cholangiopancreatiography.

mas in the management of GI complications of EDS type Ⅳ and stresses the importance of conservative management. Surgical interventions should be reserved for hemodynamically/clinically unstable patients who fail to respond to supportive measures. Colonoscopy or small bowel enteroscopy carry a higher risk when compared to upper GI endoscopy, which can be safely performed. Angiography can be associated with arterial dissection[16]. Endoscopists should be prepared for bleeding and perforations in these high-risk patients with appropriate pre-endoscopic surgical back up.

REFERENCES

1 **Pepin M**, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type Ⅳ, the vascular type. *N Engl J Med* 2000; **342**: 673-680 [PMID: 10706896 DOI: 10.1056/NEJM200003093421001]

2 **Byers PH**, Ehlers-Danlos syndrome type Ⅳ: a genetic disorder in many guises. *J Invest Dermatol* 1995; **105**: 311-313 [PMID: 7665905]

3 **Pepin MG**, Byers PH. Ehlers-Danlos Syndrome Type Ⅳ. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, Fong CT, editors. SourceGeneReviews™ [Internet]. Seattle (WA): University of Washington, 1993-2013 [PMID: 20301667]

4 **Bläker H**, Funke B, Hausser I, Hackert T, Schirmacher P, Autschbach F. Pathology of the large intestine in patients with vascular type Ehlers-Danlos syndrome. *Virchows Arch* 2007; **450**: 713-717 [PMID: 17487505]

5 **Germain DP**, Herrera-Guzman Y. Vascular Ehlers-Danlos syndrome. *Ann Genet* 2004; **47**: 1-9 [PMID: 15127738]

6 **Beighton P**, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998; **77**: 31-37 [PMID: 9557891 DOI: 10.1002/(SICI)1096-8628(19980428)77]

7 **Barabas AP**. Vascular complications in the Ehlers-Danlos syndrome, with special reference to the "arterial type" or Sack's syndrome. *J Cardiovasc Surg (Torino)* 1972; **13**: 160-167 [PMID: 5034837]

8 **Watanabe A**, Shimada T. Vascular type of Ehlers-Danlos syndrome. *J Nippon Med Sch* 2008; **75**: 254-261 [PMID: 19023163]

9 **Oderich GS**, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, Kalra M, Sullivan T, Gloviczki P. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type Ⅳ: a 30-year experience. *J Vasc Surg* 2005; **42**: 98-106 [PMID: 16012458]

10 **Sigurdson E**, Stern HS, Houpt J, el-Sharkawy TY, Huizinga JD. The Ehlers-Danlos syndrome and colonic perforation. Report of a case and physiologic assessment of underlying motility disorder. *Dis Colon Rectum* 1985; **28**: 962-966 [PMID: 4064860]

11 **Leake TF**, Singhal T, Chandra A, Ashcroft A, Doddi S, Hussain A, Smedley F. Occult small bowel perforation in a patient with Ehlers Danlos syndrome: a case report and review of the literature. *Cases J* 2010; **3**: 57 [PMID: 20205912 DOI: 10.1186/1757-1626-3-57]

12 **Nardone DA**, Reuler JB, Girard DE. Gastrointestinal complications of Ehlers-Danlos syndrome. *N Engl J Med* 1979; **300**: 863-864 [PMID: 423929]

13 **Beighton PH**, Murdoch JL, Votteler T. Gastrointestinal complications of the Ehlers-Danlos syndrome. *Gut* 1969; **10**: 1004-1008 [PMID: 5308459]

14 **Baichi MM**, Arifuddin RM, Mantry PS. Gastrointestinal bleeding in a patient with Ehlers-Danlos syndrome: an endoscopic dilemma. *Dig Dis Sci* 2005; **50**: 1342-1343 [PMID: 16047484]

15 **Hawk JS**, Dellon ES, Martinie JB, Grimm IS. Successful ERCP and sphincterotomy in a patient with Ehlers-Danlos syndrome and a history of spontaneous bowel perforation. *Gastrointest Endosc* 2008; **67**: 755-758 [PMID: 18179794 DOI: 10.1016/j.gie.2007.09.013]

16 **Freeman RK**, Swegle J, Sise MJ. The surgical complications of Ehlers-Danlos syndrome. *Am Surg* 1996; **62**: 869-873 [PMID: 8813174]

17 **Wenstrup RJ**, Hoechstetter LB. Ehlers-Danlos Syndromes. In: Management of Genetic Syndromes. 2nd ed. Hoboken: John Wiley and Sons, 2005: 211-223

18 **Steinmann B**, Royce P, Superti-Furga A. The Ehlers-Danlos syndromes. In Connective Tissue and its Heritable Disorders: Molecular, Genetic, and Medical aspects. 2nd ed. New York: Wiley-Liss, 2002: 431-524

19 **Kahn T**, Reiser M, Gmeinwieser J, Heuck A. The Ehlers-Danlos syndrome, type IV, with an unusual combination of organ malformations. *Cardiovasc Intervent Radiol* 1988; **11**: 288-291 [PMID: 3145144]

20 **Rana M**, Aziz O, Purkayastha S, Lloyd J, Wolfe J, Ziprin P. Colonoscopic perforation leading to a diagnosis of Ehlers Danlos syndrome type IV: a case report and review of the literature. *J Med Case Rep* 2011; **5**: 229 [PMID: 21699676 DOI: 10.1186/1752-1947-5-229]

P- Reviewers Cho YS, Yoshida S
S- Editor Zhai HH **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.v5.i8.402

World J Gastrointest Endosc 2013 August 16; 5(8): 402-406
ISSN 1948-5190 (online)

CASE REPORT

Endoscopic closure of a gastrocolic fistula using the over-the-scope-clip-system

Klaus Mönkemüller, Shajan Peter, Basem Alkurdi, Jayapal Ramesh, Daniel Popa, C Mel Wilcox

Klaus Mönkemüller, Shajan Peter, Basem Alkurdi, Jayapal Ramesh, Daniel Popa, C Mel Wilcox, Division of Gastroenterology and Hepatology, Basil Hirschowitz Endoscopic Center of Excellence, University of Alabama at Birmingham, Birmingham, AL 35249, United States
Author contributions: All the authors substantial contributed to conception and design, acquisition of data, or analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published; Mönkemüller K and Popa D contributed to drafting the article.
Correspondence to: Klaus Mönkemüller, MD, PhD, FASGE, Division of Gastroenterology and Hepatology, Basil Hirschowitz Endoscopic Center of Excellence, University of Alabama at Birmingham, JT 664, 619 19th Street S, Birmingham, AL 35249, United States. klaus1@uab.edu
Telephone: +1-205-9346110 Fax: +1-205-9341537
Received: April 14, 2013 Revised: May 10, 2013
Accepted: June 5, 2013
Published online: August 16, 2013

Abstract

Gastrointestinal (GI) defects such as fistulas and leaks can be potentially closed endoscopically using hemoclips and loops. However, hemoclips may not allow for closure of large defects and they do not exert enough tensile force to keep fibrotic defects larger than 5 mm approximated. Herein we present a case of successful endoscopic closure of a gastrocolic fistula in a severely malnourished patient with complex post-surgical upper GI anatomy. We strongly believe that this device is a major breakthrough for the management of various types of discontinuity defects or fistulas. In addition, we show the usefulness of placing a direct jejunostomy using the double balloon enteroscopy (DBE) technique during the same procedure. The concept of providing direct jejunal feedings while allowing for upper gastrointestinal bowel rest to promote the healing of the minimally invasive endoscopic operation is novel. Thus, our case is unique and exemplifies the utility of minimally invasive endoscopic endoluminal surgery.

Key words: Over-the-scope-clip; Bear claw; Fistula; Endoscopic closure; Gastrocolic fistula; Over the scope clip; Clip

Core tip: Herein we present the endoscopic closure of a gastro-colic fistula in a severely malnourished patient with complex post-surgical upper Gastrointestinalanatomy using the over-the-scope-clip (OTSC-system). The OTSC-system is an endoscopic clipping device made of Nitinol, which allows for treatment of peptic ulcer bleeding and the closure of perforations, anastomotic leaks and fistulas. In addition, we show the usefulness of placing a direct jejunostomy using the double balloon enteroscopy technique during the same procedure.

Mönkemüller K, Peter S, Alkurdi B, Ramesh J, Popa D, Wilcox CM. Endoscopic closure of a gastrocolic fistula using the over-the-scope-clip-system. *World J Gastrointest Endosc* 2013; 5(8): 402-406 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/402.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.402

INTRODUCTION

The major endoscopic devices utilized to provide hemostasis and to close mucosal or luminal gastrointestinal (GI) defects are hemoclips and loops[1-3]. However, hemoclips may not allow for closure of large defects and they do not exert enough tensile force to keep fibrotic defects larger than 5 mm approximated[3]. In addition, partial and full-thickness defects resulting from perforations, fistulas and leaks may have irregular, thick and friable edges limiting the deployment of hemoclips and/or loops[4]. Recently, a new endoscopic closure device called

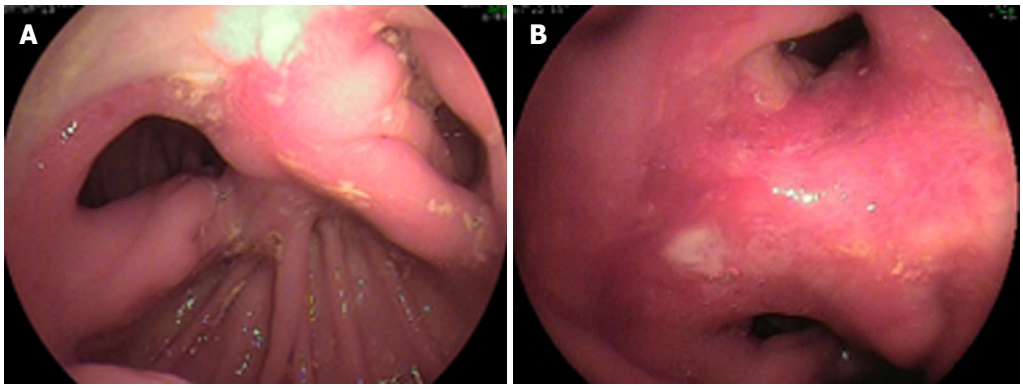


Figure 1 Billroth Ⅱ anatomy. A clean-based ulcer is present at the anastomosis (A), the lumen to both the afferent and efferent limbs is patent (A); the gastrocolic fistula opening was located at the upper end of the anastomosis (B).

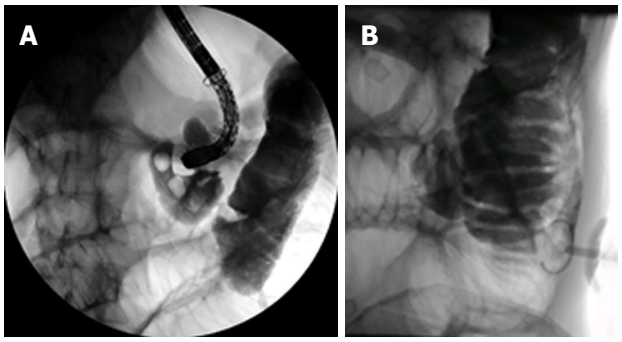


Figure 2 Insertion of the scope through this orifice lead to the colon (A), after placing the jejunostomy, water soluble contrast was injected confirming its perfect intra-jejunal position (B).

the over-the-scope-clip (OTSC)-system (Ovesco Endoscopy, Tübingen, Germany) or "bear claw" became available[5,6]. The OTSC-system is an endoscopic clipping device made of Nitinol, which allows for treatment of peptic ulcer bleeding and the closure of perforations, anastomotic leaks and fistulas[7-9]. The majority of information on the OTSC device stems from animal studies but data on the usefulness of the OTSC device in humans is increasingly recognized[7-12]. The aim of this case report is to describe the effective endoscopic closure of a large gastrocolic fistula in an extremely malnourished patient with complex post-surgical upper GI anatomy.

CASE REPORT

A 47-year-old man with history of chronic pancreatitis, alcoholism and Billroth Ⅱ gastrojejunostomy for perforated peptic ulcer presented with chronic diarrhea and severe weight loss of 32-kg over a 1 year-period. The diarrhea was watery and occurred up to 12 times per day, being worse after eating. His physical examination was remarkable for cachexia, his weight was 40 kg, his height was 170 cm (body mass index = 12.8). The laboratory data were remarkable for hypoalbuminemia (1.8 g/dL) and decreased hemoglobin (11 g/dL). An esophagogastroduodenoscopy (EGD) showed a clean based ulceration at the anastomosis and patent lumen to both the afferent and efferent limbs (Figure 1A). At the upper part of the anastomosis there was an additional orifice, which represented the fistula (Figure 1B). Insertion of the scope through this orifice lead to the colon. The patient was placed on bowel rest, NPO, total parenteral nutrition. Due to the patient's poor medical status no surgical intervention could be attempted to close the defect. The patient underwent a full GI evaluation (pananedoscopy) to exclude a malignancy or inflammatory bowel diseases leading to fistula formation. An upper GI series using barium clearly demonstrated a communication between the stomach and the colon. A colonoscopy revealed a normal colon mucosa, but no clear fistula opening could be detected. Repeat EGD disclosed the three openings at the gastrojejunal (Billroth Ⅱ) anastomosis. Both the afferent and efferent limbs were patent and had normal mucosa. The gastrocolic fistula measured about 10-12 mm in diameter (Figure 1B). The EGD was exchanged for a double balloon enteroscope. The overtube was positioned inside the stomach and the enteroscope was advanced through the fistula into the colon (Figure 2). Both the rectum and the cecum were reached. After re-examining the colon and ruling out malignancy and inflammation, the scope was brought back to the gastrojejunal anastomosis and both limbs were investigated using the double-balloon enteroscopy technique. The small bowel mucosa was normal, without evidence of obstruction, fistulization or inflammation. A direct percutaneous enteroscopic feeding jejunostomy was then placed using the double-balloon enteroscopy (DBE)-technique[13]. Multiple biopsies of the gastrocolic fistula were negative for malignancy. Serum gastrin level was also within reference range.

Closure of the gastrocolic fistula

Before closing the fistula the entrance into the orifice was marked with India ink (SPOT INK, ultrasound Enodscopy, United States) (Figure 3). This intervention was performed in order to mark the area of interest, as the fistulous tract was somewhat friable and the occurrence of edema and oozing could potentially obscure visualization of the area once the OTSC-system was loaded on the tip of the endosocpe. The gastrojejunostomy with the

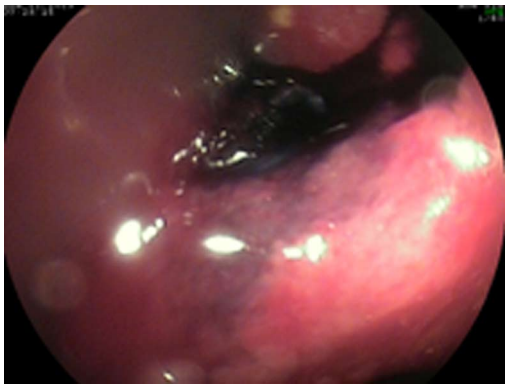


Figure 3 Before closing the fistula the entrance into the orifice was marked with India ink.

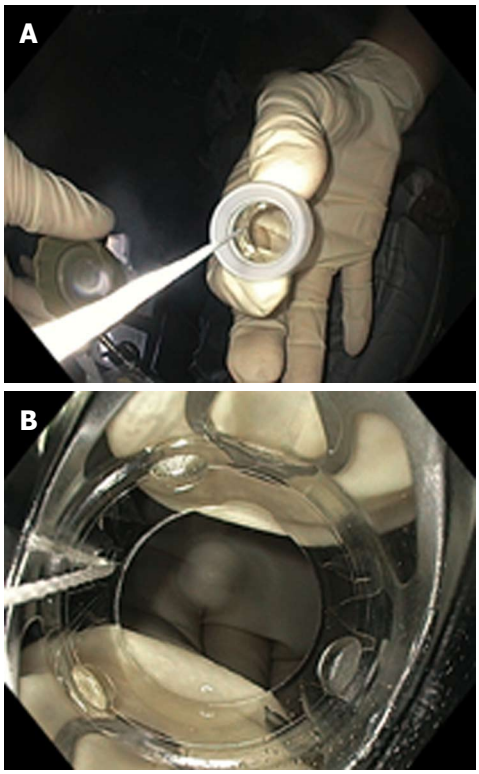


Figure 4 T the over-the-scope-clip -system come loaded onto a transparent cap which is attached to the tip of the scope.

presence of two small bowel limbs made the endosocpic operation more challenging, as there is a previous report of complete small bowel obstruction resulting form the misapplication of this closure device[10]. The atraumatic 11 mm diameter OTSC-system ("bear claw") was applied (Figure 4). The OTSC cap was approximated into the fistula and suctioned was applied (Figure 5). To achieve definite closure, the edges of the fistula were approximated with a twin grasper (OTSC Twin Grasper; Ovesco Endoscopy AG, Tubingen, Germany) (Figure 5). In addition, an ongoing effort was made to aspirate (*i.e.*, "suck") tissue into the distal transparent cap. Once enough tissue was trapped, the OTSC was released (Figures 6 and 7).

Figure 5 The over-the-scope-clip-system was approximated to the fistula (A) and the proximal edge of the fistula was pulled inside the transparent cap of the over-the-scope-clip-system using the Twin Grasper (B).

The patient was continued on high dose proton pump inhibitors (esomeprazole 40 mg *po* bid), kept NPO and 24 h later the feedings were started through the DPEJ. On the third post-operative day an upper GI study using barium was performed, documenting complete closure of the gastrocolic fistula (Figure 8). Closure was also confirmed by performing an EGD with direct visual inspection and Indigo carmine dye instillation during a simultaneously performed colonoscopy. No dye escaped into the colon from the stomach during the procedure. On day four after endoscopic closure the patient was started on a liquid diet, which was then slowly advanced to soft. Due to his poor nutritional status it was elected to keep the jejunostomy tube feedings until he has regained more weight and his condition has markedly improved. The patient was discharged home in stable condition 7 d after initial presentation and remains well one month after the procedure.

DISCUSSION

To the best of our knowledge this is the first case of successful endoscopic closure of a gastrocolic fistula in a patient with complex post-surgical upper GI anatomy. The additional challenge in this patient was his poor clinical status and hence inability to benefit from a surgical intervention. The case stands out for several reasons. First we show that this tissue-suturing device is also useful to accomplish endoscopic closure of a complex

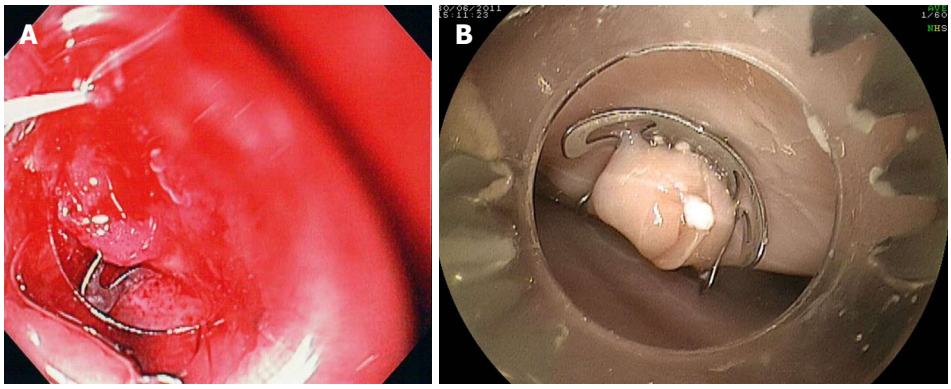


Figure 6 Once enough tissue was present inside the cap the over-the-scope-clip device was released. (A) Example of deployed over-the-scope-clip -system in experimental perforation in an *ex-vivo* pig stomach (B).

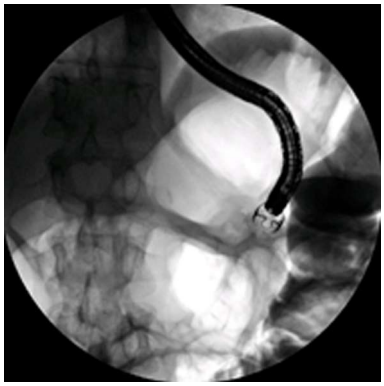


Figure 7 Radiologic view of the over-the-scope-clip -system ("bear trap").

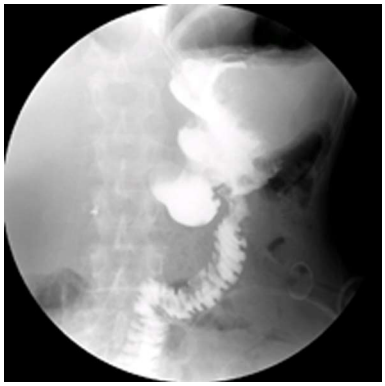


Figure 8 Barium study documents complete closure of the fistula. The contrast flows into the jejunal limbs.

fistula, located in an awkward anatomic position. We also provide useful tips and information on the utilization of this device, which is becoming more widely available. The OTSC-system is a quite innovative endoscopic suturing device made of superelastic biocompatible Nitinol, which allows for the entrapment of larger amount of tissue, allowing closure of fistula holes, and, as shown in these cases, hemostasis[7-12]. The ability to grasp and pull and/or "suck" a relative large volume of tissue into the distal transparent cap allows for potential closure of defects ranging from 10 to 20 mm in size, a situation which is usually not possible using traditional clipping devices[7-12]. Second, we also demonstrate how panendoscopic evaluation using EGD, colonoscopy and DBE was fundamental to thoroughly examine the GI tract for malignancy and inflammatory conditions. Whereas a capsule endoscopy may have also been helpful to evaluate the small bowel, its utility in patients with deranged upper GI anatomy is questionable as there is no guarantee that both limbs are examined. In addition, DBE allowed us to inspect the colon through the fistula located in the transverse colon and perform a right and left colon inspection, including the ileocecal valve. Furthermore, DBE permitted for a direct placement of a jejunal feeding tube, which was essential to aid in the enteral feeding of this severely malnourished patient. Third, this case adds to the growing evidence that the OTSC-system is a useful device to treat clinically significant endoluminal GI defects. These GI scenarios include leaks, GI bleeding, stent anchoring, fistula closure and resection of submucosal lesions[7-12].

The potential imitations of the OTSC-system should be acknowledged. Its application in tubular or torqued parts of the luminal GI tract may be difficult or impossible. In areas of curves or partially closed lumen, adequate apposition of the OTSC system against the defect may be impossible. If the defect is located in a tubular structure such as the esophagus adequate apposition of the device in a tangential manner to the defect may be more difficult. Thus, the closing forces of the OTSC-system may grasp and engulf the wrong part of the defect or normal tissue, as the vectorial forces are deranged due the angulated position of the device against the defect. Indeed, a crucial element to technical success of OTSC system placement is to accurately position the lesion within the transparent OTSC cap[10]. The misapplication of a clip to one side of such a lesion may interfere with the successful deployment of a second clip over the defect. Nonetheless, multiple OTSC applications in a single session may still be useful and allow approximation of tissue to facilitate subsequent closure[10]. Nevertheless, and as shown in our case and experience, if the defect is visible and reachable a successful application can always

be successfully accomplished[11,12]. Using marking with chromoendoscopy may improve visualization and recognition of the defect while the OTSC-system is being applied. Because the device is new it is not known how long it remains attached after deployment. A potential complication of the OTSC system is that once it is deployed it cannot be removed. We have recently demonstrated two techniques to remove the "bear claw" using the wire technique[14] or resecting the OTSC system using endoscopic mucosal resection techniques[15]. In addition, the OTSC system can be removed using Nd-YAG Laser or argon plasma coagulation[10,16].

In summary, we have presented a case of successful endoscopic closure of a gastrocolic fistula in a severely malnourished patient with complex post-surgical upper GI anatomy. Panendoscopy using EGD, colonoscopy and DBE allowed for detailed examination of the GI tract and direct DPEJ placement before endoscopic closure with the OTSC. We strongly believe that this device is a major breakthrough for the management of various types of discontinuity defects or fistulas of the GI tract. Thus, the OTSC system should be incorporated into the therapeutic armamentarium of the advanced endoscopist. In addition, we show the usefulness of placing a direct jejunostomy using the DBE technique during the same procedure. The concept of providing direct jejunal feedings while allowing for upper gastrointestinal bowel rest to promote the healing of the minimally invasive endoscopic operation is novel. Thus, our case is unique and exemplifies the utility of minimally invasive endoscopic endoluminal surgery.

REFERENCES

1 **Sung JY**, Chung SC, Lo KK, Leung JW. Heater-probe treatment of bleeding peptic ulcers. *Surg Endosc* 1988; **2**: 234-236 [PMID: 3071870]

2 **Aabakken L**. Current endoscopic and pharmacological therapy of peptic ulcer bleeding. *Best Pract Res Clin Gastroenterol* 2008; **22**: 243-259 [PMID: 18346682 DOI: 10.1016/j.bpg.2007.10.010]

3 **Anastassiades CP**, Baron TH, Wong Kee Song LM. Endoscopic clipping for the management of gastrointestinal bleeding. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 559-568 [PMID: 18711412 DOI: 10.1038/ncpgasthep1233]

4 **von Renteln D**, Denzer UW, Schachschal G, Anders M, Groth S, Rösch T. Endoscopic closure of GI fistulae by using an over-the-scope clip (with videos). *Gastrointest Endosc* 2010; **72**: 1289-1296 [PMID: 20951989 DOI: 10.1038/ncpgasthep12335]

5 **von Renteln D**, Rudolph HU, Schmidt A, Vassiliou MC, Caca K. Endoscopic closure of duodenal perforations by using an over-the-scope clip: a randomized, controlled porcine study. *Gastrointest Endosc* 2010; **71**: 131-138 [PMID: 19883907 DOI: 10.1016/j.gie.2009.07.0066]

6 **Matthes K**, Jung Y, Kato M, Gromski MA, Chuttani R. Efficacy of full-thickness GI perforation closure with a novel over-the-scope clip application device: an animal study. *Gastrointest Endosc* 2011; **74**: 1369-1375 [PMID: 21981814 DOI: 10.1016/j.gie.2011.07.0577]

7 **Pohl J**, Borgulya M, Lorenz D, Ell C. Endoscopic closure of postoperative esophageal leaks with a novel over-the-scope clip system. *Endoscopy* 2010; **42**: 757-759 [PMID: 20806160 DOI: 10.1055/s-0030-12556348]

8 **Gray DM**, Mullady DK. Attempted endoscopic closure of a pancreaticocolonic fistula with an over-the-scope clip. *JOP* 2012; **13**: 712-714 [PMID: 23183409 DOI: 10.6092/1590-8577/12209]

9 **Neumann H**, Nägel A, Bernatik T, Wickles N, Neurath MF, Raithel M. Endoscopic closure of large, spontaneous, choledochoduodenal fistula by using an over-the-scope clip. *Gastrointest Endosc* 2011; **74**: 200-202; discussion 202 [PMID: 21481859 DOI: 10.1016/j.gie.2011.01.057]

10 **Baron TH**, Song LM, Ross A, Tokar JL, Irani S, Kozarek RA. Use of an over-the-scope clipping device: multicenter retrospective results of the first U.S. experience (with videos). *Gastrointest Endosc* 2012; **76**: 202-208 [PMID: 22726484 DOI: 10.1016/j.gie.2012.03.25011]

11 **Mönkemüller K**, Toshniwal J, Zabielski M, Vormbrock K, Neumann H. Utility of the "bear claw", or over-the-scope clip (OTSC) system, to provide endoscopic hemostasis for bleeding posterior duodenal ulcers. *Endoscopy* 2012; **44** Suppl 2 UCTN: E412-E413 [PMID: 23169041 DOI: 10.1055/s-0032-132573712]

12 **Toshniwal J**, Zabielski M, Fry LC, Mönkemüller K. Combination of the "bear claw" (over-the-scope-clip system) and fully covered stent for the treatment of post-operative anastomotic leak. *Endoscopy* 2012; **44** Suppl 2 UCTN: E288-E289 [PMID: 22933259 DOI: 10.1055/s-0032-1310033]

13 **Mönkemüller K**, Vormbrock K, Kassalik M, Sancar A. Direct percutaneous endoscopic jejunostomy tube placement using double-balloon enteroscopy. *Gastrointest Endosc* 2012; **75**: 463-465 [PMID: 22248617 DOI: 10.1016/j.gie.2011.09.04914]

14 **Neumann H**, Diebel H, Mönkemüller K, Nägel A, Wildner D, Vieth M, Siebler J, Neurath MF. Description of a new, endoscopic technique to remove the over-the-scope-clip in an ex vivo porcine model (with video). *Gastrointest Endosc* 2012; **76**: 1009-1013 [PMID: 23078925 DOI: 10.1016/j.gie.2012.07.03615]

15 **Mönkemüller K**, Toshniwal J, Zabielski M. Endoscopic removal of an over-the-scope-clip ("bear claw"). *Gastrointest Endosc* 2012; **76**: 1077-1078 [PMID: 23078936 DOI: 10.1016/j.gie.2012.06.00916]

16 **Fähndrich M**, Sandmann M, Heike M. Removal of over the scope clips (OTSC) with an Nd: YAG Laser. *Z Gastroenterol* 2011; **49**: 579-583 [PMID: 21557167 DOI: 10.1055/s-0029-1245871]

P- Reviewer Rabago L **S- Editor** Zhai HH
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.v5.i8.407

World J Gastrointest Endosc 2013 August 16; 5(8): 407-411
ISSN 1948-5190 (online)

CASE REPORT

Malignant peritoneal mesothelioma presenting umbilical hernia and Sister Mary Joseph's nodule

Kota Tsuruya, Masashi Matsushima, Takayuki Nakajima, Mia Fujisawa, Katsuya Shirakura, Muneki Igarashi, Jun Koike, Takayoshi Suzuki, Tetsuya Mine

Kota Tsuruya, Masashi Matsushima, Takayuki Nakajima, Mia Fujisawa, Katsuya Shirakura, Muneki Igarashi, Jun Koike, Takayoshi Suzuki, Tetsuya Mine, Division of Gastroenterology, Department of Internal Medicine, Tokai University School of Medicine, Isehara 259-1193, Japan

Author contributions: Tsuruya K and Matsushima M designed the report; Matsushima M, Nakajima T, Fujisawa M, Shirakura K, Igarashi M, Koike J and Suzuki T were attending doctors for the patients; Mine T organized the report; Tsuruya K wrote paper.

Correspondence to: Kota Tsuruya, MD, Division of Gastroenterology, Department of Internal Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara 259-1193, Japan. ktsuruya@tokai-u.jp

Telephone: +81-463-931121 Fax: +81-463-937134
Received: April 7, 2013 Revised: June 12, 2013
Accepted: July 18, 2013
Published online: August 16, 2013

Core tip: Malignant peritoneal mesothelioma is a rare aggressive tumor of the peritoneum. We performed laparoscopy which showed specific laparoscopic findings, and the pathological findings of the biopsy specimen led to the diagnosis. This case was associated with umbilical hernia and umbilical metastasis, which is also called as Sister Mary Joseph's nodule.

Tsuruya K, Matsushima M, Nakajima T, Fujisawa M, Shirakura K, Igarashi M, Koike J, Suzuki T, Mine T. Malignant peritoneal mesothelioma presenting umbilical hernia and Sister Mary Joseph's nodule. *World J Gastrointest Endosc* 2013; 5(8): 407-411 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/407.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.407

Abstract

Malignant peritoneal mesothelioma is a rare aggressive tumor of the peritoneum. An increasing number of malignant mesothelioma cases have been reported in recent years. We report here a very rare case of malignant peritoneal mesothelioma with both umbilical hernia and umbilical metastasis which is also called Sister Mary Joseph's nodule. We performed laparoscopy which showed specific laparoscopic findings, and the pathological findings of the biopsy specimen led to the diagnosis. This case was associated with umbilical hernia which could be induced by massive ascites. A newly developed abdominal hernia should be noted as a primary symptom of malignant peritoneal mesothelioma, as shown in the present case.

Key words: Malignant peritoneal mesothelioma; Umbilical hernia; Sister Mary Joseph's nodule; Umbilical metastasis; Laparoscopy

INTRODUCTION

Malignant mesothelioma is arising from the mesothelium lining of a body cavity and is associated with asbestos exposure. An increasing number of malignant mesothelioma cases have been reported in recent years. In malignant peritoneal mesothelioma, abdominal hernias are a common complication, probably due to massive ascites accompanying the disease. Most are inguinal hernias but the development of an umbilical hernia is very rare. Umbilical metastasis, which is also called Sister Mary Joseph's nodule, is a rare complication of malignant peritoneal mesothelioma. We are reporting a very rare case of malignant peritoneal mesothelioma with both umbilical hernia and umbilical metastasis.

CASE REPORT

A 64-year-old man visited our hospital for further examination of a moderate amount of ascites and multiple peritoneal masses observed during an annual health

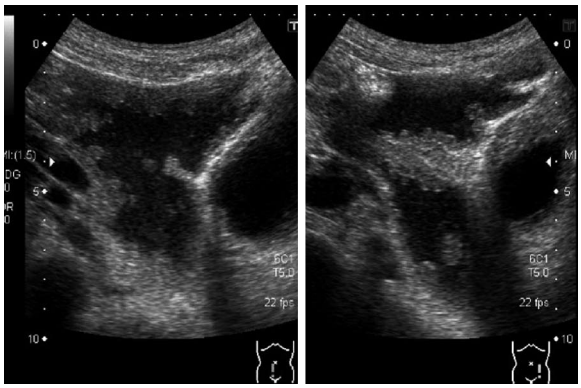


Figure 1 Abdominal ultrasonography. Moderate amount of ascites, irregular thickening of the mesentery and peritoneum, and multiple nodules were observed.

check. There was nothing noteworthy in his medical history and family history. He had no clear history of asbestos exposure. Physical examination demonstrated moderate abdominal distension with fluctuation and umbilical hernia. Bowel sounds were reduced and there was no abdominal pain or tenderness. Laboratory investigations revealed hypoalbuminemia (35 mg/L), a high level of C-reactive protein (3.5 mg/L), and levels of CEA and CA19-9 were within the normal range. No neoplastic lesions were observed by upper and lower gastrointestinal endoscopy. Abdominal ultrasound showed moderate ascites, irregular thickening of the mesentery and the peritoneum, and numerous nodules present (Figure 1). Contrast enhanced computed tomography showed a moderate amount of ascites and enhanced multiple nodules on the thickened peritoneum and mesenterium (Figure 2). By ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), mild accumulation of FDG was observed over the entire abdominal region, but no localized strong accumulation suggesting this was the primary lesion (Figure 2C). Aspirated ascites was cloudy and a muddy yellow color with increased cell populations present (7660/μL), most of which were histiocytes (93%) with some mesothelial cells (6%). Protein concentration of the ascites reached levels as high as 41 mg/L, indicating that the ascites was exudative. The hyaluronic acid concentration of the ascites was very high (436000 ng/L). Cytology indicated atypical mesothelial cells. These data strongly suggested malignant peritoneal mesothelioma and therefore, laparoscopy was performed. Laparoscopic observation showed multiple whitish nodules on the peritoneum and the mesenterium including falciform ligament of the liver with a slightly cloudy yellow ascites (Figure 3). Biopsy of the nodular lesions was performed. Additionally, Umbilical hernioplasty was performed owing to avoidance of the risk for incarceration and the pathological assessment of the umbilical region was also done. According to the histopathological findings of the nodular lesion, hematoxylin and eosin (HE) staining showed the infiltration of many tumor cells having acidophilic cytoplasm with large nuclei (Figure 4A). A mucus-like substance in the tumor background was positive by alcian blue staining, and was

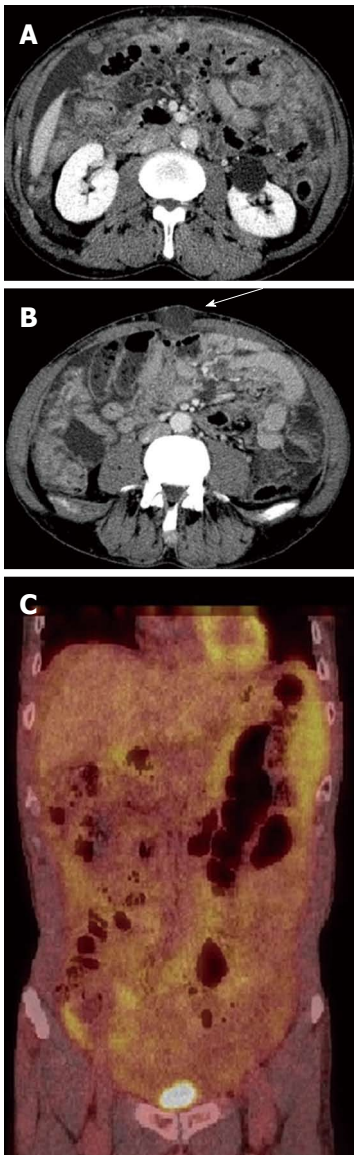


Figure 2 Contrast enhanced computed tomography and ^{18}F-fluorodeoxyglucose-positron emission tomography. A: Thickened peritoneum and mesentery with multiple nodules were positively enhanced by the contrast material; B: An umbilical hernia is also evident (arrow); C: A coronal image of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) showed no localized areas of high accumulation of FDG, but mild accumulation of FDG was observed over the entire abdominal region.

negative after hyaluronidase treatment, which suggested the presence of accumulated hyaluronic acid. Immunohistochemical stainings of calretinin, D2-40, and CK5/6, which are markers for mesothelial cells, were all positive, while Ber-EP4 and MOC31, which are markers for adenocarcinomas, were negative (Figure 5). Therefore, the final diagnosis was epithelioid type of malignant peritoneal mesothelioma. Umbilical hernia was repaired by surgery and the infiltration of tumor cells into the dermis was observed in the resected specimen of the umbilical region (Figure 4B).

The patient transferred to another hospital of his own will. According to the response mail from the hospital, he received a radical operation in which the peritoneal

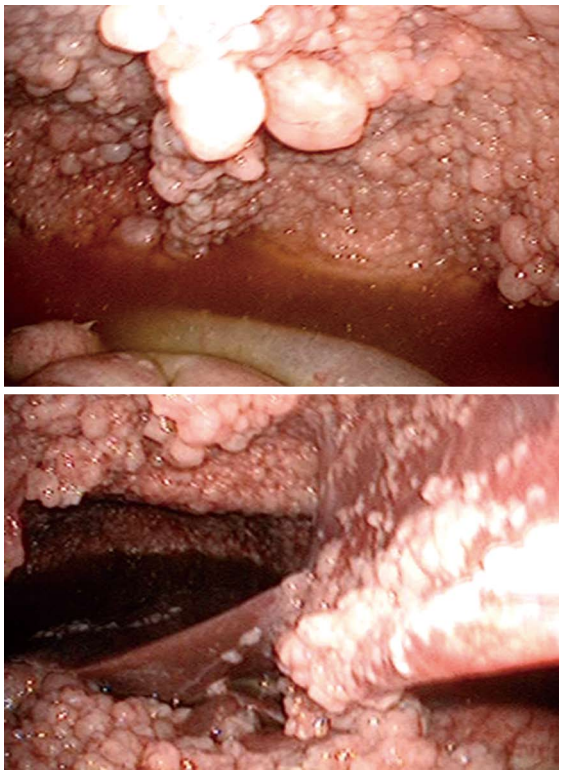


Figure 3 Laparoscopy. Multiple whitish nodules were observed on the peritoneum and the mesenterium including falciform ligament of the liver with slightly muddy yellow ascites.

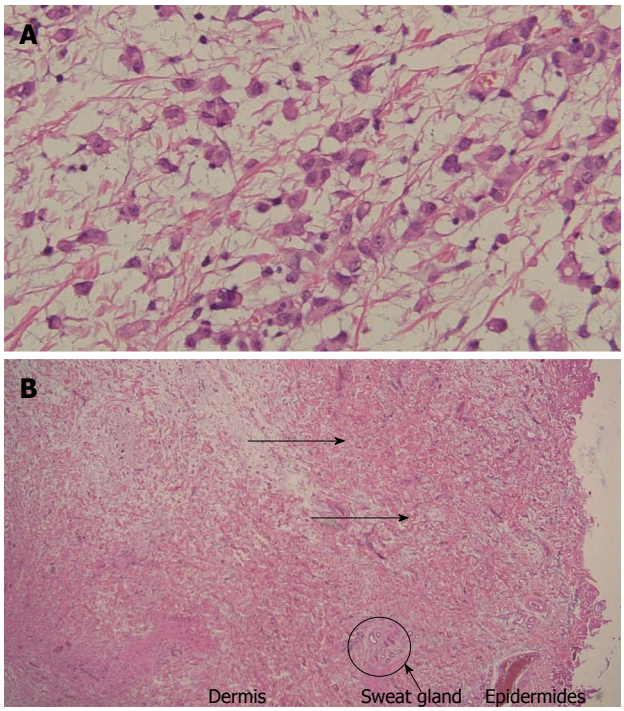


Figure 4 Pathological findings of the nodular lesion and the umbilical region. A: Diffuse infiltration of oval or polygon cells with acidophilic cytoplasm was observed [hematoxylin and eosin (HE), × 200]; B: Histopathology of the umbilical region showed the invasion of tumor cells into the dermis (arrows) (HE, × 40).

nodules were removed as much as possible, however, he got debilitated after the surgery which did not permit further chemotherapy. He died 6 mo after the diagnosis due to the progression of the malignancy.

DISCUSSION

Malignant mesothelioma originates in the pleura, peritoneum, pericardium and tunica vaginalis[1], where a lining of mesothelial cells is present. The main causes of mesothelioma are known to include exposure to asbestos[2] and erionite (natural mineral fiber). In Japan, a large amount of asbestos was used for buildings during the high-growth period (1950-1990). It is believed that the incubation period is approximately 30-40 years and it is estimated that the number of mesothelioma cases will therefore reach a peak between 2020-2030.

It has been reported that 85.5% malignant mesothelioma occurs in the pleura, 13.2% in the peritoneum, 0.8% in the pericardium, and 0.5% in the testicular tunica vaginalis[3]. According to the histological classification, malignant mesothelioma can be classified as 3 types: epithelioid type, sarcomatoid type, and biphasic type. The frequencies of the 3 types of pleural mesothelioma, epithelioid, sarcomatoid, biphasic type, and unknown classification were reported to be 53.6%, 23.3%, 18.3%, and 4.8%, respectively[3]. In Japan, the frequencies of peritoneal mesothelioma including epithelioid, sarcomatoid, biphasic type, and unknown classification were reported to be 71.6%, 11.6%, 12.6%, and 4.2%, respectively[3]. In the United States, Yan *et al*[4] reported that there were no sarcomatoid type cases, and that the incidence of epithelioid and biphasic type were 92% and 8%, respectively. In both reports, fewer sarcomatoid type and increased epithelioid type cases were observed in malignant peritoneal mesothelioma, compared with pleural mesothelioma.

The clinical symptoms associated with malignant peritoneal mesothelioma include abdominal distention, abdominal pain, abdominal mass, a loss of appetite, weight loss, fever and diarrhea, but there are no disease specific symptoms[5]. Abdominal hernia was reported to occur in 6%-12% of patients with malignant peritoneal mesothelioma[6,7], but the majority of these were in the inguinal region. According to a report by Acherman *et al*[6], the primary symptoms in 51 cases of malignant peritoneal mesothelioma included 17 cases (33%) of abdominal pain, 5 cases (10%) of abdominal pain and distention, 16 cases (31%) of abdominal swelling, and 6 cases (12%) with the new onset of hernias. Among these, 5 of the hernias occurred in the inguinal region while one occurred in the umbilical region. Thus, although umbilical hernia is rare, a newly developed abdominal hernia should be noted as a primary symptom of malignant peritoneal mesothelioma.

Moreover, the present case was associated with umbilical invasion of the tumor. Metastasis of malignant tumors to the umbilicus is also known as Sister Mary Joseph's nodule[8]. The vascular system around the um-

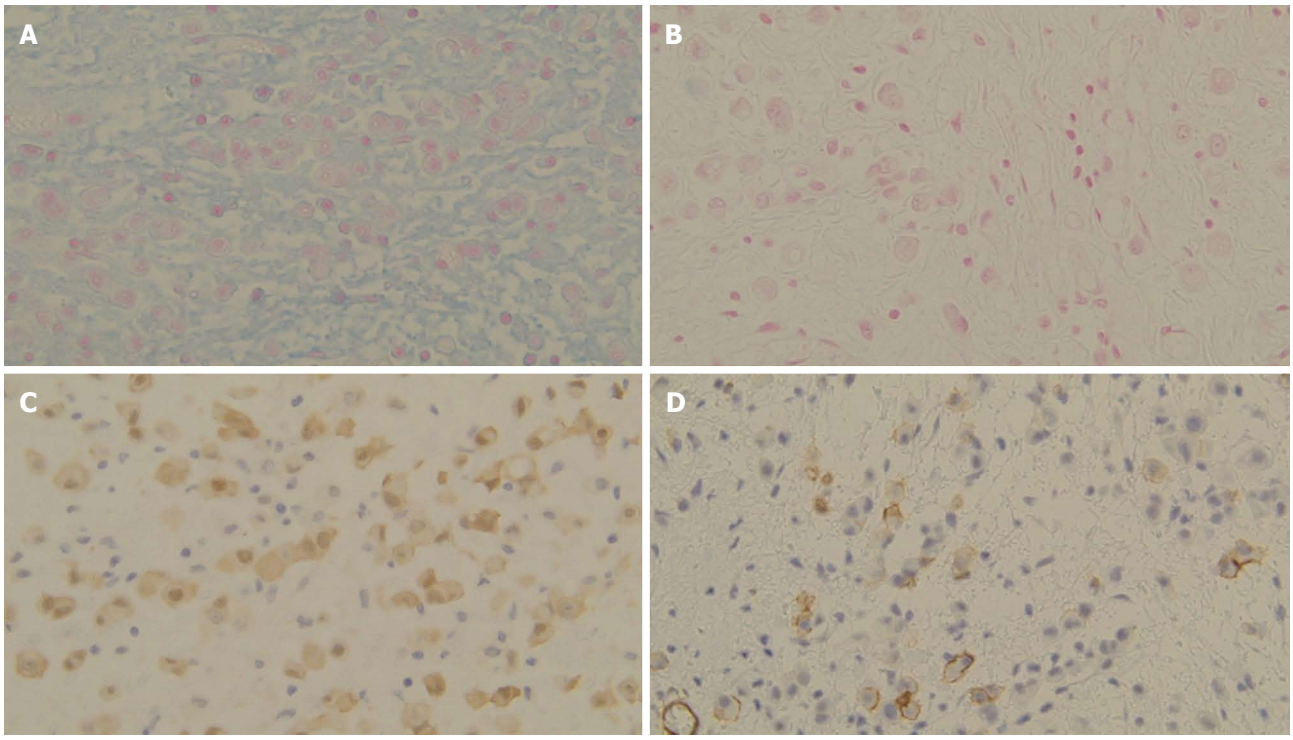


Figure 5 Immunohistochemical staining results. A mucus-like substance was stained positive by alcian blue staining, and was negative after hyaluronidase treatment. Staining of calretinin and CD146 (MCAM) were positive. A: Alcian blue; B: Alcian blue (after hyaluronidase treatment); C: Calretinin; D: CD146 (MCAM).

bilicus forms an arteriovenous loop and lymphoid vessel network, which continues to the round ligament of the liver. Regarding the metastasis pathway to the umbilicus, lymphogenous and hematogenous metastasis, and direct invasion from the surrounding tumor or along the round ligament of the liver have been reported[9-11]. In the present case, laparoscopy revealed numerous thick nodules growing on both the parietal peritoneum and the round ligament of the liver next to the umbilical region. Thus, direct invasion by either or both of the above pathways was most likely. Boyde *et al*[12] reported 4 cases (3.4%) of umbilical metastasis in 89 cases of malignant peritoneal mesothelioma. In all 4 cases, the histological types were epithelioid type and the present case was similar. The umbilicus is one of the weakest regions in the abdominal wall, where the umbilical cord was previously penetrated and aponeurosis and subcutaneous fat are lacking. It is thought that umbilical hernia occurs in adults when the abdominal pressure increases due to pregnancy, obesity, large abdominal tumor, ascites, or peritoneal dialysis[13,14]. In the present case, we observed umbilical metastasis, which might have weakened the surrounding connective tissue, and caused high intraabdominal pressure due to massive ascites. Both factors might contribute to the development of the umbilical hernia.

In summary, we experienced an extremely rare case of malignant peritoneal mesothelioma associated with umbilical metastasis and umbilical hernia. The incidence of malignant peritoneal mesothelioma is expected to increase in the near future. Although it is rare, a newly developed abdominal hernia should be noted as a primary symptom of malignant peritoneal mesothelioma, as shown in the present case.

REFERENCES

1 **Raptopoulos V**. Peritoneal mesothelioma. *Crit Rev Diagn Imaging* 1985; **24**: 293-328 [PMID: 3896651]
2 **Newhouse ML**, Thompson H. Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. *Br J Ind Med* 1965; **22**: 261-269 [PMID: 5836565 DOI: 10.1136/oem.22.4.261]
3 **Gemba K**, Fujimoto N, Kato K, Aoe K, Takeshima Y, Inai K, Kishimoto T. National survey of malignant mesothelioma and asbestos exposure in Japan. *Cancer Sci* 2012; **103**: 483-490 [PMID: 22126592 DOI: 10.1111/j.1349-7006.2011.02165.x]
4 **Yan TD**, Popa E, Brun EA, Cerruto CA, Sugarbaker PH. Sex difference in diffuse malignant peritoneal mesothelioma. *Br J Surg* 2006; **93**: 1536-1542 [PMID: 17048277 DOI: 10.1002/bjs.5377]
5 **Mirarabshahii P**, Pillai K, Chua TC, Pourgholami MH, Morris DL. Diffuse malignant peritoneal mesothelioma--an update on treatment. *Cancer Treat Rev* 2012; **38**: 605-612 [PMID: 22104079 DOI: 10.1016/j.ctrv.2011.10.006]
6 **Acherman YI**, Welch LS, Bromley CM, Sugarbaker PH. Clinical presentation of peritoneal mesothelioma. *Tumori* 2003; **89**: 269-273 [PMID: 12908781]
7 **Mirabella F**. [Peritoneal mesothelioma and abdominal hernias]. *Minerva Med* 1996; **87**: 21-24 [PMID: 8610021]
8 **Powell FC**, Cooper AJ, Massa MC, Goellner JR, Su WP. Sister Mary Joseph's nodule: a clinical and histologic study. *J Am Acad Dermatol* 1984; **10**: 610-615 [PMID: 6715609 DOI: 10.1016/S0190-9622(84)80265-0]
9 **Steck WD**, Helwig EB. Tumors of the umbilicus. *Cancer* 1965; **18**: 907-915 [PMID: 14308240]
10 **Dubreuil A**, Dompmartin A, Barjot P, Louvet S, Leroy D. Umbilical metastasis or Sister Mary Joseph's nodule. *Int J Dermatol* 1998; **37**: 7-13 [PMID: 9522229 DOI: 10.1046/

j.1365-4362.1998.00326.x]
11 **Heatley MK**. Sister Mary Joseph's nodule in malignant mesothelioma. *Histopathology* 2004; **45**: 299-300 [PMID: 15330811 DOI: 10.1111/j.1365-2559.2004.01865.x]
12 **Boyde AM**, Attanoos RL. Sister Mary Joseph's nodule in malignant peritoneal mesothelioma. *Histopathology* 2003; **43**: 303-304 [PMID: 12940787 DOI: 10.1046/j.1365-2559.2003.01669.x]
13 **Arroyo A**, García P, Pérez F, Andreu J, Candela F, Calpena R. Randomized clinical trial comparing suture and mesh repair of umbilical hernia in adults. *Br J Surg* 2001; **88**: 1321-1323 [PMID: 11578284 DOI: 10.1046/j.0007-1323.2001.01893.x]
14 **Cherney DZ**, Siccion Z, Chu M, Bargman JM. Natural history and outcome of incarcerated abdominal hernias in peritoneal dialysis patients. *Adv Perit Dial* 2004; **20**: 86-89 [PMID: 15384802]

P- Reviewer Hussain A **S- Editor** Zhai HH **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.v5.i8.412

World J Gastrointest Endosc 2013 August 16; 5(8): 412-416
ISSN 1948-5190 (online)

CASE REPORT

Dilation of a severe bilioenteric or pancreatoenteric anastomotic stricture using a Soehendra Stent Retriever

Koichiro Tsutsumi, Hironari Kato, Ichiro Sakakihara, Naoki Yamamoto, Yasuhiro Noma, Shigeru Horiguchi, Ryo Harada, Hiroyuki Okada, Kazuhide Yamamoto

Koichiro Tsutsumi, Hironari Kato, Ichiro Sakakihara, Naoki Yamamoto, Yasuhiro Noma, Shigeru Horiguchi, Ryo Harada, Kazuhide Yamamoto, Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama 700-8558, Japan
Hiroyuki Okada, Department of Endoscopy, Okayama University Hospital, Okayama 700-8558, Japan
Author contributions: Tsutsumi K, Kato H, Sakakihara I, Yamamoto N, Noma Y, Horiguchi S and Harada R designed the research; Okada H and Yamamoto K finally approved the paper; Tsutsumi K wrote the paper.
Correspondence to: Koichiro Tsutsumi, MD, PhD, Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama 700-8558,
Japan. tsutsumi@cc.okayama-u.ac.jp
Telephone: +81-86-2357219 Fax: +81-86-2255991
Received: June 4, 2013 Revised: July 7, 2013
Accepted: July 17, 2013
Published online: August 16, 2013

Abstract

Bilioenteric or pancreatoenteric anastomotic strictures often occur after surgery for a pancreaticobiliary disorder. Therapeutic endoscopic retrograde cholangiopancreatography using balloon enteroscopy has been shown to be feasible and effective in patients with such strictures. However, when a benign anastomotic stricture is severe, a dilation catheter cannot pass through the stricture despite successful insertion of the guidewire. We report on the usefulness of the Soehendra Stent Retriever over a guidewire for dilating a severe bilioenteric or pancreatoenteric anastomotic stricture under short double-balloon enteroscopy, in two patients with surgically altered anatomies.

Key words: Bilioenteric anastomotic stricture; Soehendra Stent Retriever; Dilation; Pancreatoenteric anastomotic stricture; Double-balloon enteroscopy

Core tip: The Soehendra Stent Retriever can be useful for the dilation of severe, tight bilioenteric or pancreatoenteric anastomotic strictures over a guidewire, and it is available for endoscopic dilation even under short double-balloon enteroscopy for patients with surgically altered anatomies.

Tsutsumi K, Kato H, Sakakihara I, Yamamoto N, Noma Y, Horiguchi S, Harada R, Okada H, Yamamoto K. Dilation of a severe bilioenteric or pancreatoenteric anastomotic stricture using a Soehendra Stent Retriever. *World J Gastrointest Endosc* 2013; 5(8): 412-416 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/412.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.412

INTRODUCTION

Bilioenteric or pancreatoenteric anastomotic strictures often occur after surgery for a pancreaticobiliary disorder. For the management of these benign strictures in patients with surgically altered anatomies, push enteroscopes and pediatric colonoscopes have been used, but their failure rates have been high. Due to advances in endoscopy, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) including the dilation of a bilioenteric or pancreatoenteric anastomotic stricture by balloon enteroscopy has been shown to be feasible and safe for these patients[1], and has been commonly performed as the initial attempt to manage various postoperative disorder.

However, when a benign anastomotic stricture is severe, a dilation catheter cannot pass through the stricture, and it may not be possible to accomplish dila-

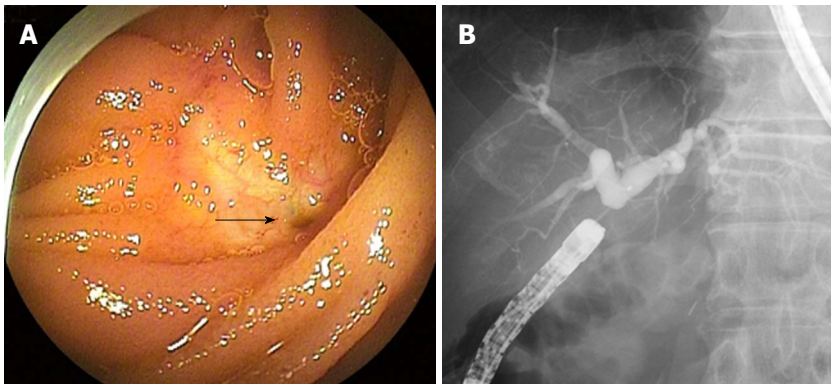


Figure 1 Endoscopic view and cholangiography by short double-balloon enteroscopy in a 66-year-old male. A: Bilioenteric anastomotic stricture looking like a pinhole (arrow); B: Dilated bilateral intrahepatic bile ducts were revealed.

tion despite successful insertion of the guidewire. Here we provide two case reports that involved the use of the Soehendra Stent Retriever (Cook Medical Inc., Winston-Salem, NC, United States), which was designed to facilitate the removal of a biliary or pancreatic plastic stent[2]. We found that this stent retriever was useful for dilating procedures in such difficult situations, in two patients treated with short double-balloon enteroscopy (DBE).

CASE REPORT

Case 1

A 66-year-old male had undergone pylorus-preserving pancreatoduodenectomy (PPPD) by modified Child method due to an ampulla of vater adenoma. Three years later, fever and elevated serum transaminase occurred. Regarding the cause of the cholangitis, we suspected a bilioenteric anastomotic stricture because magnetic resonance cholangiopancreatography (MRCP) imaging revealed dilation of the intrahepatic bile ducts.

For the resolution of the cholangitis, we performed endoscopic retrograde cholangiography with short DBE (EC-450BI5; Fujifilm, Tokyo, Japan). When the DBE reached the bilioenteric anastomosis, the benign severe anastomotic stricture, which looked like a pinhole, was revealed (Figure 1A). The cholangiography showed dilated bilateral intrahepatic bile ducts due to the stricture (Figure 1B). For the endoscopic dilation of this stricture, a 0.035-inch angled guidewire was advanced across the stricture, but a tapered 5.5-Fr catheter would not pass the tight stricture. Thus, the catheter was removed, and the guidewire was left in place. A 7-Fr Soehendra Stent Retriever (SSR) was introduced to the anastomosis over the guidewire and turned clockwise carefully with pressure to advance through the stricture into the bile duct (Figure 2A and B). Following this procedure and the removal of the SSR by counter-clockwise rotation, a 5.5-Fr catheter was allowed to pass the stricture (Figure 2C). In addition, an 8-mm dilation balloon catheter passed easily through the stricture, and consequently further dilation was achieved (Figure 2D and E).

In this case, direct cholangioscopy with an ultraslim enteroscope (EG-530NW; Fujifilm) using overtube guidance was subsequently performed to ascertain whether any hepaticolithiasis existed; none was seen. No relevant complications, such as hemorrhage and perforation, were encountered. No recurrent cholangitis occurred within the 10-month period after the dilation.

Case 2

A 78-year-old female had undergone PPPD with Roux-en Y reconstruction by modified Child method due to an ampulla of vater adenocarcinoma. One year after the PPPD, she reported abdominal pain and her serum pancreatic enzymes were elevated. Computed tomography imaging showed pancreatitis and marked diffuse dilation of pancreatic duct. Regarding the cause of the pancreatitis, MRCP imaging suggested a pancreatoenteric anastomotic stricture with pancreatic stone.

For resolution of the pancreatitis, endoscopic retrograde pancreatography (ERP) with a short DBE (EC-450BI5) was attempted. Although the anastomosis was cicatricial and obscure, pancreatic juice flowing out slightly from the pinhole-like anastomosis was identified (Figure 3A), and cannulation to the pancreatic duct by a tapered 5.5-Fr catheter was barely achieved with preceding 0.018-inch angled guidewire insertion. The ERP showed a dilated pancreatic duct due to the stricture and pancreatic stone (Figure 3B). For the dilation of this stricture, a 0.035-inch angled guidewire was advanced across the stricture into the pancreatic duct, but a 7-Fr Soehendra Bilialy Dilation Catheter (SBDC) and a balloon dilation catheter whose top was non-tapered could not pass the tight stricture despite several attempts. Therefore, the catheter was removed and the guidewire was left in place. Here the 7-Fr SSR was used in the same manner as that described above for Case 1 (Figure 4A and B). Following this procedure and removal of the SSR, a 7-Fr SBDC and balloon dilation catheter easily passed through the stricture and dilation to 6-mm dia. was obtained (Figure 4C-E).

Lastly, 7-Fr × 7-cm Geenen pancreatic stent (Cook Medical) was inserted into the pancreatic duct proximal to the stricture to prevent pancreatic stone impaction.

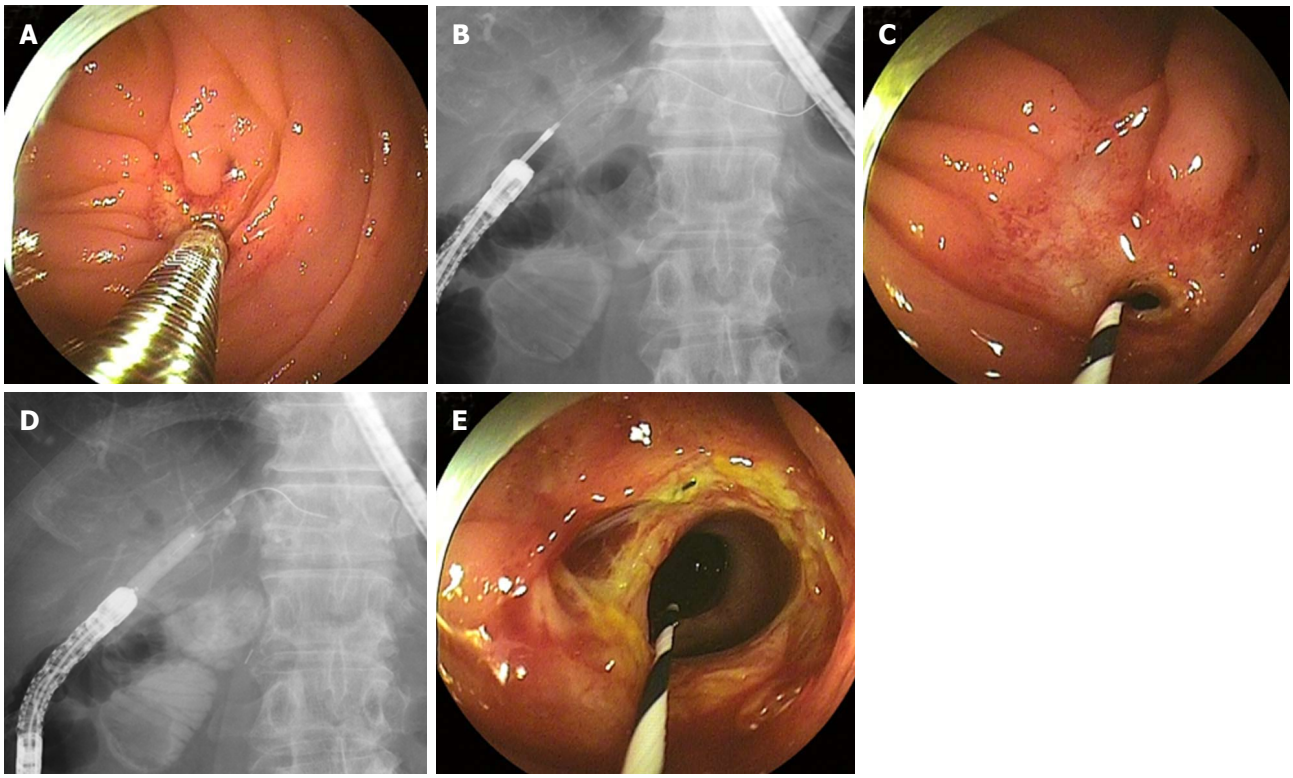


Figure 2 Dilation of the severe bilioenteric anastomotic stricture using a 7-Fr Soehendra Stent Retriever. A: The Soehendra Stent Retriever (SSR) was introduced to the anastomosis over the guidewire, and turned clockwise carefully with pressure to advance through the stricture into the bile duct; B: Fluoroscopic view showing dilation for the stricture by the SSR; C: Endoscopic view showing the dilated anastomosis by the SSR; D: Fluoroscopic view showing subsequent balloon dilation to 8-mm dia; E: Conclusive endoscopic view after balloon dilation for this severe bilioenteric anastomotic stricture.

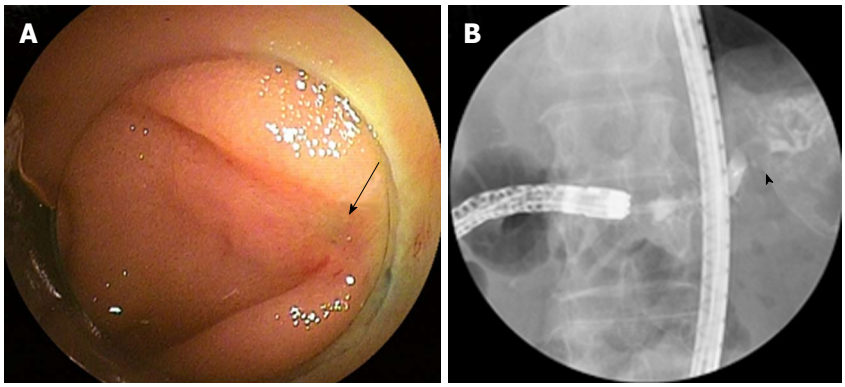


Figure 3 Endoscopic view and pancreatography by short double-balloon enteroscopy in a 78-year-old female. A: Pancreatoenteric anastomotic stricture looking like a pinhole with pancreatic juice flowing out slightly (arrow); B: Dilated pancreatic duct and pancreatic stone (arrowhead) were revealed.

No relevant complications occurred. A follow-up ERP 3 mo later showed improvement in the stricture, and the stone was removed after additional dilation.

DISCUSSION

In recent years, balloon enteroscopy has enabled endoscopists to access bilioenteric and pancreatoenteric anastomoses in patients with surgically altered anatomies, more definitively and safely[1]. Thus, therapeutic ERCP including endoscopic dilation for these anastomotic strictures using balloon enteroscopy (particularly a short DBE which makes almost all conventional accessories) has been commonly performed in initial attempts to manage various postoperative disorder.

As a matter of course, the successful endoscopic management of bilioenteric or pancreatoenteric anastomotic strictures requires the identification of the choledochojejunostomy or pancreaticojejunostomy, the insertion of a guidewire through the narrowed region, and the passage of a dilation catheter through it, followed by balloon dilation. However, anastomoses and the degree of stricture vary. Practically, the anastomosis is sometimes nowhere to be found because of marked stricture, localization at an ob-

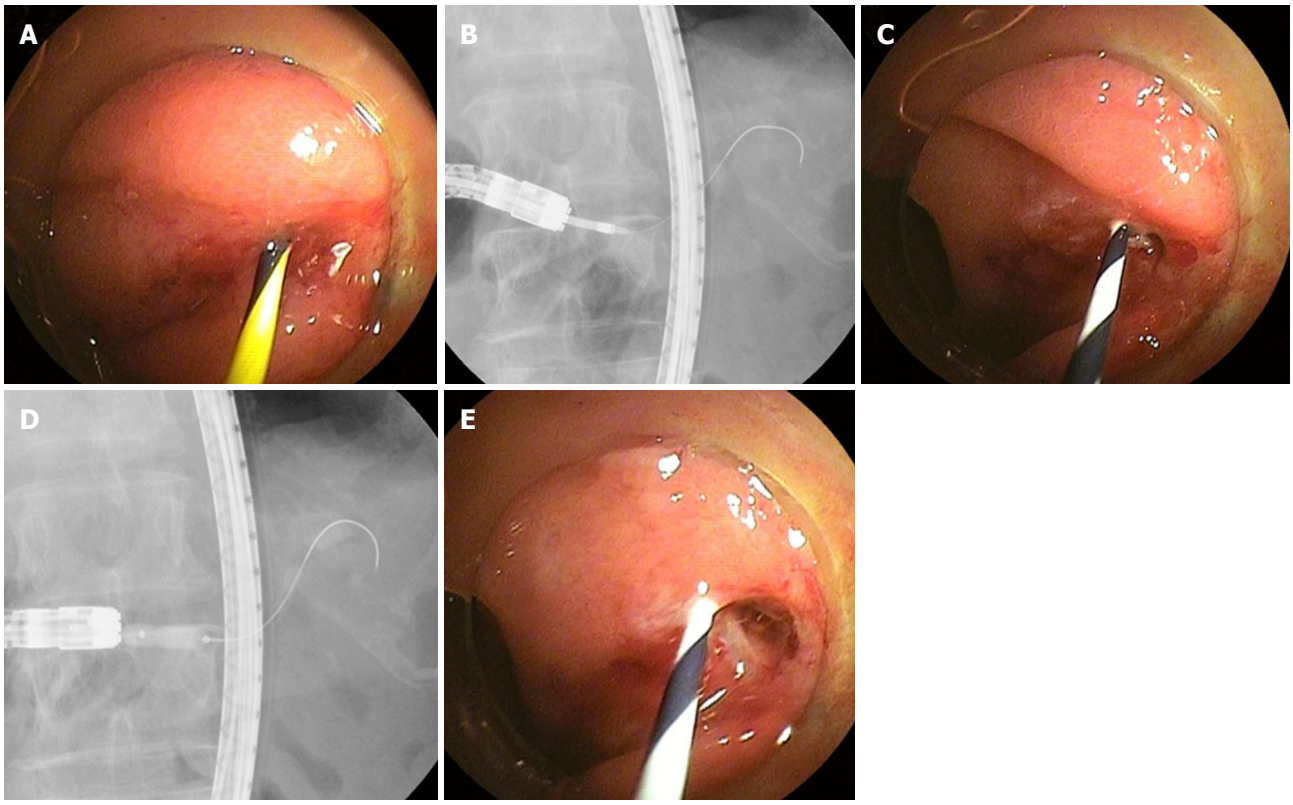


Figure 4 Dilation of the severe pancreatoenteric anastomotic stricture using a 7-Fr Soehendra Stent Retriever. A: The Soehendra Stent Retriever (SSR) was introduced to the anastomosis over the guidewire, and turned clockwise carefully with pressure to advance through the stricture into the pancreatic duct; B: Fluoroscopic view showing dilation for the stricture by the SSR; C: Endoscopic view showing the dilated anastomosis by the SSR; D: Fluoroscopic view showing subsequent balloon dilation to 6-mm dia; E: Conclusive endoscopic view after balloon dilation for this severe pancreatoenteric anastomotic stricture.

scure area, or mucosa-to-mucosa anastomosis, especially in pancreaticojejunostomy. Chahal *et al*[3] reported that the success rate of cannulation and endoscopic therapy was significantly lower for pancreatic indications (3/37, 8%) than biliary indications (37/44, 84%) due to the above reasons. Therefore, if the guidewire insertion is achieved across a severe stricture, a dilation catheter could somehow be introduced to the bile or pancreatic duct through it. Our results indicate that the SSR was useful in dilating these strictures and subsequently allowing a dilation catheter to pass them to achieve sufficient dilation under a short DBE.

The 7-Fr SSR used in the present cases is a metal device comprised of a 180-cm-long, 7-Fr coiled cable with a 4-mm-long threaded tip of 4- to 6-Fr tapered calibers. The use of the SSR with its "self-tapping" screw design has been described for malignant biliary strictures as well as benign biliary and pancreatic duct strictures, and for the treatment of impacted bile duct stones[4]. In addition, the SSR has been used successfully in many advanced therapeutic applications, including the expansion of mesh holes of metallic stents for bilateral biliary stenting[5] and the dilation of a transduodenal or transgastric fistula for the endoscopic ultrasonography (EUS)-guided biliary or pancreatic pseudocyst drainage[6,7]. In all of these studies, no occurrence of complications was reported. The present report is the first about the use of the SSR for dilating severe bilioenteric or pancreatoenteric anastomotic stricture under a short DBE in two patients with surgically altered anatomies.

In cases in which it is impossible to insert a dilation catheter or guidewire through the stricture using a standard technique (including the use of a variety of tapered catheters and guidewires) due to severe stricture or complete obstruction, there is a report describing a direct incision for a short cicatricial ring at the anastomosis by needle knife[8], but safety considerations indicate the need for further studies of this method. Accordingly, a percutaneous or EUS-guided approach is considerable as an alternative, excluding surgical approaches[9-11]. A rendezvous or antegrade technique is also available by using these approaches. However, the EUS-guided procedure needs advanced expertise, and approaches to the pancreatic duct by these alternatives are especially challenging. In addition, these rendezvous techniques are complicated and require very careful maneuvers. Therefore, the SSR with its ability to stretch and lacerate the tissue bluntly seems to be the device of choice in situations in which a dilation catheter will not pass through a severe anastomotic stricture despite the successful insertion of a guidewire.

In conclusion, the SSR can be useful for the dilation of severe, tight bilioenteric or pancreatoenteric anastomotic strictures over a guidewire, and it is available for endoscopic dilation even under short DBE used for pa-

tients with surgically altered anatomies.

REFERENCES

1 **Shimatani M**, Matsushita M, Takaoka M, Koyabu M, Ikeura T, Kato K, Fukui T, Uchida K, Okazaki K. Effective "short" double-balloon enteroscope for diagnostic and therapeutic ERCP in patients with altered gastrointestinal anatomy: a large case series. *Endoscopy* 2009; **41**: 849-854 [PMID: 19750447 DOI: 10.1055/s-0029-1215108]

2 **Soehendra N**, Maydeo A, Eckmann B, Brückner M, Nam VC, Grimm H. A new technique for replacing an obstructed biliary endoprosthesis. *Endoscopy* 1990; **22**: 271-272 [PMID: 2272295]

3 **Chahal P**, Baron TH, Topazian MD, Petersen BT, Levy MJ, Gostout CJ. Endoscopic retrograde cholangiopancreatography in post-Whipple patients. *Endoscopy* 2006; **38**: 1241-1245 [PMID: 17163326]

4 **Brand B**, Thonke F, Obytz S, Binmoeller KF, Rathod V, Seitz U, Bohnacker S, Jäckle S, Soehendra N. Stent retriever for dilation of pancreatic and bile duct strictures. brand@uke.uni-hamburg.de. *Endoscopy* 1999; **31**: 142-145 [PMID: 10223363]

5 **Silverman W**, Slivka A. New technique for bilateral metal mesh stent insertion to treat hilar cholangiocarcinoma. *Gastrointest Endosc* 1996; **43**: 61-63 [PMID: 8903821]

6 **Yamaguchi T**, Ishihara T, Tadenuma H, Kobayashi A, Nakamura K, Kouzu T, Saisho H. Use of a Soehendra stent retriever to treat a pancreatic pseudocyst with EUS-guided cystogastrostomy. *Endoscopy* 2004; **36**: 755 [PMID: 15280996]

7 **Vila JJ**, Goñi S, Arrazubi V, Bolado F, Ostiz M, Javier Jiménez F. Endoscopic ultrasonography-guided transgastric biliary drainage aided by Soehendra stent retriever. *Am J Gastroenterol* 2010; **105**: 959-960 [PMID: 20372144]

8 **Haber GB**. Double balloon endoscopy for pancreatic and biliary access in altered anatomy (with videos). *Gastrointest Endosc* 2007; **66**: S47-S50 [PMID: 17709030]

9 **Ota Y**, Kikuyama M, Suzuki S, Nakahodo J, Koide S. Percutaneous pancreatic-duct puncture with rendezvous technique can treat stenotic pancreaticojejunostomy. *Dig Endosc* 2010; **22**: 228-231 [PMID: 20642615]

10 **Itoi T**, Kikuyama M, Ishii K, Matsumura K, Sofuni A, Itokawa F. EUS-guided rendezvous with single-balloon enteroscopy for treatment of stenotic pancreaticojejunal anastomosis in post-Whipple patients (with video). *Gastrointest Endosc* 2011; **73**: 398-401 [PMID: 20875640]

11 **Park do H**, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided transhepatic antegrade balloon dilation for benign bilioenteric anastomotic strictures in a patient with hepaticojejunostomy. *Gastrointest Endosc* 2012; **75**: 692-693 [PMID: 21679943]

P- Reviewers Figueiredo P, Tsujikawa T
S- Editor Wen LL **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.v5.i8.417

World J Gastrointest Endosc 2013 August 16; 5(8): 417-419
ISSN 1948-5190 (online)

CASE REPORT

Endoscopic management of Dieulafoy's lesion using Isoamyl-2-cyanoacrylate

Abd Elrazek M Aly Abd Elrazek, Nakamura Yoko, Moriguchi Hiroki, Mohamed Afify, Mohamed Asar, Badr Ismael, Magdy Salah

Abd Elrazek M Aly Abd Elrazek, Mohamed Afify, Medicine of Liver Transplantation, Department of Tropical Medicine, Faculty of Medicine, Al Azhar University, Cairo 712-572, Egypt
Abd Elrazek M Aly Abd Elrazek, Mohamed Asar, Magdy Salah, Department of General Surgery and Endoscopy, Faculty of Medicine, Al Azhar University, Cairo 712-572, Egypt
Nakamura Yoko, Moriguchi Hiroki, Department of Medical Informatics, Institute of Biomedical Science-University of Tokushima, Tokushima 770-8503, Japan
Badr Ismael, Department of Anesthesia and Intensive Care, Al Azhar University, Cairo 712-572, Egypt
Author contributions: All the authors contributed to this paper.
Correspondence to: Abd Elrazek M Aly Abd Elrazek, MD, PhD, Medicine of Liver Transplantation, Department of Tropical Medicine, Faculty of Medicine, Al Azhar University, Al-Darrasa Cairo, Cairo 712-572, Egypt. ahmadrazek@gmail.com
Telephone: +20-115-3201333 Fax: +20-115-3201333
Received: March 17, 2013 Revised: May 31, 2013
Accepted: June 28, 2013
Published online: August 16, 2013

Abstract

Dieulafoy's lesion (DL) is a rare but important cause of obscure gastrointestinal bleeding that may be overlooked during diagnostic endoscopy. Mortality rates are similar to those of other causes for gastrointestinal bleeding. Diagnosis by upper endoscopy is the modality of choice during acute bleeding. In the absence of active bleeding, the lesion resembles a raised nipple or visible vessel. There are no guidelines regarding effective selective therapy for DL, when diagnosed, endoscopist experience is the major determinant of the treatment strategy. Following our strategy, an expert endoscopist with a skilled assistant should have a high rate of successful DL diagnosis when an obscured gastrointestinal lesion is suspected. Cyanoacryltes compounds have been used successfully in management of Gastric varices and DLs. To our knowledge, there have been no previous reports regarding use of isoamyl-2-cyanoacrylate (AMCRYLATE®; Concord Drugs Ltd., Hyderabad, India) as an effective therapy for gastric DL without serious complications. In our case study, Isoamyl-2-cyanoacrylate (AMCRYLATE®) was effective and safe for treating DL. Surgical wedge resection of the lesion should be considered as a therapeutic option if endoscopic therapy fails.

Key words: Dieulafoy's lesion; Isoamyl-2-cyanoacrylate; Gastrointestinal bleeding; Endoscopy; Stomach

Core tip: The etiology of Dieulafoy's lesion (DL) is unknown. The hemorrhage is often torrential and life threatening. Diagnosis by upper endoscopy is the modality of choice during acute bleeding. In the absence of active bleeding, the lesion resembles a raised nipple or visible vessel. There are no guidelines regarding effective selective therapy for DL. When diagnosed, endoscopist experience is the major determinant of the treatment strategy. To our knowledge, there have been no previous reports regarding use of isoamyl-2-cyanoacrylate (AMCRYLATE®; Concord Drugs Ltd., Hyderabad, India) as an effective therapy for gastric DLs without serious complications.

Abd Elrazek AEMA, Yoko N, Hiroki M, Afify M, Asar M, Ismael B, Salah M. Endoscopic management of Dieulafoy's lesion using Isoamyl-2-cyanoacrylate. *World J Gastrointest Endosc* 2013; 5(8): 417-419 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i8/417.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i8.417

INTRODUCTION

Dieulafoy's lesion (DL) is an important cause of obscure gastrointestinal bleeding that may be overlooked during diagnostic endoscopy or even laparotomy. The hemor-

rhage is often torrential and life threatening. The French pathologist Dieulafoy, who described three cases, discovered the lesion in 1889, although the first case was actually reported by Gallard in 1884. DLs can occur in any part of the gastrointestinal tract with a tendency toward the lower end of the esophagus, cardia, lesser curvature of the stomach, and caecum[1].

The etiology of DL is unknown. Patients who bleed from DLs are typically males with comorbidities including hypertension, diabetes or alcohol abuse. The use of nonsteroidal anti-inflammatory drugs is also common among patients with bleeding, although many patients have no triggering events. DLs can appear any time between 20 mo and 92 years of age[2,3].

Diagnosis by upper endoscopy is the modality of choice during acute bleeding. In the absence of active bleeding, the lesion resembles a raised nipple or visible vessel. In massive bleeding, active arterial pumping can be visualized in an area without an associated ulcer or mass lesion, although the aberrant vessel is often not seen. Endoscopic ultrasonography is useful for confirmation of the diagnosis[4].

There are no guidelines regarding effective selective therapy for DL. When diagnosed, endoscopist experience is the major determinant of the treatment strategy. Many therapeutic approaches exist, including endoscopic hemostasis with a combination of epinephrine followed by bipolar probe coagulation; heater probe thermal coagulation; hemoclip placement; band ligation; argon plasma coagulation; arterial angiographic embolization; endoscopic sclerotherapy using ethanolamine oleate, polidocanol, or *N*-butyl-2-cyanoacrylate; and surgical wedge resection of the lesion, which is now rarely performed due to the availability of more advanced endoscopic technologies and increased operator experience[5].

In the 1940s, various surgical cyanoacrylate adhesives were developed; these are a series of homologous alkyl-cyanoacrylate compounds. These compounds polymerize on contact with common substances, such as blood and water, at room temperature without requiring a solvent or catalyst. Adhesive glue is particularly useful for day surgeries, *e.g.*, circumcision. Cyanoacrylate is superior to sutures and its clinical use is becoming increasingly common due to its ease of application, decreased scarring, decreased pain, and superior cosmetic results with no discomfort, as can occur due to sutures snagging clothing and/or the dressing[6-8]. Many authors have reported the disadvantages of *N*-butyl-2-cyanoacrylate as a treatment of choice for DL because of serious complications of extravasation, rebleeding due to massive ulceration, and even gastric perforation[9]. Radiographically evident Pulmonary Embolism was reported after endoscopic injection sclerotherapy (EIS) for gastric variceal bleeding using *N*-butyl-2-cyanoacrylate[10].

To our knowledge, there have been no previous reports regarding use of isoamyl-2-cyanoacrylate (AMCRYLATE®; Concord Drugs Ltd., Hyderabad, India) as an effective therapy for gastric DLs without serious complications.

CASE REPORT

A 29-year-old male patient was admitted with hematemesis with no history of the use of nonsteroidal anti-inflammatory drugs, aspirin, paracetamol, caffeine or alcohol abuse. There was no family history of bleeding disorders. The patient denied having taken medications for any illness, and no abnormalities were detected on ultrasound examination. Upper endoscopy revealed no masses, ulcers, varices, or any lesions. Six hours later, the patient developed massive hematemesis following the administration of 500 mL of packed red blood cells. Upper endoscopy was repeated, but no lesion was seen. The patient was administered hemostatic medications. One day after discharge, a massive attack of hematemesis recurred 48 h after the previous attack. The patient was transferred to our clinic, where upper endoscopy was repeated for the third time. A gastric wash was performed and an endoscopy expert was called. Upper endoscopy revealed a nipple-like protrusion on the greater curvature just 5 cm below the cardia. Touching the lesion with the blind, smooth end of a probe led to massive hemorrhage (Figure 1). The gastric wash was repeated with the administration of another 500 mL of packed red blood cells. Endoscopic sclerotherapy was performed using 1 mL of isoamyl-2-cyanoacrylate (AMCRYLATE®) in 1 mL of Lipidol in a 1:1 ratio. The bleeding was stopped (Figures 2 and 3). Post-endoscopic erect abdominal X-ray showed no extravasation. The caliber of the Dieulafoy's arteriole was relatively large; it opened directly into the stomach without branching, making it more than ten times larger than other gastric capillaries (Figure 4). Follow-up 3 mo later showed no complications due to the therapy and no extravasations, ulcerations or any other hemostatic disorders.

DISCUSSION

The use of isoamyl-2-cyanoacrylate (AMCRYLATE®) could be an effective treatment for gastric DLs because the viscosity and adhesive problems that can occur with *N*-butyl-2-cyanoacrylate are significantly reduced by use of isoamyl-2-cyanoacrylate (AMCRYLATE®). We expect fewer complications with almost identical results. Another advantage is that AMCRYLATE® is significantly more cost-effective than *N*-butyl-2-cyanoacrylate, especially when large amounts are required.

According to our experience, it is convenient to use isoamyl-2-cyanoacrylate as effective endoscopic management for gastric varices. The use of isoamyl-2-cyanoacrylate significantly reduced post endoscopic ulceration compared to *N*-butyl-2-cyanoacrylate.

In summary, DL is an infrequent but severe and obscure cause of gastrointestinal hemorrhage, which occurs predominantly in males. Repeated endoscopy is often required to determine the diagnosis. An expert endoscopist with a skilled assistant should have a high rate of successful diagnosis of DL. Thus, use of isoamyl-2-cyanoacrylate (AMCRYLATE®) seems effective and safe for treatment of gastric DLs. Surgical wedge resection should be reserved

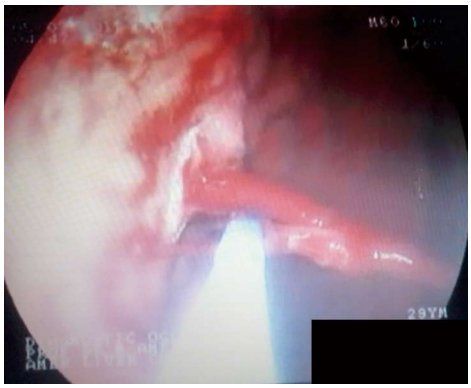


Figure 1 Dieulafoy's lesion in male patient presented with active haematemesis. Note the haemorrhagic arterior in greater gastric curvature.

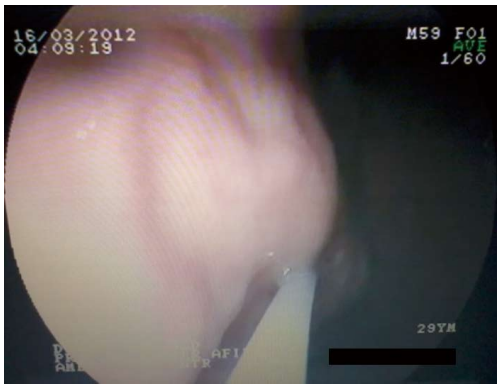


Figure 2 Injection of Dieulafoy's lesion with 1 cm Isoamyl 2-Cyanoacrylate dissolved in 1 cm Lipidol, 1:1 ratio.

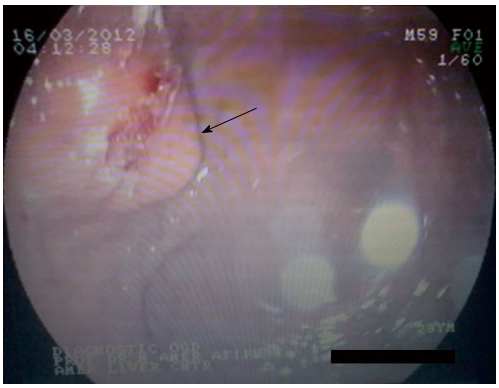


Figure 3 Successfully Injected dieulafoy (arrow) and no more bleeding.

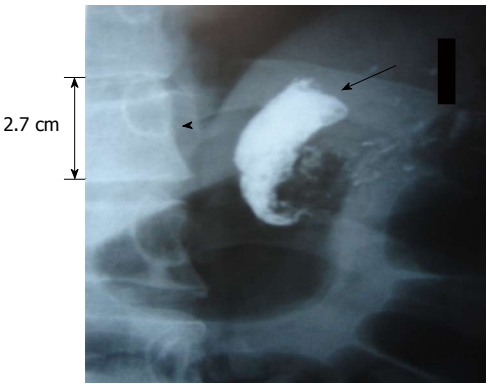


Figure 4 Erect X-ray, showing Dieulafoy large Arteriole after Iso Amyl-2-cyanoacrylate injection. It opens directly into the gastric cavity. Note the large caliber of the Arteriole (arrow) corresponding to the adjacent Lumbar Vertebra (arrow head).

for difficult-to-control bleeding. Death may occur if bleeding is not controlled.

REFERENCES

1 **Pollack R**, Lipsky H, Goldberg RI. Duodenal Dieulafoy's lesion. *Gastrointest Endosc* 1993; **39**: 820-822 [PMID: 8293911]
2 **Lara LF**, Sreenarasimhaiah J, Tang SJ, Afonso BB, Rockey DC. Dieulafoy lesions of the GI tract: localization and therapeutic outcomes. *Dig Dis Sci* 2010; **55**: 3436-3441 [PMID: 20848205 DOI: 10.1007/s10620-010-1385-0]
3 **Lee YT**, Walmsley RS, Leong RW, Sung JJ. Dieulafoy's lesion. *Gastrointest Endosc* 2003; **58**: 236-243 [PMID: 12872092 DOI: 10.1067/mge.2003.328]
4 **Squillace SJ**, Johnson DA, Sanowski RA. The endosonographic appearance of a Dieulafoy's lesion. *Am J Gastroenterol* 1994; **89**: 276-277 [PMID: 8304318]
5 **Liu D**, Lu F, Ou D, Zhou Y, Huo J, Zhou Z. [Endoscopic band ligation versus endoscopic hemoclip placement for bleeding due to Dieulafoy lesions in the upper gastrointestinal tract]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2009; **34**: 905-909 [PMID: 19779265]
6 **Quinn J**, Wells G, Sutcliffe T, Jarmuske M, Maw J, Stiell I, Johns P. A randomized trial comparing octylcyanoacrylate tissue adhesive and sutures in the management of lacerations. *JAMA* 1997; **277**: 1527-1530 [PMID: 9153366 DOI: 10.1001/jama.1997.03540430039030]
7 **Aubert A**, Hammel P, Zappa M, Kianmanesh R, O'Toole D, Lévy P, Ruszniewski P. [Gastric perforation by histoacryl extravasation as a complication of endoscopic sclerotherapy for bleeding Dieulafoy ulcer]. *Gastroenterol Clin Biol* 2006; **30**: 155-156 [PMID: 16514402 DOI: 10.1016/S0399-8320(06)73136-0]
8 **Mertz PM**, Davis SC, Cazzaniga AL, Drosou A, Eaglstein WH. Barrier and antibacterial properties of 2-octyl cyanoacrylate-derived wound treatment films. *J Cutan Med Surg* 2003; **7**: 1-6 [PMID: 12362261 DOI: 10.1007/s10227-002-1154-6]
9 **Lee GH**, Kim JH, Lee KJ, Yoo BM, Hahm KB, Cho SW, Park YS, Moon YS. Life-threatening intraabdominal arterial embolization after histoacryl injection for bleeding gastric ulcer. *Endoscopy* 2000; **32**: 422-424 [PMID: 10817185 DOI: 10.1055/s-2000-9002]
10 **Hwang SS**, Kim HH, Park SH, Kim SE, Jung JI, Ahn BY, Kim SH, Chung SK, Park YH, Choi KH. N-butyl-2-cyanoacrylate pulmonary embolism after endoscopic injection sclerotherapy for gastric variceal bleeding. *J Comput Assist Tomogr* 2001; **25**: 16-22 [PMID: 11176287 DOI: 10.1097/00004728-200101000-00003]

P- Reviewer Islam RS **S- Editor** Zhai HH **L- Editor** A
E- Editor Zhang DN

WJGE World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2013 August 16; 5(8): 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 peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WJGE covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal endoscopy diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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

WJGE is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 OA clinical medical journals, including 41 in English, has a total of 15 471 editorial board members or peer reviewers, and is a world first-class publisher.

Columns

The columns in the issues of *WJGE* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers; (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in gastrointestinal endoscopy; (12) Brief Articles: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (13) Meta-Analysis: To summarize a given quantitative effect, *e.g.*, the clinical effectiveness and safety of clinical treatments by combining data from two or more randomized controlled trials, thereby providing more precise and externally valid estimates than those which would stem from each individual dataset if analyzed separately from the others; (14) Case Report: To report a rare or typical case; (15) 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; (16) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

Name of journal

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

Launch date

October 15, 2009

Frequency

Monthly

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

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

SPECIAL STATEMENT

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

Biostatistical editing
Statistical 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 conform 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, Abstract, Introduction, Materials and Methods, Results, Discus-

sion, 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 ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United 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: http://www.wjgnet.com/esps/. 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 wjge@wjgnet.com, or by telephone: +86-10-85381892. 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 ICMJE, 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: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; 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, $P < 0.001$), and 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.

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, 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.

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. 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 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**. Hypertension, 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/1948-5190/g_info_20100107135346.htm.

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

All types of articles' writing style and requirement will be found in the link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system via the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@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.

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 papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

STATEMENT ABOUT ANONYMOUS PUBLICATION OF THE PEER REVIEWERS' COMMENTS

In order to increase the quality of peer review, push authors to carefully revise their manuscripts based on the peer reviewers' comments, and promote academic interactions among peer reviewers, authors and readers, we decide to anonymously publish the reviewers' comments and author's responses at the same time the manuscript is published online.

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 and format, 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. All invited articles are published free of charge.

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com