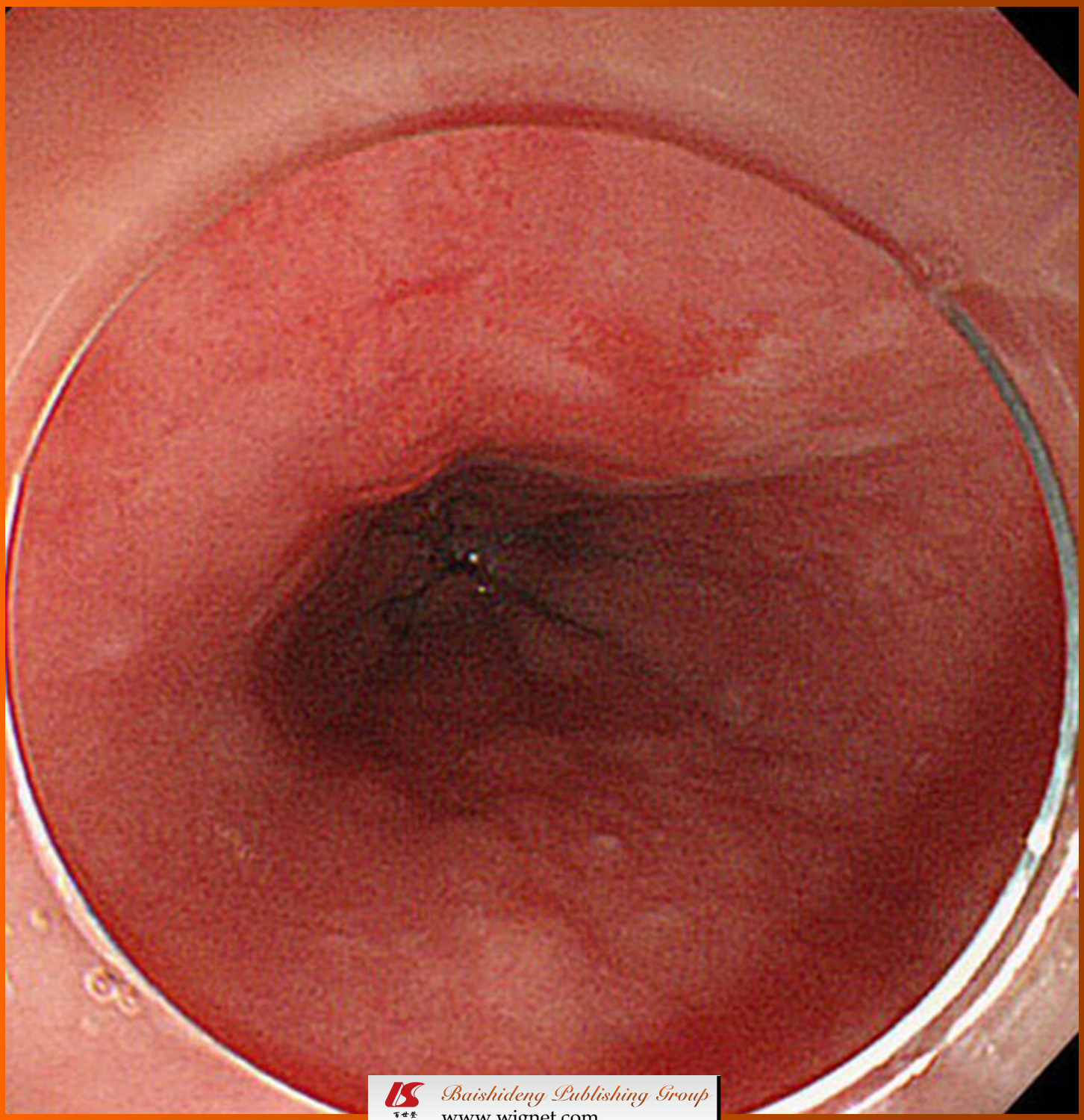
ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2012 May 16; 4(5): 157-200



Baishideng Publishing Group
www.wjgnet.com

WJGE World Journal of Gastrointestinal Endoscopy

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

Editorial Board

2009-2013

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

Czech Republic

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

Denmark

Peter Bytzer, *Koege*

Ecuador

Carlos Robles-Medranda, *Portoviejo*

Egypt

Nabil Ali Gad El-Hak, *Mansoura*

Finland

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

France

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

Germany

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

Greece

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

Hungary

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

India

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

Iran

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

Ireland

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

Israel

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

Italy

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

Japan

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

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

Lebanon

Kassem A Barada, *Beirut*

Lithuania

Laimas Virginijus Jonaitis, *Kaunas*

Malaysia

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

Mexico

OT Teramoto-Matsubara, *México*

Netherlands

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

New Zealand

Michael PG Schultz, *Dunedin*

Norway

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

Pakistan

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

Poland

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

Portugal

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

Romania

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

Singapore

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

South Africa

Roland N Ndip, *Alice*

South Korea

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

Spain

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

Sweden

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

Thailand

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

Turkey

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

United Arab Emirates

Margit Gabriele Muller, *Abu Dhabi*

United Kingdom

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

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 4 Number 5 May 16, 2012

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

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

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

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

PUBLICATION DATE
May 16, 2012

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

ONLINE SUBMISSION
http://www.wjgnet.com/1948-5190office/

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.157

World J Gastrointest Endosc 2012 May 16; 4(5): 157-161
ISSN 1948-5190 (online)

EDITORIAL

Management of an occluded biliary metallic stent

Wiriyaporn Ridtitid, Rungsun Rerknimitr

Wiriyaporn Ridtitid, Rungsun Rerknimitr, Director of Endoscopy Unit, Division of Gastroenterology, Department of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
Author contributions: Ridtitid W and Rerknimitr R substantially contributed to the conception and design; Ridtitid W drafted the article; Rerknimitr R critically revised the important intellectual content; and Ridtitid W and Rerknimitr R approved the final version before publishing.
Correspondence to: Rungsun Rerknimitr, MD, Professor of Medicine, Director of Endoscopy Unit, Division of Gastroenterology, Department of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. ercp@live.com
Telephone: +66-2-2564356 Fax: +66-2-2527839
Received: October 13, 2011 Revised: November 15, 2011
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

In patients with a malignant biliary obstruction who require biliary drainage, a self-expandable metallic stent (SEMS) provides longer patency duration than a plastic stent (PS). Nevertheless, a stent occlusion by tumor ingrowth, tumor overgrowth and biliary sludge may develop. There are several methods to manage occluded SEMS. Endoscopic management is the preferred treatment, whereas percutaneous intervention is an alternative approach. Endoscopic treatment involves mechanical cleaning with a balloon and a second stent insertion as stent-in-stent with either PS or SEMS. Technical feasibility, patient survival and cost-effectiveness are important factors that determine the method of re-drainage and stent selection.

Key words: Occluded biliary metallic stent; Re-drainage; Cost effectiveness

Peer reviewer: Gianpiero Gravante, MD, BSC, MBBS, PhD, Department of Upper Gastrointestinal Surgery, Frenchay Hospital-North Bristol NHS Trust, Flat 8 Room 25, Clark Hall-Frenchay Hospital, Frenchay Park Road, Bristol-BS16 1LE, United Kingdom

Ridtitid W, Rerknimitr R. Management of an occluded biliary metallic stent. *World J Gastrointest Endosc* 2012; 4(5): 157-161 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/157.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.157

INTRODUCTION

Many studies have shown that the outcomes of palliative endoscopic biliary drainage in patients with malignant biliary obstruction were similar to those with surgical bypass with regards to technical success and functional biliary decompression[1-5]. However, an endoscopic approach provided lower rates of procedure-related mortality and complications, and shorter hospital stay[4,5]. Currently, there are two types of stent that can be selected for endoscopic palliation; plastic stent (PS) and self expandable metallic stent (SEMS). Although a plastic stent is less expensive than SEMS, it provides shorter patency duration due to its smaller diameter[6-12]. For the cost effectiveness purpose, many studies demonstrated that endoscopic placement of SEMS is more appropriate in a patient who may survive longer than 3 mo[7,8,10,11]. In contrast, PS insertion is recommended in a patient with shorter survival[7,8,10,11]. Although SEMS can provide longer patency duration, there are certain factors that may cause recurrent biliary obstruction after the insertion of SEMS[13]. Tumor ingrowth, tumor overgrowth, stent migration and stent occlusion by sludge or debris can occur. The appropriate management of occluded SEMS is still unclear and controversial. We herein present a review on the management of SEMS occlusion based on our own experience and previous reports of this context.

CAUSES OF BILIARY METALLIC STENT OCCLUSION

The occlusion of SEMS is a major late adverse event of SEMS insertion. Many retrospective series have demonstrated that it developed in 5%-40% of patients who underwent an endoscopic palliative treatment with SEMS[14-19]. The causes of occluded SEMS include tumor ingrowth, overgrowth, sludge/debris formation and stent migration (Table 1). The most common cause of SEMS occlusion is tumor ingrowth, which accounted for 60%-90% of all SEMS occlusion[14-19]. This complication is more common in uncovered SEMS, which has an open-mesh, resulting in tissue growing into the stent easily[20,21]. To overcome the problem of tumor ingrowth, a covered stent has been introduced, a membrane made of polyurethane and polyethylene designed to cover the mesh, and therefore tissue and tumor cannot grow into the SEMS lumen. As a trade off, a covered SEMS contains a higher risk for migration because of a smaller degree of biliary tissue embedment.

Many studies have shown that one fourth of all SEMS occlusions resulted from tumor overgrowth[14-19]. Because tumor can grow and invade over both ends of the stent, covered and uncovered SEMSs have an equal chance to develop tumor overgrowth. Hypothetically, a longer SEMS may possibly decrease the risk for tumor overgrowth. However, no studies have been done to confirm this hypothesis.

Colonization or infection by bacteria can create materials that occlude a stent, such as bacterial clump, bile glycoprotein mucin and sludge[22]. Thus, recurrent cholangitis is an important risk developing biliary sludge. This process usually develops after PS insertion; unfortunately, SEMS placement is not exempt. In addition, duodenobiliary reflux was reported as another factor for PS occlusion[23]. Perhaps the larger diameter of SEMS may increase the risk for stent blocking from more duodenobiliary reflux.

To date, the standard approaches for SEMS occlusion are percutaneous biliary drainage, endoscopic cleaning with balloon, and endoscopic re-stenting (PS, uncovered SEMS and covered SEMS). The techniques, results and complications are different among those approaches.

Table 1 The causes of occluded self-expandable metallic stent

	Tham *et al* 1998	Bueno *et al* 2003	Togawa *et al* 2008	Rogart *et al* 2008	Ridtitid *et al* 2010	Cho *et al* 2011
No. of patients	152	592	95	90	154	583
No. of patients with SEMS occlu-sion (uncovered/covered)	44 (44/0)	34 (34/0)	40 (40/0)	27 (23/4)	32 (22/10)	77 (30/47)
Tumor ingrowth (%)	28 (63.6)	20 (58.8)	36 (90)	19 (70.4)	25 (78.1)	53 (68.8)
Tumor overgrowth (%)	3 (6.8)	9 (26.5)	3 (7.5)	3 (11.1)	3 (9.4)	9 (11.7)
Sludge/debris (%)	8 (18.2)	5 (14.7)	1 (2.5)	5 (18.5)	5[1] (15.6)	8 (10.4)
Others	Hyper-plasia 3 Unde-fined 2	-	-	-	Migration 4	Compres-sion/blood clot/mi-gration 7

[1]With tumor overgrowth.

ENDOSCOPIC MANAGEMENT

Endoscopic treatment is widely accepted as the primary mode of managing occluded SEMS. Currently, there are three endoscopic techniques that provide re-drainage for SEMS occlusion: (1) mechanical cleaning with a balloon; (2) PS insertion; and (3) SEMS insertion[14-19].

Placing covered SEMS, uncovered SEMS or PS?

Both SEMS and PS can provide immediate biliary relief in a patient with SEMS occlusion. Stent selection is usually determined by the performing endoscopist. Level of biliary obstruction and patient's survival are important factors for stent selection. Our previous study demonstrated a much shorter stent patency time (50%) in patients with hilar block when compared to non-hilar block[24]. In addition, a patient with advanced liver metastasis carries a significant shorter survival than a patient with early stage of disease[9]. Thus, before restenting of the SEMS occlusion, liver metastasis status needs to be evaluated. For instance, placing only a PS is justified in a patient with pancreatic head cancer with advanced liver metastasis, whereas a patient with low grade hilar cholangiocarcinoma (Bismuth Ⅱ) without liver spread deserves SEMS as a second stent.

Moreover, for a country with financial constraints, cost-effectiveness should be the main concern since there is a significant difference in the cost between PS and SEMS. Therefore, the balance between cost and clinical concern, including stent patency and patient survival, has to be judged individually in every patient according to local expertise and the economic level of each country.

Stent patency: There are several studies that used additional stent placement as stent-in-stent for a re-drainage of SEMS occlusion[14-19]. The patency times of a second stent are shown in Table 2. A study by Tham *et al*[14] demonstrated that there was no significant difference in the duration of second stent patency after placement of either SEMS or PS (75 d; 95% CI 43-107 *vs* 90 d; 95% CI 71-109). Some studies demonstrated that mechanical cleaning with a balloon was less effective than placing the second stent[15,17,18]. In addition, our recent study reported that all patients with stent occlusion by debris were also found to have a concomitant tumor ingrowth. At first, mechanical cleaning was performed but it was insufficient to maintain stent patency and eventually all of our patients required a placement of second stent to maintain patency[18].

A covered SEMS provides a more durable patency

Table 2 The patency time of second drainage and patient survival

	Tham *et al* 1998	Bueno *et al* 2003	Togawa *et al* 2008	Rogart *et al* 2008	Ridtitid *et al* 2010	Cho *et al* 2011
No. of SEMS occlusion	44	34	40	27	32	77
Type of initial SEMS (patients)						
Covered SEMS	0	0	0	4	10	47
Uncovered SEMS	44	34	40	23	22	30
Initial stent patency (d): total				118[a]	60-150[a]	
Covered SEMS	NA	NA	NA	NA	NA	189
Uncovered SEMS	102	125	153	NA	NA	132
Type of second drainage (patients)						
Covered SEMS	0	0	26	9	4	40
Uncovered SEMS	19	4	7	5	10	26
Plastic stent	20	24	7	11	11	11
Mechanical cleaning	5	6	0	2	0	0
PTBD	0	0	0	0	7	0
Second drainage patency (median, d)						
Covered SEMS	NA	NA	220[e]	214[b]	NA	138[c]
Uncovered SEMS	75	192	141[e]	54	100	109
Plastic stent	90	90	58[e]	66	60	88
Mechanical cleaning	34	21	NA	43	NA	NA
PTBD	NA	NA	NA	NA	75	NA
Survival (d)						
Covered SEMS	NA	NA	NA	227	NA	440[d]
Uncovered SEMS	70	NA	NA	389	230[f]	243
Plastic stent	98	NA	NA	188	130	296
Mechanical cleaning	34	NA	NA	194	NA	NA
PTBD	NA	NA	NA	NA	150	NA

NA: Not available; [a]Overall initial stent patency (d); [b]$P < 0.05$ for SEMS *vs* PS and mechanical cleaning; [c]$P < 0.05$ for covered SEMS *vs* PS; [d]$P < 0.001$ for covered SEMS *vs* uncovered SEMS; [e]Mean patency time (d); [f]$P < 0.05$ for SEMS *vs* PS and PTBD. SEMS: Self-expandable metallic stent; PTBD: Percutaneous transhepatic biliary drainage; PS: Plastic stent.

than an uncovered SEMS as the first stent[25]. A recent meta-analysis reported that a covered SEMS provided a longer patency than an uncovered SEMS when inserted as the first stent in patients with unresectable distal malignant biliary obstruction (weight mean difference 60.56 d; 95% CI 25.96-95.17)[25]. In addition, tumor ingrowth was likely to occur more in patients with uncovered SEMS [relative risk (RR) 2.03; 95% CI: 0.08-0.67; P = 0.01], whereas stent migration, tumor overgrowth and sludge formation were more likely to develop in patients with covered SEMS (RR 8.11; 95% CI: 1.47-44.76; P = 0.02; RR: 2.02; 95% CI: 1.08-3.78; P = 0.03; RR: 2.89; 95% CI: 1.27-6.55; P = 0.01, respectively)[25]. Hypothetically, covered SEMS should also provide a longer patency duration when inserted as a second stent after the first SEMS becomes occluded[16,19]. This hypothesis has been supported by two reports[16,19]. Togawa *et al*[16] placed a covered stent in patients with occluded uncovered SEMS and showed that the cumulative duration of the covered SEMS patency was significantly longer than the uncovered one (mean second stent patency = 219.6 d; range 19-1972 d *vs* 141.3 d; range 6-1949 d; P = 0.04). Likewise, Cho *et al*[19] reported a similar outcome (median second stent patency of covered SEMS *vs* uncovered SEMS = 360 d *vs* 221 d; P = 0.002).

The level of biliary obstruction can influence the patency duration of the second stent. Two studies supported that the level of biliary obstruction near the hepatic hilum influenced the shorter duration of a second stent patency[15,18]. Bueno *et al*[15] demonstrated that the patency time was longer for a stent inserted as stent-in-stent for distal biliary stricture as opposed to a second stent inserted for proximal biliary strictures. They reported that the median second stent patency in distal biliary stricture was longer than hilar stricture (128 d; range 11-393 d *vs* 61 d; range 15-263 d). Needless to say, the advantage of the second SEMS for occluded stent at the hepatic hilum is still suboptimal and a better SEMS designed for this purpose is required.

Patient survival: The median survival times of patients with a second intervention are shown in Table 2. The majority of studies demonstrated that that the survival of patients who had SEMS as a second stent was longer than others. There were some limitations from retrospective study designs and this finding may resulted in selection bias. A study by Tham *et al*[14] reported that patients' survival has no influence on stent selection since both SEMS and PS provided similar duration of stent patency. It speculated that patients' survival used for calculation of stent patency in that study was relatively short since it has been shown that the median survival times of the SEMS group and the PS group were only 70 d and 98 d, respectively[14]. In contrast, Rogart *et al*[17] who had patients with longer survival (285 d for SEMS group and 188 d for PS group, respectively) demonstrated the longer patency duration of SEMS than PS (172 d *vs* 66 d, respectively). Similar results have been confirmed by other studies[16,18].

Cost-effectiveness: The best parameter to determine the cost effectiveness of different approaches is the incremental cost effectiveness ratio (ICER) that requires the calculation of stent costs, number of endoscopic retrograde cholangiopancreatography (ERCP) sessions and the cost for one ERCP. The selected intervention can be determined as cost effective if its ICER is less expensive than having an additional procedure. The results of the three studies on ICER of SEMS *vs* ICER of PS are shown in Table 3[14,17,18,26]. We assumed that the SEMS costs in different countries are comparable. The ICERs from those three studies ranged from US $ 1518 to US $ 7015 as a result from the differences in ERCP-procedure cost and number of ERCP sessions. The ERCP-procedure cost is dependent on the cost of living and healthcare reimbursement in different countries. Thus, we can state that SEMS placement for a patient who will survive long enough to require the second stent is cost-effective when the cost of ERCP is at least higher than US $ 1518; otherwise PS placement is more cost-effective.

Table 3 Incremental cost-effectiveness ratio analysis of a second self-expandable metallic stent *vs* plastic stent

Studies	*n*	Approximate cost of each procedure (US $)		Mean number of ERCPs		ICER (US $)
		PS	SEMS	PS	SEMS	
Tham *et al*[14] 1998	38	1044	1956	1.44	1.31	7015
Rogart *et al*[17] 2008	27	2289	3807	1.27	0.89	1518
Ridtitid *et al*[18] 2010	32	460	1500	2	2.45	2311

ICER: Incremental cost-effectiveness ratio; ERCP: Endoscopic retrograde cholangiopancreatography; SEMS: Self-expandable metallic stent; PS: Plastic stent.

Mechanical cleaning with balloon

Generally, mechanical cleaning is performed by flushing with water or saline solution and sludge/debris extraction can succeed with an inflated balloon sweeping through the stent. Hypothetically, this method is definitely correct for an occlusion by only sludge or debris. Three studies compared this procedure to a second stent insertion as stent-in-stent after SEMS occlusion[14,15,17] (shown in Table 2). Bueno *et al*[15] suggested that mechanical cleaning was less effective than SEMS and PS stent insertions (median duration of stent patency after re-intervention 21 d; range 3-263 d, 192 d; range 81-257 d, and 90 d; range 11-393 d, respectively). A similar outcome has also been shown by Rogart *et al*[17] (median days to re-intervention 43 d, 172 d and 66 d; $P < 0.05$ respectively). Although, Tham *et al*[14] demonstrated no significant differences in the durations of the biliary patency among the three methods, there was a trend toward lower patency duration in a group who underwent mechanical cleaning when compared with groups who underwent SEMS and PS insertions (median duration of second patency 34 d; 95% CI: 30-38 d, 75 d; 95% CI: 43-107 d, 90 d; 95% CI: 71-109 d, respectively).

PERCUTANEOUS MANAGEMENT

Percutaneous transhepatic biliary drainage (PTBD) is effective and appropriate for both tumor ingrowth and overgrowth. It is an alternative intervention after failed endoscopic management, particularly in a patient with post bilateral SEMS insertion for hilar block who has an inaccessible desired intrahepatic duct *via* endoscopy. However, the main disadvantages of PTBD are pain, inconvenience and volume/electrolyte loss[18,27]. Our previous study reported that PTBD for re-drainage after SEMS occlusion provided no difference in patency time when compared with PS insertion (75 d; 95% CI: 36-113 d *vs* 60 d; 95% CI: 51-68 d; $P > 0.05$)[18]. However, its patency duration was significantly shorter than the second SEMS (75 d; 95% CI: 36-113 d *vs* 100 d; 95% CI: 72-127 d; $P < 0.05$)[18]. In addition, we found that the main cause of PTBD occlusion was tube re-clogging by debris. Alternatively, a percutaneous approach can provide internal drainage by placing SEMS either directly or under a rendezvous technique[28].

CONCLUSION

In summary, the current management of occluded SEMS includes a second stent insertion (covered SEMS, uncovered SEMS or PS), mechanical cleaning and percutaneous drainage. Mechanical cleaning with a balloon is less effective in a patient with concomitant tumor ingrowth. Endoscopic insertion of SEMS or PS is equally effective for SEMS occlusion in a patient with short survival. In a patient with longer survival and where the cost of ERCP in that institution is higher than US $ 1518, another SEMS insertion is preferred. PTBD is an alternative method when an endoscopic approach is impossible.

REFERENCES

1 **Andersen JR**, Sørensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989; **30**: 1132-1135
2 **Smith AC**, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**: 1655-1660
3 **Huibregtse K**, Cheng J, Coene PP, Fockens P, Tytgat GN. Endoscopic placement of expandable metal stents for biliary strictures--a preliminary report on experience with 33 patients. *Endoscopy* 1989; **21**: 280-282
4 **Castaño R**, Lopes TL, Alvarez O, Calvo V, Luz LP, Artifon EL. Nitinol biliary stent versus surgery for palliation of distal malignant biliary obstruction. *Surg Endosc* 2010; **24**: 2092-2098
5 **Moss AC**, Morris E, Leyden J, MacMathuna P. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. *Cancer Treat Rev* 2007; **33**: 213-221
6 **Knyrim K**, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993; **25**: 207-212
7 **Schmassmann A**, von Gunten E, Knuchel J, Scheurer U, Fehr HF, Halter F. Wallstents versus plastic stents in malignant biliary obstruction: effects of stent patency of the first and second stent on patient compliance and survival. *Am J Gastroenterol* 1996; **91**: 654-659
8 **Perdue DG**, Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Overby CS, Ryan ME, Bochna GS, Snady HW, Moore JP. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. *J Clin Gastroenterol* 2008; **42**: 1040-1046
9 **Rerknimitr R**, Kongkam P, Kullavanijaya P. Outcome of self-expandable metallic stents in low-grade versus advanced hilar obstruction. *J Gastroenterol Hepatol* 2008; **23**: 1695-1701
10 **Davids PH**, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; **340**: 1488-1492
11 **Kaassis M**, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, Canard JM, Fritsch J, Rey JF, Burtin P. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. *Gastroin-*

test Endosc 2003; **57**: 178-182
12 **O'Brien S**, Hatfield AR, Craig PI, Williams SP. A three year follow up of self expanding metal stents in the endoscopic palliation of longterm survivors with malignant biliary obstruction. *Gut* 1995; **36**: 618-621
13 **Leung J**, Rahim N. The role of covered self-expandable metallic stents in malignant biliary strictures. *Gastrointest Endosc* 2006; **63**: 1001-1003
14 **Tham TC**, Carr-Locke DL, Vandervoort J, Wong RC, Lichtenstein DR, Van Dam J, Ruymann F, Chow S, Bosco JJ, Qaseem T, Howell D, Pleskow D, Vannerman W, Libby ED. Management of occluded biliary Wallstents. *Gut* 1998; **42**: 703-707
15 **Bueno JT**, Gerdes H, Kurtz RC. Endoscopic management of occluded biliary Wallstents: a cancer center experience. *Gastrointest Endosc* 2003; **58**: 879-884
16 **Togawa O**, Kawabe T, Isayama H, Nakai Y, Sasaki T, Arizumi T, Matsubara S, Ito Y, Yamamoto N, Sasahira N, Hirano K, Tsujino T, Toda N, Tada M, Yoshida H, Omata M. Management of occluded uncovered metallic stents in patients with malignant distal biliary obstructions using covered metallic stents. *J Clin Gastroenterol* 2008; **42**: 546-549
17 **Rogart JN**, Boghos A, Rossi F, Al-Hashem H, Siddiqui UD, Jamidar P, Aslanian H. Analysis of endoscopic management of occluded metal biliary stents at a single tertiary care center. *Gastrointest Endosc* 2008; **68**: 676-682
18 **Ridtitid W**, Rerknimitr R, Janchai A, Kongkam P, Treeprasertsuk S, Kullavanijaya P. Outcome of second interventions for occluded metallic stents in patients with malignant biliary obstruction. *Surg Endosc* 2010; **24**: 2216-2220
19 **Cho JH**, Jeon TJ, Park JY, Kim HM, Kim YJ, Park SW, Chung JB, Song SY, Bang S. Comparison of outcomes among secondary covered metallic, uncovered metallic, and plastic biliary stents in treating occluded primary metallic stents in malignant distal biliary obstruction. *Surg Endosc* 2011; **25**: 475-482
20 **Isayama H**, Komatsu Y, Tsujino T, Sasahira N, Hirano K, Toda N, Nakai Y, Yamamoto N, Tada M, Yoshida H, Shiratori Y, Kawabe T, Omata M. A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. *Gut* 2004; **53**: 729-734
21 **Nakai Y**, Isayama H, Komatsu Y, Tsujino T, Toda N, Sasahira N, Yamamoto N, Hirano K, Tada M, Yoshida H, Kawabe T, Omata M. Efficacy and safety of the covered Wallstent in patients with distal malignant biliary obstruction. *Gastrointest Endosc* 2005; **62**: 742-748
22 **Zhang H**, Tsang TK, Jack CA. Bile glycoprotein mucin in sludge occluding biliary stent. *J Lab Clin Med* 2003; **142**: 58-65
23 **Weickert U**, Venzke T, König J, Janssen J, Remberger K, Greiner L. Why do bilioduodenal plastic stents become occluded? A clinical and pathological investigation on 100 consecutive patients. *Endoscopy* 2001; **33**: 786-790
24 **Rerknimitr R**, Kladcharoen N, Mahachai V, Kullavanijaya P. Result of endoscopic biliary drainage in hilar cholangiocarcinoma. *J Clin Gastroenterol* 2004; **38**: 518-523
25 **Saleem A**, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. *Gastrointest Endosc* 2011; **74**: 321-327.e1-3
26 **Ridtitid W**, Rerknimitr R, Janchai A, Kongkam P, Treeprasertsuk S, Kullavanijaya P. Reply to Dr. Viroj Wiwanikit. *Surg Endosc* 2012; **26**: 278-279
27 **Ferrucci JT**, Mueller PR, Harbin WP. Percutaneous transhepatic biliary drainage: technique, results, and applications. *Radiology* 1980; **135**: 1-13
28 **Cwikiel W**. Percutaneous management of occluded biliary duct endoprostheses. *Acta Radiol* 2000; **41**: 338-342

S- Editor Yang XC **L- Editor** Roemmele A **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.162

World J Gastrointest Endosc 2012 May 16; 4(5): 162-166
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

Eduardo Redondo-Cerezo, PhD, Professor, *Series Editor*

Endoscopic submucosal dissection for superficial esophageal neoplasms

Satoshi Ono, Mitsuhiro Fujishiro, Kazuhiko Koike

Satoshi Ono, Center for Epidemiology and Preventive Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan
Mitsuhiro Fujishiro, Department of Endoscopy and Endoscopic Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan
Kazuhiko Koike, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan
Author contributions: Ono S, Fujishiro M and Koike K contributed equally to this paper.
Correspondence to: Satoshi Ono, MD, PhD, Center for Epidemiology and Preventive Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan. satoshi-tky@umin.ac.jp
Telephone: +81-3-38155411 Fax: +81-3-58008806
Received: October 13, 2011 Revised: April 2, 2012
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

Endoscopic submucosal dissection (ESD) is currently accepted as the major treatment modality for superficial neoplasms in the gastrointestinal tract including the esophagus. An important advantage of ESD is its effectiveness in resecting lesions regardless of their size and severity of fibrosis. Based on excellent outcomes for esophageal neoplasms with a small likelihood of lymph node metastasis, the number of ESD candidates has increased. On the other hand, ESD still requires highly skilled endoscopists due to technical difficulties. To avoid unnecessary complications including perforation and postoperative stricture, the indications for ESD require careful consideration and a full understanding of this modality. This article, in the highlight topic series, provides detailed information on the indication, procedure, outcome, complications and their prevention in ESD of superficial esophageal neoplasms.

Key words: Complications; Endoscopic submucosal dissection; Esophageal neoplasm; Indication; Outcome; Squamous cell carcinoma

Peer reviewer: Mauro Manno, MD, Nuovo Ospedale Civile S. Agostino-Estense, Gastroenterology and Digestive Endoscopy Unit, Via Giardini, 1355, 41126 Baggiovara di Modena (Mo), Italy

Ono S, Fujishiro M, Koike K. Endoscopic submucosal dissection for superficial esophageal neoplasms. *World J Gastrointest Endosc* 2012; 4(5): 162-166 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/162.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.162

INTRODUCTION

Endoscopic submucosal dissection (ESD), which was developed for stomach neoplasms[1-3], has also been accepted as an established procedure for superficial neoplasms of the esophagus. The most important advantage of ESD is its effectiveness in resecting large-sized lesions in an *en bloc* fashion, as conventional endoscopic mucosal resection (EMR) sometimes results in piece-meal resection followed by a high rate of local recurrence[4]. ESD theoretically enables the resection of lesions regardless of their size and severity of fibrosis. Based on previously reported excellent outcomes, the number of ESD candidates with esophageal neoplasms have increased similar to those with stomach neoplasms undergoing ESD[5,6]. In this review, an outline of the current status of ESD for esophageal neoplasms is described.

INDICATIONS

As with candidates suffering from other gastrointestinal

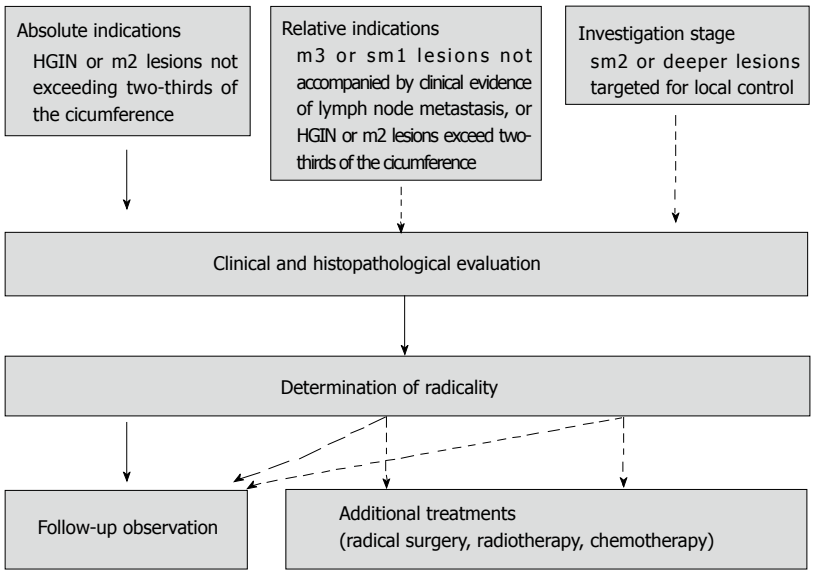


Figure 1 Indication for endoscopic resection in the Japan Esophageal Society guideline.

tract diseases, patients scheduled for esophageal ESD are determined by two factors: a small likelihood of lymph node metastasis and technical resectability.

The former was determined by a large number of surgical resection cases with extensive histological investigations[7,8]. These studies showed that high-grade intraepithelial neoplasms (HGINs), including noninvasive squamous cell carcinomas (SCCs) (carcinoma *in situ*, m1) and intramucosal invasive SCCs limited to the lamina propria mucosae (m2) without vessel infiltration have no lymph node or distant metastases. Accordingly, in the national guideline of the Japan Esophageal Society (JES), these are allocated to absolute indication of endoscopic local resection including ESD[9]. Deeper lesions of 200 μm in the submucosa (m3 and sm1) are allocated to relative indication because they have a probability of lymph node metastasis of 10%-15% (Figure 1).

The latter depends principally on circumferential extension. In the JES guideline, absolute indication is limited to lesions of less than two-thirds of the circumferential extension. Lesions of more than two-thirds of the circumferential extension are allocated to relative indication. Circumferential extension not only affects technical resectability but also the risk of postoperative stricture after ESD, as mentioned below[10,11]. In this regard, ESD can minimize the risk of unnecessary postoperative stricture by precisely controlling the resected area. This is another advantage of ESD in avoiding excessive resection compared with conventional EMR.

Therefore, considering the above factors, we decided that in patients with lesions allocated to relative indication general status and comorbidities should be considered.

On the other hand, the indication for ESD of esophageal adenocarcinoma is still controversial because the incidence of esophageal adenocarcinoma is extremely low in Japan where ESD is widely performed. However, Hirasawa *et al*[12] reported a promising long-term outcome after ESD for differentiated adenocarcinoma of the esophagogastric junction limited to a depth of invasion of 500 μm in the submucosa. In this regard, ESD for esophageal adenocarcinoma might also be acceptable although further research data is mandatory especially in Western countries.

PROCEDURES

ESD requires special electrosurgical knives, such as the insulated-tipped (IT) knife, the flex knife, the hook knife, the triangle-tip (TT) knife, and the dual knife[2,13,14]. The results obtained using each of these electrosurgical knives are similar to those in patients with stomach neoplasms. Therefore, selection of these knives depends mainly on operator preference and expertise. Of these knives, we mostly use the dual knife (KD-650L, Olympus) for ESD of the esophagus. The knife is fixed at a length of 2 mm during procedures.

We mainly use a slim, single-channel, high-definition endoscope with a water-jet system (GIF-Q260J; Olympus, Tokyo, Japan) and a high frequency generator (VIO300; ERBE Elektromedizin, Tübingen, Germany) with a special cutting mode and coagulation current, as mentioned below. The transparent attachment is fitted to the top of the endoscope to maintain a constant endoscopic view and to create counter-traction on connective tissue during dissection.

In our recent ESD procedures, patients underwent ESD under conscious sedation using periodic intravenous administration of diazepam (in total, 0.1-0.5 mg/kg body weight) and pentazocine (in total, 0.3-0.7 mg/kg body weight) or under general anesthesia with careful consideration of the estimated operation time, location of the lesion, and general status of the patient. Prophylactic antibiotics are not administered routinely as there is no evidence for their use during the periendoscopic

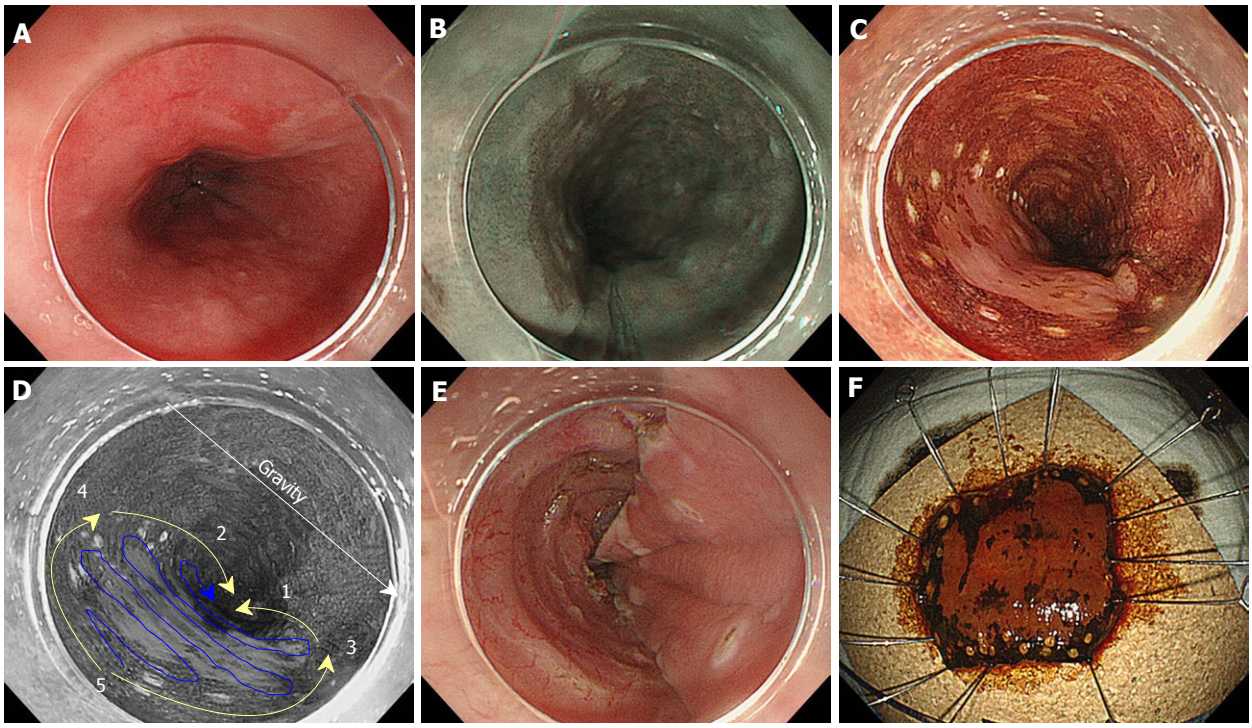


Figure 2 Endoscopic submucosal dissection of an esophageal neoplasm. A: The reddish mucosa in the anterior wall of the middle thoracic esophagus shown by conventional endoscopy with white light; B: The brownish mucosa in one-third of the circumferential extension shown by endoscopy with narrow band imaging; C: Marking around the lesion under chromoendoscopy with iodine staining to demarcate the lesion; D: Mucosal incision at the anal side (yellow line 1-2), followed by incision at the oral side (yellow line 3-4). Incision is made from the lower side to lift it up from the collection of fluid taking gravity into consideration. After circumferential incision, dissection of the submucosa is begun from the oral end to the anal end (blue line 5); E: Artificial ulcer after removal of the lesion; F: Resected specimen in an *en bloc* fashion.

period. Second-generation cephalosporins are only administered during a few days of fasting in cases with perforation.

ESD procedures in the esophagus are principally the same as those in other areas of the gastrointestinal tract. They consist of four steps; marking, lifting, incision and dissection (Figure 2). For marking around the lesion, dots are placed about 5 mm outside the lesion using soft coagulation mode (effect 5, output 50 W). To demarcate the lesion margin, narrow band imaging with magnifying endoscopy and Lugol staining are very useful. In lifting, we mainly use 0.4% hyaluronic acid preparation (MucoUp; Johnson and Johnson KK, Tokyo, Japan) double diluted with normal saline for submucosal injection to lift the lesion up from the muscular layer. Approximately 2 mL solution is injected into the submucosa, and the injection is repeated several times until the mucosa is lifted to an acceptable level. An incision in the mucosa around the lesion is made using cutting mode (Endocut I, effect 3, duration 3, interval 3). The anal half of the incision which is horseshoe-shaped is completed first, followed by the oral half. Incision from the left-wall side is preferable with consideration of gravity as submerging the lesion in the collection of fluid can disturb the endoscopic view. Dissection of the submucosa is begun from the oral end to the anal end using swift coagulation mode (effect 4, output 40 W). It is also mandatory to control minor bleeding because this can also disturb the endoscopic view. To control bleeding, hemostatic forceps are used in soft coagulation mode (effect 5, 50 W). The water-jet system is also useful to maintain a clear view and to treat visible bleeding vessels.

OUTCOMES AND COMPLICATIONS

Outstanding *en bloc* resection rates (90%-100%), curative resection rates (88%-97%), and low rates of major complications (perforation, 0-6%; bleeding, 0%) have been reported as shown in Table 1[14-18]. In a previous comparative study of conventional EMR and ESD, ESD was reported to be more reliable in achieving curative resection due to the higher local recurrence rate after conventional EMR[4]. Although perforation can be a substantial risk, our experience has shown that cases of minor perforation can recover well following conservative treatment if noticed as soon as it occurs. With regard to long-term outcomes, the cause-specific survival rates at 5 years for patients with HGINs/m2 SCCs and m3/sm SCCs are reported to be 100% and 85%, respectively[18]. These survival rates are consistent with the findings of a comparative study of conventional EMR and surgical resection[19]. Considering the higher comorbidities of esophagoectomy and the higher incidence of incomplete resection by conventional EMR[4,20], ESD is accepted as a superior treatment option for esophageal squamous cell neoplasms.

Table 1 Recent outcomes for endoscopic submucosal dissection of esophageal neoplasms

Author	Yr	Electrosurgical knife	*En bloc* resection rate	Local recurrence rate	Perforation
Oyama[14]	2005	Hook knife	95% (95/102)	0% (0/102)	6% (6/102)
Ishihara[17]	2008	Hook knife	100% (31/31)	0% (31/31)	3% (1/31)
Ono[18]	2009	Flex knife or Splash needle	100% (107/107)	1% (1/87)	4% (4/107)
Repici[16]	2010	Hook knife	90% (18/20)	0% (0/20)	10% (2/20)
Ishii[15]	2010	Flex knife or Hook knife	100% (37/37)	0% (0/37)	0% (0/37)

On the other hand, postoperative stricture has arisen as a major concern during long-term follow-up because postoperative stricture can compromise patient quality of life. Almost all semicircular resections can cause postoperative stricture shortly after ESD[10,18]. Although various effective preventive treatments have been reported including balloon dilatation, and local injection or systemic administration of steroids[21-24], there is still no solid protocol for preventive treatment. In addition, perforation during dilatation for esophageal stricture is reported to be another risk[25].

FUTURE PERSPECTIVES

ESD has been proved to be a promising technique for esophageal neoplasms. Although there is a substantial risk of perforation and postoperative stricture, these are preventable complications. However, ESD techniques still require highly skilled endoscopists. To prevent severe complications and to popularize ESD as a safe and easy treatment, further advances in the technique and protocol during the periendoscopic period is mandatory.

In terms of the prevention of perforation, effective use of ESD and conventional EMR is important to minimize unnecessary perforation. Ishihara *et al*[17] reported that no significant differences were found between *en bloc* and curative resection rates in EMR using a transparent cap (EMR-C) and ESD in lesions less than 15 mm. They also proposed that ESD may be the best method for lesions more than 20 mm. In other words, EMR-C might be an effective substitute for treating lesions less than 15 mm, depending on the general status of the patient and skill-level of the endoscopist.

In terms of the prevention of postoperative stricture, more evidence is needed to identify high-risk patients and to treat them appropriately. In this regard, a predictive flowchart which we previously proposed might be an option in coping with this problem[11]. In addition, new technologies, such as a biodegradable stent or an autologous mucosal epithelial sheet, may be a breakthrough in overcoming postoperative stricture[26,27].

Undoubtedly, the final goal of ESD for esophageal neoplasms is not to resect the lesions in an *en bloc* fashion, but to prevent the patient dying of esophageal cancer without unnecessary risks. To achieve this goal, standardization of ESD procedures including preventive protocols for complications during the periendoscopic period should be established as soon as possible.

REFERENCES

1 **Yamamoto H**, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, Sugano K. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointest Endosc* 2002; **56**: 507-512

2 **Yahagi N**, Fujishiro M, Kakushima N, Kobayashi K, Hashimoto T, Oka M, Iguchi M, Enomoto S, Ichinose M, Niwa H and Omata M. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). *Dig Endosc* 2004; **16**: 34-38

3 **Oda I**, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, Bhandari P, Emura F, Saito D and Ono H. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005; **17**: 54-58

4 **Katada C**, Muto M, Manabe T, Ohtsu A, Yoshida S. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. *Gastrointest Endosc* 2005; **61**: 219-225

5 **Gotoda T**. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11

6 **Goto O**, Fujishiro M, Kodashima S, Ono S, Omata M. Outcomes of endoscopic submucosal dissection for early gastric cancer with special reference to validation for curability criteria. *Endoscopy* 2009; **41**: 118-122

7 **Natsugoe S**, Baba M, Yoshinaka H, Kijima F, Shimada M, Shirao K, Kusano C, Fukumoto T, Mueller J, Aikou T. Mucosal squamous cell carcinoma of the esophagus: a clinicopathologic study of 30 cases. *Oncology* 1998; **55**: 235-241

8 **Tajima Y**, Nakanishi Y, Ochiai A, Tachimori Y, Kato H, Watanabe H, Yamaguchi H, Yoshimura K, Kusano M, Shimoda T. Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: analysis of 240 surgically resected tumors. *Cancer* 2000; **88**: 1285-1293

9 **Kuwano H**, Nishinuma Y, Ohtsu A, Kato H, Kitagawa Y, Tamai S, Toh Y and Matsubara H. Guidelines for diagnosis and treatment of carcinoma of the esophagus. April 2007 edition: part I. Edited by the Japan Esophageal Society. *Esophagus* 2008; **5**: 61-73

10 **Mizuta H**, Nishimori I, Kuratani Y, Higashidani Y, Kohsaki T, Onishi S. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. *Dis Esophagus* 2009; **22**: 626-631

11 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. *Endoscopy* 2009; **41**: 661-665

12 **Hirasawa K**, Kokawa A, Oka H, Yahara S, Sasaki T, Nozawa A, Tanaka K. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. *Gastrointest Endosc* 2010; **72**: 960-966

13 **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

14 **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

15 **Ishii N**, Horiki N, Itoh T, Uemura M, Maruyama M, Suzuki S, Uchida S, Izuka Y, Fukuda K, Fujita Y. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife is a safe and effective treatment for superficial esophageal neoplasias. *Surg Endosc*

2010; **24**: 335-342
16 **Repici A**, Hassan C, Carlino A, Pagano N, Zullo A, Rando G, Strangio G, Romeo F, Nicita R, Rosati R, Malesci A. Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. *Gastrointest Endosc* 2010; **71**: 715-721
17 **Ishihara R**, Iishi H, Uedo N, Takeuchi Y, Yamamoto S, Yamada T, Masuda E, Higashino K, Kato M, Narahara H, Tatsuta M. Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. *Gastrointest Endosc* 2008; **68**: 1066-1072
18 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. *Gastrointest Endosc* 2009; **70**: 860-866
19 **Shimizu Y**, Tsukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Long-term outcome after endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper. *Gastrointest Endosc* 2002; **56**: 387-390
20 **Shimura T**, Sasaki M, Kataoka H, Tanida S, Oshima T, Ogasawara N, Wada T, Kubota E, Yamada T, Mori Y, Fujita F, Nakao H, Ohara H, Inukai M, Kasugai K, Joh T. Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. *J Gastroenterol Hepatol* 2007; **22**: 821-826
21 **Ezoe Y**, Muto M, Horimatsu T, Morita S, Miyamoto S, Mochizuki S, Minashi K, Yano T, Ohtsu A, Chiba T. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. *J Clin Gastroenterol* 2011; **45**: 222-227
22 **Yamaguchi N**, Isomoto H, Nakayama T, Hayashi T, Nishiyama H, Ohnita K, Takeshima F, Shikuwa S, Kohno S, Nakao K. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc* 2011; **73**: 1115-1121
23 **Kochhar R**, Makharia GK. Usefulness of intralesional triamcinolone in treatment of benign esophageal strictures. *Gastrointest Endosc* 2002; **56**: 829-834
24 **Altintas E**, Kacar S, Tunc B, Sezgin O, Parlak E, Altiparmak E, Saritas U, Sahin B. Intralesional steroid injection in benign esophageal strictures resistant to bougie dilation. *J Gastroenterol Hepatol* 2004; **19**: 1388-1391
25 **Takahashi H**, Arimura Y, Okahara S, Uchida S, Ishigaki S, Tsukagoshi H, Shinomura Y, Hosokawa M. Risk of perforation during dilation for esophageal strictures after endoscopic resection in patients with early squamous cell carcinoma. *Endoscopy* 2011; **43**: 184-189
26 **Ohki T**, Yamato M, Murakami D, Takagi R, Yang J, Namiki H, Okano T, Takasaki K. Treatment of oesophageal ulcerations using endoscopic transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets in a canine model. *Gut* 2006; **55**: 1704-1710
27 **Saito Y**, Tanaka T, Andoh A, Minematsu H, Hata K, Tsujikawa T, Nitta N, Murata K, Fujiyama Y. Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. *Dig Dis Sci* 2008; **53**: 330-333

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.167

World J Gastrointest Endosc 2012 May 16; 4(5): 167-179
ISSN 1948-5190 (online)

REVIEW

Endoscopic extraction of large common bile duct stones: A review article

Gerasimos Stefanidis, Christos Christodoulou, Spilios Manolakopoulos, Ram Chuttani

Gerasimos Stefanidis, Christos Christodoulou, Department of Gastroenterology, Athens Naval Hospital, 70 Deinokratous St, 115 21 Athens, Greece
Spilios Manolakopoulos, 2nd Department of Internal Medicine, Athens University Medical School, Hippokration General Hospital of Athens, 114 Vas. Sophias Ave, 115 27 Athens, Greece
Ram Chuttani, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, United States
Author contributions: Stefanidis G designed, wrote and revised the paper; Christodoulou C reviewed the literature and wrote the paper; Manolakopoulos S reviewed the literature and revised the paper; Chuttani R revised the paper.
Correspondence to: Gerasimos Stefanidis, MD, Department of Gastroenterology, Athens Naval Hospital, 70 Deinokratous St, 115 21, Athens, Greece. stefanidis2001@yahoo.com
Telephone: +30-210-7261871 Fax: +30-210-7261368
Received: October 13, 2011 Revised: April 14, 2012
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

Since therapeutic endoscopic retrograde cholangiopancreatography replaced surgery as the first approach in cases of choledocolithiasis, a plethora of endoscopic techniques and devices appeared in order to facilitate rapid, safe and effective bile duct stones extraction. Nowadays, endoscopic sphincterotomy combined with balloon catheters and/or baskets is the routine endoscopic technique for stone extraction in the great majority of patients. Large common bile duct stones are treated conventionally with mechanical lithotripsy, while the most serious complication of the procedure is "basket and stone impaction" that is predominately resolved surgically. In cases of difficult, impacted, multiple or intrahepatic stones, more sophisticated procedures have been used. Electrohydraulic lithotripsy and laser lithotripsy are performed using conventional mother-baby scope systems, ultra-thin cholangioscopes, thin endoscopes and ultimately using the novel single use, single operator SpyGlass Direct Visualization System, in order to deliver intracorporeal shock wave energy to fragment the targeted stone, with very good outcomes. Recently, large balloon dilation after endoscopic sphincterotomy confirmed its effectiveness in the extraction of large stones in a plethora of trials. When compared with mechanical lithotripsy or with balloon dilation alone, it proved to be superior. Moreover, dilation is an ideal alternative in cases of altered anatomy where access to the papilla is problematic. Endoscopic sphincterotomy followed by large balloon dilation represents the onset of a new era in large bile duct stone extraction and the management of "impaction" because it seems that is an effective, inexpensive, less traumatic, safe and easy method that does not require sophisticated apparatus and can be performed widely by skillful endoscopists. When complete extraction of large stones is unsuccessful, the drainage of the common bile duct is mandatory either for bridging to the final therapy or as a curative therapy for very elderly patients with short life expectancy. Placing of more than one plastic endoprostheses is better while the administration of Ursodiol is ineffective. The great majority of patients with large stones can be treated endoscopically. In cases of unsuccessful stone extraction using balloons, baskets, mechanical lithotripsy, electrohydraulic or laser lithotripsy and large balloon dilation, the patient should be referred for extracorporeal shock wave lithotripsy or a percutaneous approach and finally surgery.

Key words: Large bile duct stones; Endoscopic sphincterotomy; Papillary balloon dilation; Large papillary balloon dilation; Mechanical lithotripsy; Electrohydraulic lithotripsy; Laser lithotripsy

Peer reviewer: Hirokazu Takahashi, MD, PhD, Assistant Professor, Gastroenterology Division, Yokohama City University

Graduate School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan

Stefanidis G, Christodoulou C, Manolakopoulos S, Chuttani R. Endoscopic extraction of large common bile duct stones: A review article. *World J Gastrointest Endosc* 2012; 4(5): 167-179 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/167.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.167

INTRODUCTION

Bile duct stone management has changed dramatically in the last two decades when open surgery has been replaced by per-oral endoscopic procedures. Nowadays, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) is performed worldwide as the first approach in the management of extrahepatic bile duct stones and is superior to surgical or percutaneous approaches, although it can be challenging in some cases[1]. Endoscopic therapy involves stone extraction using conventional methods after performing endoscopic biliary sphincterotomy. The routine devices used for stone retrieval are balloon catheters, Dormia baskets and mechanical lithotripters. Alternatively, other therapeutic options such as intra or extracorporeal shock wave lithotripsy may offer adjuvant therapy in selected patients or in particularly challenging cases. In the last thirty years, endoscopic biliary sphincterotomy (EST) is considered the established method for bile duct stone extraction and it is well known that the great majority of the stones can be successfully removed by using conventional techniques. However, stone removal can be difficult and unsuccessful in less than 10% of cases, when managing large, barrel-shaped, piston-like, multiple stones, strictured common bile duct (CBD) or in cases of altered anatomy[2].

In this article, we try to approach the large stone issue, reviewing the current literature and searching for alternatives.

LARGE BILE DUCT STONES

The main problem that has to be solved regarding endoscopic extraction of large bile duct stones is extraction of something larger than the orifice through which access has been achieved. This is obtained by either enlarging the ampulla of vater (cutting, dilation) or reducing the size of the stone that has to be extracted (fragmentation, crushing) using adequate devices[3]. The second problem is the size of the stone itself.

It is not clear and there is no consensus in the literature of the definition of "large stone". Some authors use the term "difficult stone" when referring to a large stone size, although actually "difficult" could mean multiple, intrahepatic, barrel-shaped, impacted stones or the presence of another comorbidity. Stricture below the stone, stenosis of the intrapancreatic CBD or difficult anatomic access to the papilla caused by duodenal diverticuli are conditions which increase the rate of unsuccessful stone retrieval[3]. Overall, only a small number of "difficult stones" are "large stones"[4]. Regardless of the chosen endoscopic procedure, the large stone issue is still a concern due to high failure rates, even for experienced endoscopists.

Many authors define a stone larger than 10-15 mm in diameter as "large". Others support that a stone with a diameter equal to the CBD diameter is large[3]. Sharma *et al*[5], in a recent letter to the Editor of the *World Journal of Gastroenterology*, tried to redefine the "large stone", analyzing retrospectively three hundred and four patients with CBD calculi. Patients were enrolled in two groups. The first group comprised of patients with a median stone diameter of 15.5 mm and a median lower CBD diameter of 16 mm, while the second group enrolled patients with a median CBD stone diameter of 8 mm and a median lower CBD diameter of 3 mm. In the second group, the stones were not extracted successfully as the size was disproportionate to the lower CBD diameter. Therefore, definition of a large stone should include the lower CBD diameter so that any stone exceeding that should be called "large", regardless of the stone size.

ENDOSCOPIC SPHINCTEROTOMY: "FIRST STEP ON THE MOON"

In 1974, Kawai *et al*[6] first described EST, currently considered worldwide as the established method, as the first step for CBD stone clearance. The size of the EST has to be adapted to the CBD and papilla size. Treated with conventional EST followed by conventional balloons and baskets, up to 90% of CBD stones can be extracted. On the other hand, EST alone for the removal of large stones (over 15 mm in diameter) is usually unsuccessful.

Lauri *et al*[7] reported successful large stone removal in only 12% of cases using EST alone. Sphincterotomy is a technically complex endoscopic procedure used either in cases of surgically altered anatomy or of a small papilla where there is not enough intraluminal room for a safe complete muscular fiber incision. The current, in combination with mechanical damage, may develop well known complications (bleeding, pancreatitis, cholangitis, perforation). As a consequence, limitation of EST to provide successful removal of large CBD stones and the reported complications ranging from 5% to 10%[8] requires alternative endoscopic options in order to overcome these restrictions.

ENDOSCOPIC PAPILLARY BALLOON DILATION

The original attractive concept was to achieve bile duct clearance while maintaining an intact biliary sphincter. As an alternative to EST, in 1982, Staritz *et al*[9] published

the first trial about the possible role of endoscopic papillary balloon dilation (BD) in the management of CBD stones. BD is easily performed with the wire-guided method using a small diameter balloon catheter (usually 8-10 mm), dilating the papilla while intact for 45-60 s prior to EST. Some authors strongly supported that dilating the papilla without cutting it meant that papillary functions are preserved and complication rates decreased when compared to EST[10,11].

A prospective randomized trial from East Asia tried to determine whether a longer duration of dilation (five minutes *vs* the conventional one minute) can expand the papilla in order to permit stone extraction and reduce the rates of pancreatitis. Compared with the conventional one minute, five minutes of BD seemed to improve the efficacy of stone extraction and reduce the risk of pancreatitis[12].

BD without prior EST became a popular method of stone extraction, mainly in Asia, and many studies tried to compare the two techniques, supporting the safety and effectiveness of BD without EST and reporting low complication and mortality rates at the same time[13-15].

A current East Asian study analyzed large stone removal (mean stone size 16.4 mm) in a large series of patients that underwent BD from 10 mm to 20 mm (mean size of dilating balloon 13.2 mm), with the duration of the dilation ranging from 2 to 6 min. The authors reported a remarkable success rate of 81.8% of complete retrieval within the first session; however, the stone recurrence rate after six months of follow-up was considerable with the minimum of complications[16].

Previously, a Japanese group published a well designed controlled prospective trial enrolling two hundred and eighty-two patients with choledocolithiasis from eleven national institutions. Patients were randomized in an EST group and a BD without prior EST group. The authors compared the two techniques and reported that they are approximately equal regarding successful stone extraction and complication rate, so they suggest BD without prior EST as an alternative option to EST[17].

Studies from Western countries revealed completely opposite results. In a randomized controlled multicenter trial, Disario *et al*[18] compared primary BD with EST in patients with choledocolithiasis. The reported outcome was that BD was associated with increased short term morbidity, while two deaths were reported due to severe pancreatitis. This study was stopped at the first analysis, suggesting that BD for stone extraction should be avoided in every day clinical practice.

An American group, searching the Cochrane Library, Medline, Embase and reviewing fifteen randomized trials which included one thousand, seven hundred and sixty-eight patients, reported that primary BD is less successful and more risky, presenting higher rates of pancreatitis when compared with EST[19].

Thus, guidelines for the management of CBD stones published in the "*Gut*" in 2008 suggested that BD should be avoided due to a high risk of severe pancreatitis. With a lot of skepticism, it could be an alternative in a special group of patients with coagulopathy, altered anatomy or the presence of duodenal diverticuli[20].

ENDOSCOPIC SPHINCTEROTOMY FOLLOWED BY LARGE BALLOON DILATION

In the case of large stones, a promising endoscopic technique is EST followed by large balloon dilation (ESLBD). In patients who underwent a prior sphincterotomy, dilation with large balloons to increase the diameter of the distal CBD opening into the duodenal lumen, instead of extending the already existing sphincterotomy, was found to be very safe. Based on this evidence, some endoscopists tried to do it in the same session and it also proved to be very safe. Ersoz *et al*[21] first reported the use of ESLBD as an alternative technique for the management of difficult bile duct stones with a very good outcome.

Recently, Maydeo and Bhandari[22] reported their analysis regarding ESLBD for large stone extraction, enrolling sixty patients with large CBD stones (stone diameter from 12 mm to 20 mm). They performed "maximum" ESLBD using a controlled radial expansion (CRE) balloon from Boston Scientific (Natick, MA) with a diameter range of 12 mm to 15 mm, inflated gradually up to 15 mm. The procedure with the fully inflated balloon duration lasted 30 s. After performing ESLBD, three attempts of stone removal were made using balloons or Dormia baskets. In the case of failure after the third attempt, they performed ML with an Olympus BML-3Q or a Microvasive Trapezoid lithotriptor. Post-procedure, the stones were extracted in 95% of the patients. In 5% of the patients, ML was required, while the most common complication was bleeding in 8.3% of the cases. The trial supported the idea of ESLBD in cases of large stones as an effective, technically easy and safe technique.

Heo *et al*[23] also randomized patients with large stones (over 15 mm in diameter) in an ESLBD group (12 mm to 20 mm balloon diameter, dilation time 60 s) and in an EST group. When EST was performed alone, it was completed to its full length (major EST), whereas combined with dilation it stopped after reaching one third of the full length that could be theoretically reached (minor EST). The reported successful stone removal was 94.4% for the ESLBD group and 96.7% for the EST group, while complication rates were similar between the 2 groups (5% *vs* 7% respectively). Pancreatitis and cholangitis appeared in the same proportion (4% and 1% respectively). ML for stone extraction after failure of the conventional methods was required in 8% of the ESLBD group and in 9% of the EST group. Based on the similar rates of successful stone removal and complications, the analysis suggested ESLBD as an alternative option in large stone endoscopic treatment.

In another series, Minami *et al*[24] enrolled eighty-eight patients with large (over 12 mm in diameter) and/or multiple stones that underwent EST "with small inci-

sion" combined with large dilation using a 20 mm × 5 cm balloon from Boston Scientific (Watertown, MA). Complete stone removal was achieved in 99% of the patients, while the procedure-related complications were bleeding (1%), pancreatitis (1%) and cholangitis (1%). Moreover, the stone extraction procedure was less time consuming compared to EST and BD alone.

In a multi center retrospective trial involving patients with a median stone size of 13 mm, Attasaranya *et al*[25] evaluated the efficacy and complications of the method. Five ERCP referral centers and one hundred and three patients were enrolled in that analysis from 1999 to 2007. Complete stone removal was accomplished in 95% of the procedures with the first attempt, while ML was required in 27% of the cases due to failure of stone extraction after ESLBD. Procedure-related complications developed in 5.4% of the patients, with one case of severe bleeding and one case of cystic duct perforation reported.

In a retrospective Indian trial, ESLBD was performed in cases of large (up to 25 mm in diameter) or difficult stones that could not be extracted with routine methods. ML was required in 10% of cases, 32% of the patients presented minor self-limiting bleeding, and mild pancreatitis occurred in 8% of them[26].

Draganov *et al*[27] evaluated the efficacy and safety of ESLBD in patients with difficult stones who had failed stone extraction with standard techniques after full length EST. Successful complete stone removal was achieved in 95% of the patients, while in 84% the stone clearance was accomplished without additional ML. Mild complications occurred in 6% of the cases.

In another retrospective analysis, Itoi *et al*[28] randomized one hundred and one patients in an ESLBD group and an EST group, comparing outcome, complications, procedural and fluoroscopy time between the two groups. The successful stone removal in the first session was 96% *vs* 85% respectively, higher for the ESLBD group but not statistically significant. ML was required more often (statistically significant) in the EST group than in the ESLBD group (25% *vs* 6%). Total procedure time and total fluoroscopy time in the ESLBD group were significantly shorter (32 min *vs* 40 min and 13 min *vs* 22 min respectively).

Investigating a large series of patients, a Korean group tried to manage the question of whether a small EST followed by large balloon dilation can reduce the use of ML in patients with large stones. Complete stone removal from the first session was accomplished in 87.5% of the patients in the ESLBD group *vs* 74% in the EST group. ML for large stones was required in 17.9% for the ESLBD group and 45.8% for the EST group. The study suggested that ESLBD could reduce the need for ML in the case of large stones[29]. A Korean series analyzing patients with large stones reported similar conclusions for both techniques[30].

The majority of published series regarding ESLBD for large stones report a success rate of 83% to 99% using balloons with a diameter of 12 mm to 20 mm, dilating up to 60 s (Table 1). Although there are plenty of trials in the literature on the dilation issue, few of them are well designed, randomized and prospective.

Our group reported a prospective randomized controlled trial, the first in the literature that compared ESLBD with EST followed by ML, in order to evaluate the therapeutic benefits and complications between the two options in the management of large stones. Ninety patients with large CBD stones (diameter from 12 mm to 20 mm) were randomized in ESLBD and ML groups. Both groups of patients underwent a complete EST. ESLBD was performed with a CRE balloon with diameter from 15 mm to 20 mm and the duration of dilation after disappearance of the waist of the balloon was 10-12 s. For the ML group, an Olympus BML 4Q, Lithocrush 201 or 202Q was used in order to fragment large stones. Complete stone clearance was achieved in 97.7% in the ESLBD group, while it was lower (91.1%) in the ML group. Complications were observed in 4.4% in the ESLBD group compared with 20% in ML group. The major complication when ML was performed was cholangitis. In one patient from the ESLBD group, a tiny perforation occurred that was treated conservatively with a stent placement. None of our patients died. Our analysis concluded that the two techniques are similar in effectiveness but ESLBD is followed by fewer complications compared to ML. A significant observation was that in patients from the ESLBD group to whom a plastic stent was placed due to residual stone fragments, the CBD was found to be completely clean during the second ERCP that was done to retrieve the stent. In patients from ML group, residual stone material had to be extracted after stent retrieval in that second ERCP[31].

Khan *et al*[32], analyzing eighteen retrospective and prospective studies including more than one thousand, three hundred patients, published a systematic review regarding ESLBD for large stones. The stone size was up to 35 mm; the EST performed was reported as "limited" in nine, "moderate" in four and "large" in four studies. The balloon dilation ranged from 10-20 mm in diameter and the maximum dilation time lasted from 20 s to 60 s. Overall, 0-33% of the patients required complementary ML when successful stone removal with the first ERCP was achieved in 72%-97% of the patients. The complications were pancreatitis (0-9.6%), bleeding (0-12%) and perforation (0-1%).

Recently, a Japanese group reported their first experience with a new prototype large diameter balloon-equipped sphincterotome in a small number of patients. The new device is a combination of a dilating balloon and a sphincterotome and was made by the manufacturers apparently because of the tremendous expansion of this new technique among ERCP units worldwide and the potential commercial need for such a device. In this study, bile duct clearance was accomplished in 94% of the patients when ML was required in 22% of them[33].

Table 1 Endoscopic sphincterotomy plus large balloon dilation in the management of large bile duct stones: outcome, complications

Author	Nr.	Balloon size (mm)	Success rate (%)	Need of ML (%)	Complications (%)
Ersoz *et al*[21] 2003	58	12-20	83	7	16
Maydeo *et al*[22] 2007	62	12-15	92	5	8
Minami *et al*[24] 2007	88	Up to 20	99	1	6
Heo *et al*[23] 2007	200	12-20	97	8	5
Attasaranya *et al*[25] 2008	107	12-18	95	27	6
Misra *et al*[26] 2008	55	15-20	90	10	8
Kim *et al*[30] 2009	55	15-18	85	33	None
Draganov *et al*[27] 2009	44	-	95	11	6
Kim *et al*[29] 2011	149	Up to 20	87	20	-

MECHANICAL LITHOTRIPSY: "THE CLASSIC"

For more than two decades, ML was the unique endoscopic approach for large stone removal after failure of conventional techniques. ML is a relatively inexpensive option and should be available in all ERCP units. The procedure requires capturing the stone within the lithotripter basket into the strong metallic wire mesh, using the same technique as for conventional stone retrieval. After advancement of the sheath onto the basket with the entrapped stone, the handle of the cranking device should be turned slowly in order to reduce the risk of basket break down, to crush the stone and extract it in smaller fragments[34]. The main complication during ML is "basket and stone impaction" that could occur even during a routine stone extraction or in cases of a small diameter stone and is observed in up to 6% of the cases[35,36]. A usual cause of failure is lack of enough space for the basket to open. That makes capturing of the stone unsuccessful.

Two main types of mechanical lithotripters are commercially available: through-the-scope lithotripsy baskets with a reusable cranking handle (integrated device) and another type that is used after removal of the duodenoscope over the basket wires under fluoroscopy (salvage device).

Emergency lithotripsy over the basket is required when the standard basket with the captured stone is impacted. All ERCP units should have the appropriate devices to perform this procedure because the removal of the impacted basket is essential. Although impaction could be managed surgically, nonsurgical endoscopic maneuvers should be attempted by experienced endoscopists in order to avoid it. A comprehensive retrospective study that involved seven American referral centers showed that impaction was resolved by using alternative options like extending prior EST, performing electrohydraulic lithotripsy, by using a per-oral Soehendra lithotripter, performing intracorporeal or extracorporeal lithotripsy, inserting biliary stents and finally surgery. The study concluded that extension of EST and electrohydraulic lithotripsy was the most popular approaches among endoscopists[37].

The most widely used mechanical lithotripters and some of their characteristics are presented in Table 2. ML was first described by Riemann *et al*[38] in 1982. In 1988, Schneider *et al*[36] published one of the first studies referring to ML using self-constructed mechanical lithotripters in a large series of two hundred and nine patients with a median stone diameter of 18 mm, while more than 30% of the enrolled patients had stones over 20 mm in diameter. Authors reported successful lithotripsy in 87.6% of the patients but in cases of very large stones (over 25 mm in diameter), successful lithotripsy decreased to 67.6%.

In a large series that enrolled three hundred and four patients with large stones (over 15 mm in diameter), ML was performed using the Olympus BML-4Q lithotripter. The reported success rate for the first session was 70% and the overall rate of successful stone removal after multiple sessions of ML was 90%. When ML was unsuccessful, patients were referred for surgery. The reported post-procedure complication rates after the first ML session was 3.3% for pancreatitis and 1.4% for cholangitis, while no perforation was reported[39].

A previous American multi center prospective trial that enrolled one hundred and sixteen patients from nine medical institutions, reported that stones with a size of less than 20 mm were associated with high rate of successful removal (90%-100%), while for very large stones, the success rate ranged from 68% to 83%.

The complication rates for pancreatitis and bleeding were not greater than that occurring after EST[40].

Garg *et al*[41] reported the Indian experience of ML using an Olympus mechanical lithotripter and an extraendoscopic lithotripter in cases of impaction in order to remove large stones (over 15 mm in diameter). The overall success rate was 79.3%. Biliary drainage by nasobiliary catheter or stent placement was performed in cases of unsuccessful attempts of stone removal and subsequently the patients were referred for surgical intervention. The study concluded that the impaction, size, shape and composition of the stone could represent some valuable predictive factors for unsuccessful ML.

In another series from Italy, the rate of successful removal of very large stones (over 28 mm in diameter) was 68%, while for smaller stones (less than 10 mm in diameter) it was over 90%. Due to low rates of stone removal in patients with very large stones, surgery or other alternative non-surgical procedures such as extracorporeal shock wave lithotripsy or long term biliary stenting could be a better option[42].

A recent study analyzed five hundred and ninety-two

Table 2 Mechanical lithotripters-basic characteristics

Device (integrated)	Assembly required	Contrast injection capability	Minimum accessory channel
Microvasive Endoscopy, Boston Scientific Corp			
Monolith	No	Yes	3.2 mm
Trapezoid Rx	Yes	Yes	3.2 mm
Alliance Ⅱ handle Olympus America Corp,LithoCrush V	-	-	-
BML-3Q	Yes	Yes	4.2 mm
BML-4Q	Yes	No	3.2 mm
BML – 202Q-204Q	Yes	Yes	4.2 mm
BML – V242QR – 30	Yes	No	4.2 mm
BML – V237QR – 30	Yes	No	3.7 mm
BML – V232QR – 30	Yes	No	3.2 mm
BML – V232QR – 26	Yes	No	3.2 mm
BML – V442QR – 30	Yes	No	4.2 mm
Xeon medical			
Xemex crusher catheter (salvage)	-	No	2.8-3.2 mm
Olympus			
BML – 110A-1	Yes	No	3.2-4.2 mm
MAJ – 403 (sheath)	Yes	No	Remove scope
Cook Endoscopy			
Conquest TTC Lithotriptor Cable			
TTCL – 1 (sheath)	Yes	No	3.2 mm
TTCL – 10 (sheath)	Yes	No	3.7 mm
SLH – 1	-	-	-

patients with choledocholithiasis. Failure to extract difficult or large stones was reported in about 12% of them, while stone impaction happened in 5% of the patients. The stone extraction rate in patients with impaction was 96% and in patients with non-impacted stones it was 97%. The success rate was 96% for stones smaller than 20 mm and 100% for stones more than 20 mm. The procedure was successful in the first session in 81% of the patients while in 19% of them multiple ERCPs were required in order for CBD clearance to be accomplished. Basket impaction occurred in 5.7% of the patients that underwent ML. The impaction was resolved using a second mechanical lithotriptor. Pancreatitis, cholangitis and bleeding rates were lower compared with the non-ML group[43].

ELECTROHYDRAULIC LITHOTRIPSY-LASER LITHOTRIPSY: "THE ALTERNATIVES"

Electrohydraulic lithotripsy (EHL) is a not a widely available technique because it is a second line method of stone therapy. When available, it is used in cases of large stones, in cases of stones above a strictured CBD segment or in cases of stones impacted within the cystic duct, but it can be applied in cases of failure of the conventional techniques. Initially it was used by urologists for the treatment of urinary tract lithiasis. An EHL probe consists of a coaxial bipolar probe and a separate charge unit. A shock wave is generated and an electric spark created, causing an explosive formation of plasma channel and vaporization of the water surrounding the electrode. Continuous saline irrigation is required to provide a media for shock wave energy transmission, to ensure visualization and to clear the debris. Therefore, a nasobiliary catheter is sometimes necessary to irrigate alongside the probe. EHL is usually performed under direct cholangioscopy with the aid of an EHL probe that is inserted in the common bile duct through the working channel of a cholangioscope. The best option is for the procedure to be performed under direct cholangioscopy in order to avoid application of shock waves directly on the duct wall, causing bleeding or perforation.

When direct cholangioscopic control is not available, an EHL probe can be inserted through a modified balloon catheter that centers the probe onto the stone under fluoroscopic guidance. The tip of the EHL probe looks directly at the stone and is positioned 5 mm from the tip of the scope and 1-2 mm from the stone[44]. Shock waves can be delivered in brief pulses that range from a single discharge to continuous discharging by a foot switch device according to manufacturers' recommendations, until the stone is fragmented[45].

In a retrospective multicenter Canadian study, efficacy and safety of EHL was assessed in ninety-four patients with difficult stones, eighty-one of them presenting with large ones (over 20 mm in diameter) referred for endoscopic therapy. EHL was performed under direct cholangioscopy using a "mother-baby" system with the Nortech probe and a Northgate SD-100 generator. Overall, successful stone fragmentation was achieved in 96% of the patients. In 66% of the patients, the fragmentation was complete while in 30% it was partial. The great majority of the patients required one session only for successful stone fragmentation while a small amount of patients underwent additional ML or Extracorporeal Shock Wave Lithotripsy (ESWL). Overall, 18% of the patients presented with post-procedural complications, the most common being recurrent jaundice and/or cholangitis. Rare complications were hemobilia and pancreatitis, while one patient developed a biliary leak that was resolved with stent placement[46].

The currently available mother-baby cholangioscopes are not widely used nowadays due to several disadvantages (high cost, requirement of two skillful endoscopists, difficult maneuverability and fragility, as a baby scope can be easily damaged at the level of the duodenoscope elevator). However, several new choledocoscopes offer therapeutic options for interventions for large stones. One of the novel ultra-slim choledocoscopes with a 2 mm working channel dedicated to EHL and laser lithotripsy is under research. One of the limitations of the ultra slim cholangioscopes is that direct insertion through the ampulla is technically difficult and not always successful[47,48].

SpyGlass Direct Visualization System (DVS) (Boston

Scientific, Natick, MA) is a new tool that enables direct examination of bile ducts, optically-guided tissue sampling and therapeutic interventions. It is a novel single-operator endoscope. The system uses the SpyScope, a 10Fr single-use catheter-cholangioscope that offers four-way maneuverability, one channel for an optical probe and separate irrigation channels and one working channel that permits direct biopsy and EHL or Holmium Laser probes to pass through into the bile ducts. It is reported that is a safe and effective method of lithotripsy for large stone fragmentation[49].

Chen and Pleskow[50] first published the initial experience, evaluating the use of SpyGlass DVS for diagnostic and therapeutic reasons. They reported EHL in a few cases with very good results.

Recently it has been reported that complete stone therapy was achieved in 68% of patients with difficult stones, while the complication rate was comparable to that of conventional ERCP, with cholangitis being the most common adverse event[51].

An American group performed SpyGlass and EHL in twenty-six patients with large CBD stones. EHL was used in thirty-eight patients, while in five cases the probe could not be advanced up to the tip of the SpyScope and in seven cases it could not target the stone. However, it is reported that EHL was effective and most of the patients did not require complementary sessions of therapy[52].

Laser lithotripsy (LL) works with the same principle as EHL and the two methods share the same indications. LL focuses a laser light of a high power density onto the stone and a plasma of a gaseous collection of ions and free electrons is created. This plasma bubble induces cavitation with tensile and compressive waves that conduces stone fragmentation. The laser light wavelength is in the near-infrared spectrum and delivers high energy pulses of about 500 to 1000 mJ[53]. The procedure is usually performed under direct visualization of the stone. The ideal procedure is performed under direct visualization of the stone in order to prevent ductal trauma or perforation. However, when direct cholangioscopy is not available, the LL fiber probe can be inserted through centering balloons under fluoroscopic guidance. The LL units are portable and smaller than a classic endoscope processor tower. The main LL systems are the Holmium: YAG and the frequency-double pulse neodymium:YAG (FREDDY). Subsequently, other "smart" lasers have been designed in order to limit ductal injury, recognizing the difference between soft tissue and stone. Flashlamp Pulse Dye Laser uses Coumarin dye to produce selectively absorbable pigments by 504 nm light. Another system uses Rhodamine 6G dye in order to create a 595 nm wavelength that delivers energy strictly to the targeted stone[54].

The LL probe passes through the working channel of several choledocoscopes. The classic "mother-baby" endoscopic system, the newer ultra-slim upper endoscopes (nasal endoscopes with a 4.9-5 mm diameter and a working channel of 2 mm) and ultimately the SpyGlass DVS are compatible with laser fiber probes.

The disadvantages of LL could be the multiple sessions that are usually required, the fragility of the probe, the expensive equipment and the requirement of two skillful endoscopists.

More than two hundred patients were enrolled in an analysis of the effective fragmentation of difficult stones with pulsed Dye Laser. In 92% of the patients, the procedure was successful and in the majority fragmentation was achieved in one session[55]. Complications of LL include bleeding and cholangitis and are reported in 7% of the patients[56].

Compared with LL, the stone fragments resulting after EHL are usually larger and occasionally have sharp edges. The main advantage of the LL compared with EHL is that the ultra thin laser probe can be inserted through working channels of mini scopes or 5Fr catheters. Both techniques have been reported to be safe and effective[57,58] but they are not widely used in every day clinical practice.

In a recent prospective international cohort from fifteen centers in Europe and the United States, authors evaluated the efficacy and safety of SpyGlass DVS in the treatment of large or difficult stones by performing EHL and LL. All patients had one month of follow-up after cholangioscopy. The mean diameter of the largest stone was 18 mm and in 63% of cases, the stones were impacted. EHL and LL was performed in 69% and conventional methods in 31% of cases. The reported procedural success for the EHL and LL group was 91% and 93% in the conventional group. The adverse events were minimum and resolved without sequel[59].

BILE DUCT STONE DISSOLUTION

Stone dissolution was investigated in the 1980s as an alternative option in elderly patients with co-morbidities, in poor candidates for stone extraction or in cases of failure of stone clearance with other traumatic techniques. We refer herein to the dissolution option, although it does not represent an endoscopic technique of large stone extraction because the placement of a nasobiliary tube *via* ERCP is required. The tip of the nasobiliary catheter has to be placed above the stone in order to provide continuous infusion of adequate chemical agents. Several dissolution agents have been proposed but no particular agent has shown its efficacy. Monooctanoin with an infusion rate of 3-5lt/h is the most studied agent. It is reported that it can dissolve cholesterol stones "*in vitro*" and "*in vivo*". With Methyl tert-butyl ether (MTBE), there is less experience and data for bile duct stones is limited, while EDTA/bile acid solution can dissolve calcium-containing stones. Dissolution agents rarely lead to complete stone disappearance, even although they can shorten and change the stone form, volume and consistency in order to be extracted by routine techniques[60]. The results of these particular

studies were disappointing, with low success rates. Data regarding the use of Mono-octanoin infusion for 4-7 d in a large series of patients indicated complete or partial stone dissolution in 46% of patients, with the major side effect of diarrhea[61]. MTBE in a limited number of patients had a poor outcome and caused side effects such as duodenitis and altered hepatic biochemistry[62].

Therefore, the dissolution option is a rather abandoned method of CBD stone clearance with no application in every day clinical practice.

ENDOPROSTHESES: "ALWAYS DRAIN"

Biliary endoprosthesis (stenting) has been proposed as an alternative for bridging or curative therapy, in the elderly or in cases of co-morbidities in patients who are unlikely to tolerate prolonged endoscopic attempts or surgery[63]. In every day clinical practice, biliary stenting is required on a temporary basis in cases of large, difficult to retrieve stones in order to establish continuous bile drainage, to "keep the route open", to prevent stone enlargement or impaction and, finally, to avoid complete ductal occlusion. The proximal end of the stent has to be placed above the stone and the distal end protrudes through the papilla into the duodenum. Usually 7Fr double pig-tail polyethylene stents are used, while 10-11.5Fr straight stents are usually preferred in cases of large stones associated with CBD stricture. Routine replacement is not required since it appears to obstruct the stent and cause cholangitis[34]. Stent insertion usually is safe and easy, although can be challenging in cases of stenosis of the distal CBD or in altered anatomy where there is no straight access to the papilla.

Some authors support that after biliary stenting for 3-6 mo, some large stones disappear and some other decrease in size or may fragment. That could be an effective adjuvant method to clear large or difficult stones[64].

Jain *et al*[65], in a prospective trial, studied patients with large or difficult to extract stones after the placement of a 7Fr pig-tail stent, repeating ERCP after six months. In 20% of the patients, the stones fragmented spontaneously and the stone clearance was achieved with balloon, while in 35% of patients, the duct was found without stones.

Hong *et al*[66], in a recent trial, reported that EST plus biliary stent placement without performing stone extraction as primary therapy in the treatment of large or multiple stones is a safe and effective method. Following the patients for a median of 120 d after the stent placement, the mean CBD diameter and the stone diameter decreased significantly since pancreatitis occurred in 1.9%. Although it is not sufficiently studied thus far, the procedure when performed using one plastic stent is associated with high rates of stent occlusion and cholangitis within the first 6-36 mo[67,68]. Therefore, multiple double pig-tail stents seem to contribute to a reduction in stone size, especially in cases of large CBD diameter[69].

In another Japanese series, patients with large and/or multiple stones had placement of a 7Fr double pig-tail plastic stent without stone extraction at the initial ERCP. Two months later in the follow-up ERCP, it was seen that larger stones decreased and smaller ones disappeared; however, complication rates after the second ERCP were 13% for cholangitis and 5% for pancreatitis[70].

ALTERED ANATOMY: "THE CHALLENGE"

Therapeutic ERCP for large stone extraction in patients with Billroth Ⅱ gastrectomy, Roux-en-Y reconstruction or Mirizzi syndrome is very challenging and in some cases unsuccessful.

Namely, for the Billroth Ⅱ anastomosis, the crucial part of the procedure is to reach the papilla positioned in the afferent loop. Another problem is what type of endoscope to chose. According to patient's anatomy status, availability and group experience, side-viewing, forward-viewing, single/double balloon or spiral endoscopes can be used.

In most of Billroth Ⅱ patients, the papilla can be easily found in the afferent loop by side-viewing regular duodenoscopes, but in patients with Roux-en-Y it is really difficult and time-consuming[63]. Many endoscopists prefer to use forward-viewing endoscopes in patients with a prior surgery[71]. The main disadvantage of the forward-viewing scopes is the lack of elevator that makes cannulation of an intact papilla difficult as advanced maneuvers are limited due to lack of steerability. Moreover, the working channels of the conventional forward-viewing endoscopes do not permit the use of ML.

EST in patients who underwent gastrectomy is more challenging and difficult. The most popular sphincterotomy technique in Billroth Ⅱ gastrectomy is cutting with a needle-knife over a plastic stent that has been placed beforehand for this reason and is removed immediately after the completion of the sphincterotomy[72].

Although EST or ESLBD have been performed for removal of bile duct stones in patients with Billroth Ⅱ gastrectomy, the reported results are not completely satisfactory. In a recent trial, a Korean group performed stone extraction after limited EST followed by dilation up to 15 mm. ML was required in 11.5% of the cases, while in all cases stones were successfully removed in a maximum of three consecutive sessions without significant complications (bleeding, pancreatitis or perforation). The authors consider ESLBD as an effective and safe method of stone removal in patients with Billroth II gastrectomy[73].

Similar outcomes were reported in a Japanese study. The median stone diameter was 13.5 mm, while in 18% of the cases, complementary ML was needed with no serious complications[74].

BD without a prior EST has also been investigated as an easy method with a theoretically lower risk of bleeding. However, the technique showed limited outcomes because dilating the opening of the biliary sphincter up to 10 mm is not large enough to provide stone extrac-

tion, especially in cases of large stones[75].

Mirizzi syndrome (MS) is a serious complication of gallstone disease. Open surgery remains the classic therapy, while a laparoscopic approach is contraindicated in selected patients due to increased rates of mortality[76]. MS is defined as a chronic extrinsic compression of the common hepatic duct due to cholecystitis and large or impacted gallstones in Hartman's pouch with or without formation of a fistula. It seems that capturing large stones in the common hepatic duct with conventional baskets is difficult. Thus, intracorporeal shock wave techniques for stone fragmentation are needed in order to provide stone bile duct clearance[63].

Per-oral cholangioscopy-guided lithotripsy has been successfully performed in patients with Mirizzi syndrome[77].

In an older large series of patients who underwent endoscopic therapy for Mirizzi syndrome using ML, long-term stenting and extracorporeal shock wave lithotripsy, stone clearance was achieved in 56% of the patients[78].

CONCLUSION

Endoscopic extraction of large stones can be problematic, even for experienced endoscopists in selected cases. In such cases, after failure to provide stone therapy with conventional balloons and baskets, the ERCP team has to choose a "Plan B" that has to be effective, not time-consuming and less damaging for the patient's biliary tree.

The reports regarding ESLBD are promising because it seems to be a safe and effective alternative technique for large stone therapy. A prior competent sphincterotomy is the first step before large balloon dilation and it is an absolute requirement since many authors reported lower complication rates when compared with dilation alone. Moreover, it could be an effective alternative option in cases of "basket and stone impaction". We believe that the effectiveness of this technique to extract biliary stones is attributed, not only to the radial dilation, but to the straightening of the distal CBD as well, thus the term "sphincteroplasty" is more appropriate and precise.

To date, there are many trials supporting ESLBD but it has not yet become a part of the everyday practice in ERCP units worldwide. More comparative studies with bigger numbers of patients are probably needed. Katsinelos *et al,* in a letter to the Editor of *Endoscopy* in 2008, approached the stone impaction issue under the prism of dilation when strategies in case of impaction were the use of a salvage mechanical lithotripter, EHL, LL and a percutaneous or surgical approach.

One of the limitations of ESLBD is the lack of a completely established technique yet. The usual queries are whether we perform "limited" or "maximum" EST, how long we dilate and what balloon size is required. Especially in case of periampullary diverticulum, altered anatomy (Billroth Ⅱ gastrectomy) or small papilla, our impression is that "minor" EST should be performed prior to large balloon dilation due to lower rates of bleeding and perforation. That hypothesis has to be proved by randomized, comparative, well-designed trials.

The duration of the dilation ranges in some trials from 10 s to 60 s to 2 min to 6 min. Our opinion from our analysis is "less dilation time, lower complication rates"[31]. Keeping the balloon inflated for a longer time (60 s) is common practice when dilating bile duct strictures of fibrotic nature[79]. However, in the setting of post-EST dilation where we are dilating a dissected sphincter and not a fibrotic tissue, theoretically a prolonged dilation time should not be needed and probably would provoke side effects.

Regarding the size of the dilating balloon, it has to be proportionate to the CBD and stone diameter and potential comorbidity has to be considered.

In an animal experiment, researchers studied the histological consequence of ESLBD that was performed using balloons up to 15 mm and up to 20 mm in porcine specimens and tissue sections were assessed for morphological changes. Macroscopic disruption and perforation of the ductal wall increased proportionally to the balloon diameter. Thus, large balloon dilation caused a potential impairment of sphincter function[80].

Primary BD remains unpopular in Western countries[3,19] and is not a routine technique worldwide. David Carr-Locke believes that, for unclear reasons, there are considerable differences in the post-procedure complications comparing ESLBD and BD among East and West. In China, Korea or Japan, primary BD of the papilla for the removal of stones has success and complication rates similar to those of EST, with the exception of bleeding, although there is an increased need for ML[4,81]. When balloon dilation is performed in the West, it presents a high risk of pancreatitis that makes it rather an abandoned technique in everyday clinical practice.

Pancreatitis resulting after BD alone could be explained theoretically by the edematous change of the papilla due to forced sphincter rupture, trauma and finally, the resulting obstruction of the pancreatic duct that discharges the inflammatory cascade leading to acute inflammation of the pancreas. The risk of pancreatitis after ESLBD is less than after BD alone, probably because after EST, the mechanical trauma caused by balloon expansion is directed predominantly towards the biliary part of the sphincter that is already dissected than towards the pancreatic duct[82].

The majority of endoscopists remove conventionally large stones by performing EST followed by ML. To date, there are no trials in the literature analyzing the efficacy of ESLBD after failure of ML to provide large CBD stone retrieval. However, ML is an established but quite challenging technique[83,84], since capturing the stone inside the lithotripter is difficult, time consuming and traumatic. ML seems to be effective in very large stones (over 20-25 mm in diameter). Thus, very large stones should be treated with ML by default, since balloon dilators of a diameter greater than 20 mm are not

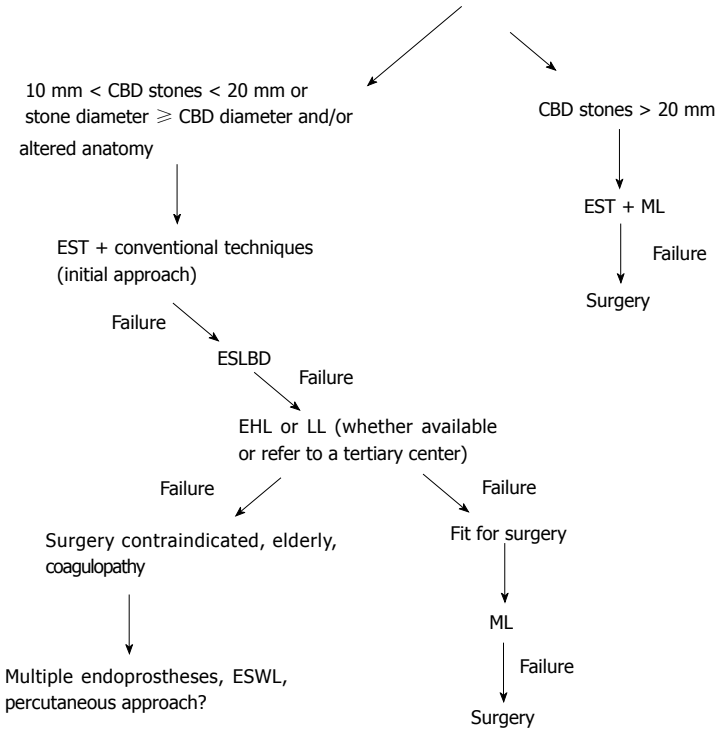


Figure 1 Strategy for endoscopic extraction of large bile duct stones. CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; ESLBD: Endoscopic sphincterotomy plus large balloon dilation; EHL: Electrohydraulic lithotripsy; ESWL: Extracorporeal Shock Wave Lithotripsy.

commercially available.

In cases of failure, we have to think about alternative non-operable options. LL or EHL could be the ideal alternative for elderly patients with an increased surgical risk.

EHL and LL yield similar success rates and may be used complementarily in referral centers. LL using smart laser systems that recognize the stone and protect the ductal tissue seems to be the best option. Dye Laser and the FREDDY system can simplify the large stone fragmentation whereas EHL is rarely used nowadays because of its higher potential of complications (bleeding, perforation)[53]. On the other hand, EHL under direct cholangioscopy or under fluoroscopy presents high rates of successful clearance in large stones (over 90%) when performed by skilled endoscopists. Smaller cohorts reported similar outcomes for EHL, reporting stone fragmentation rates ranging from 77%-100%[4,85,86].

In conclusion, ESLBD could be used as the first line therapy when balloons and baskets are unable to provide stone therapy and before ML[31], with an acceptable complication profile and good outcome[32]. Its role in patients with coagulopathy or other risks for bleeding remains to be evaluated[25,26,30,31,87]. When the stone diameter exceeds 20 mm, the most convenient technique seems to be ML. Alternatively, intracorporeal lithotripsy techniques should be attempted locally if expertise is available or in a referral center[2,20].

Biliary stenting is a short-term therapy, gaining some time since a permanent treatment is applied. In contrast, stenting as a long-term therapy can be accepted only in cases of very elderly patients with limited life expectancy as it represents the most conservative option[20]. Schematically, a management model or a strategy for endoscopic extraction of large bile duct stones is proposed in Figure 1. However, the availability of each method, the cost-effectiveness, the experience of the team, the appraisal of comorbidities and probably the patient's preference should be considered.

By using all these alternatives, almost all patients with large stones could be treated endoscopically. In cases of failure despite using advanced technology, the patient should be referred for extracorporeal shock wave lithotripsy or a percutaneous approach or surgery. The advantages and disadvantages of the therapeutic options need to be discussed with the patient and his family in order to proceed with the appropriate therapeutic option for the best outcome.

REFERENCES

1 **Yoo KS**, Lehman GA. Endoscopic management of biliary ductal stones. *Gastroenterol Clin North Am* 2010; **39**: 209-27, viii
2 **McHenry L**, Lehman G. Difficult bile duct stones. *Curr Treat Options Gastroenterol* 2006; **9**: 123-132
3 **Carr-Locke DL**. Difficult bile-duct stones: cut, dilate, or both? *Gastrointest Endosc* 2008; **67**: 1053-1055
4 **Binmoeller KF**, Brückner M, Thonke F, Soehendra N. Treatment of difficult bile duct stones using mechanical, electrohydraulic and extracorporeal shock wave lithotripsy. *Endoscopy* 1993; **25**: 201-206
5 **Sharma SS**, Jain P. Should we redefine large common bile duct stone? *World J Gastroenterol* 2008; **14**: 651-652
6 **Kawai K**, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. *Gastrointest Endosc* 1974; **20**: 148-151
7 **Lauri A**, Horton RC, Davidson BR, Burroughs AK, Dooley JS. Endoscopic extraction of bile duct stones: management related to stone size. *Gut* 1993; **34**: 1718-1721
8 **Sheth SG**, Howell DA. What are really the true late complications of endoscopic biliary sphincterotomy? *Am J Gastro-*

enterol 2002; **97**: 2699-2701
9 **Staritz M**, Ewe K, Meyer zum Büschenfelde KH. Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy. *Lancet* 1982; **1**: 1306-1307
10 **Komatsu Y**, Kawabe T, Toda N, Ohashi M, Isayama M, Tateishi K, Sato S, Koike Y, Yamagata M, Tada M, Shiratori Y, Yamada H, Ihori M, Kawase T, Omata M. Endoscopic papillary balloon dilation for the management of common bile duct stones: experience of 226 cases. *Endoscopy* 1998; **30**: 12-17
11 **Mathuna PM**, White P, Clarke E, Merriman R, Lennon JR, Crowe J. Endoscopic balloon sphincteroplasty (papillary dilation) for bile duct stones: efficacy, safety, and follow-up in 100 patients. *Gastrointest Endosc* 1995; **42**: 468-474
12 **Liao WC**, Lee CT, Chang CY, Leung JW, Chen JH, Tsai MC, Lin JT, Wu MS, Wang HP. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. *Gastrointest Endosc* 2010; **72**: 1154-1162
13 **Minami A**, Nakatsu T, Uchida N, Hirabayashi S, Fukuma H, Morshed SA, Nishioka M. Papillary dilation vs sphincterotomy in endoscopic removal of bile duct stones. A randomized trial with manometric function. *Dig Dis Sci* 1995; **40**: 2550-2554
14 **Ochi Y**, Mukawa K, Kiyosawa K, Akamatsu T. Comparing the treatment outcomes of endoscopic papillary dilation and endoscopic sphincterotomy for removal of bile duct stones. *J Gastroenterol Hepatol* 1999; **14**: 90-96
15 **Arnold JC**, Benz C, Martin WR, Adamek HE, Riemann JF. Endoscopic papillary balloon dilation vs. sphincterotomy for removal of common bile duct stones: a prospective randomized pilot study. *Endoscopy* 2001; **33**: 563-567
16 **Chan HH**, Lai KH, Lin CK, Tsai WL, Wang EM, Hsu PI, Chen WC, Yu HC, Wang HM, Tsay FW, Tsai CC, Chen IS, Chen YC, Liang HL, Pan HB. Endoscopic papillary large balloon dilation alone without sphincterotomy for the treatment of large common bile duct stones. *BMC Gastroenterol* 2011; **11**: 69
17 **Fujita N**, Maguchi H, Komatsu Y, Yasuda I, Hasebe O, Igarashi Y, Murakami A, Mukai H, Fujii T, Yamao K, Maeshiro K. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: A prospective randomized controlled multicenter trial. *Gastrointest Endosc* 2003; **57**: 151-155
18 **Disario JA**, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, Morales TG, Hixson LJ, Sherman S, Lehman GA, Jamal MM, Al-Kawas FH, Khandelwal M, Moore JP, Derfus GA, Jamidar PA, Ramirez FC, Ryan ME, Woods KL, Carr-Locke DL, Alder SC. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. *Gastroenterology* 2004; **127**: 1291-1299
19 **Weinberg BM**, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. *Cochrane Database Syst Rev* 2006; **18**: CD004890
20 **Williams EJ**, Green J, Beckingham I, Parks R, Martin D, Lombard M. Guidelines on the management of common bile duct stones (CBDS). *Gut* 2008; **57**: 1004-1021
21 **Ersoz G**, Tekesin O, Ozutemiz AO, Gunsar F. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. *Gastrointest Endosc* 2003; **57**: 156-159
22 **Maydeo A**, Bhandari S. Balloon sphincteroplasty for removing difficult bile duct stones. *Endoscopy* 2007; **39**: 958-961
23 **Heo JH**, Kang DH, Jung HJ, Kwon DS, An JK, Kim BS, Suh KD, Lee SY, Lee JH, Kim GH, Kim TO, Heo J, Song GA, Cho M. Endoscopic sphincterotomy plus large-balloon dilation versus endoscopic sphincterotomy for removal of bile-duct stones. *Gastrointest Endosc* 2007; **66**: 720-76; quiz 768, 771
24 **Minami A**, Hirose S, Nomoto T, Hayakawa S. Small sphincterotomy combined with papillary dilation with large balloon permits retrieval of large stones without mechanical lithotripsy. *World J Gastroenterol* 2007; **13**: 2179-2182
25 **Attasaranya S**, Cheon YK, Vittal H, Howell DA, Wakelin DE, Cunningham JT, Ajmere N, Ste Marie RW, Bhattacharya K, Gupta K, Freeman ML, Sherman S, McHenry L, Watkins JL, Fogel EL, Schmidt S, Lehman GA. Large-diameter biliary orifice balloon dilation to aid in endoscopic bile duct stone removal: a multicenter series. *Gastrointest Endosc* 2008; **67**: 1046-1052
26 **Misra SP**, Dwivedi M. Large-diameter balloon dilation after endoscopic sphincterotomy for removal of difficult bile duct stones. *Endoscopy* 2008; **40**: 209-213
27 **Draganov PV**, Evans W, Fazel A, Forsmark CE. Large size balloon dilation of the ampulla after biliary sphincterotomy can facilitate endoscopic extraction of difficult bile duct stones. *J Clin Gastroenterol* 2009; **43**: 782-786
28 **Itoi T**, Itokawa F, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Endoscopic sphincterotomy combined with large balloon dilation can reduce the procedure time and fluoroscopy time for removal of large bile duct stones. *Am J Gastroenterol* 2009; **104**: 560-565
29 **Kim TH**, Oh HJ, Lee JY, Sohn YW. Can a small endoscopic sphincterotomy plus a large-balloon dilation reduce the use of mechanical lithotripsy in patients with large bile duct stones? *Surg Endosc* 2011; **25**: 3330-3337
30 **Kim HG**, Cheon YK, Cho YD, Moon JH, Park do H, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304
31 **Stefanidis G**, Viazis N, Pleskow D, Manolakopoulos S, Theocharis L, Christodoulou C, Kotsikoros N, Giannousis J, Sgouros S, Rodias M, Katsikani A, Chuttani R. Large balloon dilation vs. mechanical lithotripsy for the management of large bile duct stones: a prospective randomized study. *Am J Gastroenterol* 2011; **106**: 278-285
32 **Khan AS**, Tiwari P, Nass JP, Romero RV, Rivera RE, Antillon MR, Roy PK. Large balloon dilation with sphincterotomy for large bile duct stones: a systematic review. *Gastrointest Endosc* 2011; **73**: 193
33 **Itoi T**, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Umeda J, Moriyasu F. New large-diameter balloon-equipped sphincterotome for removal of large bile duct stones (with videos). *Gastrointest Endosc* 2010; **72**: 825-830
34 **Neuhaus H**. Endoscopic and percutaneous treatment of difficult bile duct stones. *Endoscopy* 2003; **35**: S31-S34
35 **Sauter G**, Sackmann M, Holl J, Pauletzki J, Sauerbruch T, Paumgartner G. Dormia baskets impacted in the bile duct: release by extracorporeal shock-wave lithotripsy. *Endoscopy* 1995; **27**: 384-387
36 **Schneider MU**, Matek W, Bauer R, Domschke W. Mechanical lithotripsy of bile duct stones in 209 patients--effect of technical advances. *Endoscopy* 1988; **20**: 248-253
37 **Thomas M**, Howell DA, Carr-Locke D, Mel Wilcox C, Chak A, Raijman I, Watkins JL, Schmalz MJ, Geenen JE, Catalano MF. Mechanical lithotripsy of pancreatic and biliary stones: complications and available treatment options collected from expert centers. *Am J Gastroenterol* 2007; **102**: 1896-1902
38 **Riemann JF**, Seuberth K, Demling L. Clinical application of a new mechanical lithotripter for smashing common bile duct stones. *Endoscopy* 1982; **14**: 226-230
39 **Chang WH**, Chu CH, Wang TE, Chen MJ, Lin CC. Outcome of simple use of mechanical lithotripsy of difficult common bile duct stones. *World J Gastroenterol* 2005; **11**: 593-596
40 **Shaw MJ**, Mackie RD, Moore JP, Dorsher PJ, Freeman ML, Meier PB, Potter T, Hutton SW, Vennes JA. Results of a multicenter trial using a mechanical lithotripter for the treatment of large bile duct stones. *Am J Gastroenterol* 1993; **88**: 730-733
41 **Garg PK**, Tandon RK, Ahuja V, Makharia GK, Batra Y.

Predictors of unsuccessful mechanical lithotripsy and endoscopic clearance of large bile duct stones. *Gastrointest Endosc* 2004; **59**: 601-605
42 **Cipolletta L**, Costamagna G, Bianco MA, Rotondano G, Piscopo R, Mutignani M, Marmo R. Endoscopic mechanical lithotripsy of difficult common bile duct stones. *Br J Surg* 1997; **84**: 1407-1409
43 **Akcakaya A**, Ozkan OV, Bas G, Karakelleoglu A, Kocaman O, Okan I, Sahin M. Mechanical lithotripsy and/or stenting in management of difficult common bile duct stones. *Hepatobiliary Pancreat Dis Int* 2009; **8**: 524-528
44 **Moon JH**, Cha SW, Ryu CB, Kim YS, Hong SJ, Cheon YK, Cho YD, Kim YS, Lee JS, Lee MS, Shim CS, Kim BS. Endoscopic treatment of retained bile-duct stones by using a balloon catheter for electrohydraulic lithotripsy without cholangioscopy. *Gastrointest Endosc* 2004; **60**: 562-566
45 **Blind PJ**, Lundmark M. Management of bile duct stones: lithotripsy by laser, electrohydraulic, and ultrasonic techniques. Report of a series and clinical review. *Eur J Surg* 1998; **164**: 403-409
46 **Arya N**, Nelles SE, Haber GB, Kim YI, Kortan PK. Electrohydraulic lithotripsy in 111 patients: a safe and effective therapy for difficult bile duct stones. *Am J Gastroenterol* 2004; **99**: 2330-2334
47 **Moon JH**, Choi HJ, Ko BM. Therapeutic role of direct peroral cholangioscopy using an ultra-slim upper endoscope. *J Hepatobiliary Pancreat Sci* 2011; **18**: 350-356
48 **Moon JH**, Ko BM, Choi HJ, Koo HC, Hong SJ, Cheon YK, Cho YD, Lee MS, Shim CS. Direct peroral cholangioscopy using an ultra-slim upper endoscope for the treatment of retained bile duct stones. *Am J Gastroenterol* 2009; **104**: 2729-2733
49 **Seelhoff A**, Schumacher B, Neuhaus H. Single operator peroral cholangioscopic guided therapy of bile duct stones. *J Hepatobiliary Pancreat Sci* 2011; **18**: 346-349
50 **Chen YK**, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). *Gastrointest Endosc* 2007; **65**: 832-841
51 **Kalaitzakis E**, Webster G , Vlavianos P , Burnham R , Kallis Y , Hatfield A , Aljabiri R , Westaby D , Sturgess R. Diagnostic and therapeutic utility of spyglass peroral cholangioscopy for indeterminate biliary lesions and bile duct stones. *Gut* 2011; **60**: 191–192
52 **Fishman DS**, Tarnasky PR, Patel SN, Raijman I. Management of pancreaticobiliary disease using a new intra-ductal endoscope: the Texas experience. *World J Gastroenterol* 2009; **15**: 1353-1358
53 **Hochberger J**, Tex S, Maiss J, Hahn EG. Management of difficult common bile duct stones. *Gastrointest Endosc Clin N Am* 2003; **13**: 623-634
54 **Jakobs R**, Maier M, Kohler B, Riemann JF. Peroral laser lithotripsy of difficult intrahepatic and extrahepatic bile duct stones: laser effectiveness using an automatic stone-tissue discrimination system. *Am J Gastroenterol* 1996; **91**: 468-473
55 **Schreiber F**, Gurakuqi GC, Trauner M. Endoscopic intracorporeal laser lithotripsy of difficult common bile duct stones with a stone-recognition pulsed dye laser system. *Gastrointest Endosc* 1995; **42**: 416-419
56 **Jakobs R**, Adamek HE, Maier M, Krömer M, Benz C, Martin WR, Riemann JF. Fluoroscopically guided laser lithotripsy versus extracorporeal shock wave lithotripsy for retained bile duct stones: a prospective randomised study. *Gut* 1997; **40**: 678-682
57 **Piraka C**, Shah RJ, Awadallah NS, Langer DA, Chen YK. Transpapillary cholangioscopy-directed lithotripsy in patients with difficult bile duct stones. *Clin Gastroenterol Hepatol* 2007; **5**: 1333-1338
58 **Bratcher J**, Kasmin F. Choledochoscopy-assisted intraductal shock wave lithotripsy. *Gastrointest Endosc Clin N Am* 2009; **19**: 587-595
59 **Parsi M**, Neuhaus H, Pleskow D, Binmoeller KF, Hawes RH, Petersen BT, Sherman S, Stevens PD, Deviere J, Haluszka O, Costamagna G, Meisner SR, Ponchon T, Slivka A, Chen YK. Peroral cholangioscopy guided stone therapy: report of an international multicenter registry. *Gastrointest Endosc* 2008; **67**: AB102
60 **Neoptolemos JP**, Hofmann AF, Moossa AR. Chemical treatment of stones in the biliary tree. *Br J Surg* 1986; **73**: 515-524
61 **Palmer KR**, Hofmann AF. Intraductal mono-octanoin for the direct dissolution of bile duct stones: experience in 343 patients. *Gut* 1986; **27**: 196-202
62 **Diaz D**, Bories P, Ampelas M, Larrey D, Michel H. Methyl tert-butyl ether in the endoscopic treatment of common bile duct radiolucent stones in elderly patients with nasobiliary tube. *Dig Dis Sci* 1992; **37**: 97-100
63 **Katanuma A**, Maguchi H , Osanai M . Endoscopic treatment of difficult common bile duct stones. *Dig Endoscopy* 2010; **22**: 90–97
64 **Fan Z**, Hawes R, Lawrence C, Zhang X, Zhang X, Lv W. Analysis of plastic stents in the treatment of large common bile duct stones in 45 patients. *Dig Endosc* 2011; **23**: 86-90
65 **Jain SK**, Stein R, Bhuva M, Goldberg MJ. Pigtail stents: an alternative in the treatment of difficult bile duct stones. *Gastrointest Endosc* 2000; **52**: 490-493
66 **Hong WD**, Zhu QH, Huang QK. Endoscopic sphincterotomy plus endoprostheses in the treatment of large or multiple common bile duct stones. *Dig Endosc* 2011; **23**: 240-243
67 **Cotton PB**. Stents for stones: short-term good, long-term uncertain. *Gastrointest Endosc* 1995; **42**: 272-273
68 **Bergman JJ**, Rauws EA, Tijssen JG, Tytgat GN, Huibregtse K. Biliary endoprostheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. *Gastrointest Endosc* 1995; **42**: 195-201
69 **Lee TH**, Han JH, Kim HJ, Park SM, Park SH, Kim SJ. Is the addition of choleretic agents in multiple double-pigtail biliary stents effective for difficult common bile duct stones in elderly patients? A prospective, multicenter study. *Gastrointest Endosc* 2011; **74**: 96-102
70 **Horiuchi A**, Nakayama Y, Kajiyama M, Kato N, Kamijima T, Graham DY, Tanaka N. Biliary stenting in the management of large or multiple common bile duct stones. *Gastrointest Endosc* 2010; **71**: 1200-1203.e2
71 **Stellato TA**, Crouse C, Hallowell PT. Bariatric surgery: Creating new challenges for the endoscopist. *Gastrointest Endosc* 2003; **57**: 86-94
72 **van Buuren HR**, Boender J, Nix GA, van Blankenstein M. Needle-knife sphincterotomy guided by a biliary endoprosthesis in Billroth II gastrectomy patients. *Endoscopy* 1995; **27**: 229-232
73 **Choi CW**, Choi JS, Kang DH, Kim BG, Kim HW, Park SB, Yoon KT, Cho M. Endoscopic papillary large balloon dilation in Billroth II gastrectomy patients with bile duct stones. *J Gastroenterol Hepatol* 2012; **27**: 256-260
74 **Itoi T**, Ishii K, Itokawa F, Kurihara T, Sofuni A. Large balloon papillary dilation for removal of bile duct stones in patients who have undergone a billroth ii gastrectomy. *Dig Endosc* 2010; **22** Suppl 1: S98-S102
75 **Prat F**, Fritsch J, Choury AD, Meduri B, Pelletier G, Buffet C. Endoscopic sphincteroclasy: a useful therapeutic tool for biliary endoscopy in Billroth II gastrectomy patients. *Endoscopy* 1997; **29**: 79-81
76 **Ahlawat SK**, Singhania R, Al-Kawas FH. Mirizzi syndrome. *Curr Treat Options Gastroenterol* 2007; **10**: 102-110
77 **Tsuyuguchi T**, Sakai Y, Sugiyama H, Ishihara T, Yokosuka O. Long-term follow-up after peroral cholangioscopy-directed lithotripsy in patients with difficult bile duct stones, including Mirizzi syndrome: an analysis of risk factors predicting stone recurrence. *Surg Endosc* 2011; **25**: 2179-2185
78 **England RE**, Martin DF. Endoscopic management of Mir-

izzi's syndrome. *Gut* 1997; **40**: 272-276
79 **Farah M**, McLoughlin M, Byrne MF. Endoscopic retrograde cholangiopancreatography in the management of benign biliary strictures. *Curr Gastroenterol Rep* 2008; **10**: 150-156
80 **Hisatomi K**, Ohno A, Tabei K, Kubota K, Matsuhashi N. Effects of large-balloon dilation on the major duodenal papilla and the lower bile duct: histological evaluation by using an ex vivo adult porcine model. *Gastrointest Endosc* 2010; **72**: 366-372
81 **David L Carr-Locke**. Ask the expert. Management of bile duct stones. ASGE Publications 2011
82 **Shim CS**. How Should Biliary Stones be Managed? *Gut Liver* 2010; **4**: 161-172
83 **Leung JW**, Tu R. Mechanical lithotripsy for large bile duct stones. *Gastrointest Endosc* 2004; **59**: 688-690
84 **Hintze RE**, Adler A, Veltzke W. Outcome of mechanical lithotripsy of bile duct stones in an unselected series of 704 patients. *Hepatogastroenterology* 1996; **43**: 473-476
85 **Adamek HE**, Buttmann A, Wessbecher R, Kohler B, Riemann JF. Clinical comparison of extracorporeal piezoelectric lithotripsy (EPL) and intracorporeal electrohydraulic lithotripsy (EHL) in difficult bile duct stones. A prospective randomized trial. *Dig Dis Sci* 1995; **40**: 1185-1192
86 **Leung JW**, Chung SS. Electrohydraulic lithotripsy with peroral choledochoscopy. *BMJ* 1989; **299**: 595-598
87 **Attam R**, Freeman ML. Endoscopic papillary large balloon dilation for large common bile duct stones. *J Hepatobiliary Pancreat Surg* 2009; **16**: 618-623

S- Editor Yang XC **L- Editor** Roemmele A **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.180

World J Gastrointest Endosc 2012 May 16; 4(5): 180-184
ISSN 1948-5190 (online)

BRIEF ARTICLE

Endoscopic papillary large balloon dilation after limited sphincterotomy for difficult biliary stones

Ana Rebelo, Pedro Moutinho Ribeiro, António Pinto Correia, José Cotter

Ana Rebelo, Pedro Moutinho Ribeiro, António Pinto Correia, José Cotter, Gastroenterology Department, Centro Hospitalar do Alto Ave, 4835 044 Guimarães, Portugal
Author contributions: Rebelo A and Ribeiro PM contributed equally to this work; Ribeiro PM and Correia AP designed the research; Rebelo A, Ribeiro PM, Correia AP and Cotter J performed the research; Rebelo A and Ribeiro PM analysed the data; Rebelo A wrote the paper; Ribeiro PM, Correia AP and Cotter J revised and corrected the paper.
Correspondence to: Ana Rebelo, MD, Gastroenterology Department, Centro Hospitalar do Alto Ave, Guimarães, Rua dos Cutileiros-Creixomil. 4835 044 Guimarães, Portugal. airebelo_@hotmail.com
Telephone: +351-253-540330 Fax: +351-253-421308
Received: June 26, 2011 Revised: November 16, 2011
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

AIM: To assess the efficacy and safety of endoscopic papillary large balloon dilation after biliary sphincterotomy for difficult bile duct stones retrieval.

METHODS: Retrospective review of consecutive patients submitted to the technique during 18 mo. The main outcomes considered were: efficacy of the procedure (complete stone clearance; number of sessions; need of lithotripsy) and complications.

RESULTS: A total of 30 patients with a mean age of 68 ± 10 years, 23 female (77%) and 7 male (23%) were enrolled. In 10 patients, a single stone was found in the common bile duct (33%) and in 20 patients multiple stones (67%) were found. The median diameter of the stones was 17 mm (12-30 mm). Dilations were performed with progressive diameter Through-The-Scope balloons (up to 12, 15) or 18 mm. Complete retrieval of stones was achieved in a single session in 25 patients (84%) and in two sessions in 4 patients (13%). Failure occurred in 1 case (6%). Mechanical lithotripsy was performed in 6 cases (20%). No severe complications occurred. One patient (3%) had mild-grade post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

CONCLUSION: Endoscopic balloon dilatation with a large balloon after endoscopic sphincterotomy is a safe and effective technique that could be considered an alternative choice in therapeutic ERCP.

Key words: Balloon dilation; Cholelithiasis; Endoscopic retrograde cholangiopancreatography; Lithotripsy; Sphincterotomy

Peer reviewer: Wai-Keung Chow, Dr., Division of Gastroenterology, China Medical University Hospital, No. 2, Yu-Der Rd., Taichung 407, Taiwan, China

Rebelo A, Ribeiro PM, Correia AP, Cotter J. Endoscopic papillary large balloon dilation after limited sphincterotomy for difficult biliary stones. *World J Gastrointest Endosc* 2012; 4(5): 180-184 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/180.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.180

INTRODUCTION

The basic principle of common bile duct stone extraction involves destruction or dilation of the bile duct orifice. Endoscopic sphincterotomy (EST) has been accepted as the standard management for stone removal from the bile duct since its first description in 1974[1], however, it is associated with complications such as haemorrhage, pancreatitis, perforation, and recurrent infection of the biliary tree; it also causes permanent functional loss of the sphincter of Oddi[1-3]. Endoscopic papillary balloon dilation (PBD) was introduced by Staritz *et al*[4]

in 1983 and has been advocated as an alternative to EST in selected patients with bile duct stones, despite a few reports of an unacceptably high risk of pancreatitis[4-10]. The main advantage of this technique is that it does not involve cutting the biliary sphincter. Therefore, acute complications, such as haemorrhage or perforation may be less likely, and the function of the biliary sphincter may be preserved. Regardless of the theoretical merits of conventional PBD, one of the major limitations is the difficulty of removing larger stones because the biliary opening is not enlarged to the same degree as with EST[11]. To overcome these limitations, Ersoz *et al*[12] in 2003, introduced PBD with a large balloon after EST for the removal of large (≥ 15 mm) bile duct stones that are often difficult to remove with standard methods. They reported that PBD after limited EST was more effective for the retrieval of large stones and that it shortened the procedure time. This technique combines the advantages of EST and PBD by increasing the efficacy of stone extraction while minimizing complications of both EST and PBD alone[13].

In our study, we performed dilation of the sphincter with large Through-The-Scope (TTS) balloons (12-18 mm diameter) after limited EST. We analysed the efficacy, considering as primary endpoint the success rate of complete removal of stones in a single endoscopic retrograde cholangiopancreatography (ERCP) session, and as secondary endpoints the number of ERCP sessions required for complete stone removal and the frequency of use of mechanical lithotripsy. Safety was evaluated by assessing the complications of the procedure.

MATERIALS AND METHODS

Patients

From March 2009 to November 2010, a total of 30 patients were enrolled. All patients met the following selection criteria: (1) referral for ERCP by symptoms related to bile duct stones; (2) 18 years of age or older; (3) informed consent obtained before ERCP; (4) difficult bile duct stones visualized at ERCP (considered when ≥ 15 mm in diameter and/or when multiple); and (5) deep cannulation of the bile duct achieved without precut. Exclusion criteria included: acute pancreatitis (severe epigastric pain combined with serum amylase more than three times the upper normal limit), acute cholecystitis (localized pain in the right upper abdomen, fever, and a thickened gallbladder wall on ultrasonography), which could compromise the assessment of procedure-related complications, or a history of previous biliary surgery (except cholecystectomy), haemostatic disorders, intrahepatic stone diseases, concomitant pancreatic or biliary malignant disorders.

Endoscopic procedures

All the exams were performed with Olympus® TJF 160 VR and TJF 145 side-viewing endoscopes. Patients were under conscious sedation, performed by an anaesthesiologist. Prophylactic antibiotics were not routinely given. To decrease duodenal peristalsis, 20 mg butylscopolamine was administered intravenously when needed. The major papilla was located and the bile duct was deeply cannulated preferentially with a sphincterotome (Papillotomy knife, wire guided type, Olympus®). A diagnostic cholangiogram was obtained by injection of a diluted contrast medium. EST was performed over a 0.035 in guide wire (Hydra Jag wire TM guide wire, Boston Scientific Corp.®). After that, a 12 mm to 18 mm TTS balloon catheter for oesophageal/pyloric dilation (CRETM wire-guided balloon dilatation catheter, Boston Scientific Microvasive®) was passed over the guide wire and positioned across the papilla. Each balloon was gradually expanded to 12-18 mm with the instillation of diluted contrast medium, depending on the maximal diameter of the CBD, measured by cholangiography. The sphincter was considered adequately dilated when the waist in the balloon had disappeared completely. The fully expanded balloon was maintained in position for 60 s and then deflated and removed (Figure 1). After EBD, the stones were retrieved using a Dormia basket (WebTM extraction basket, Wilson-Cook Medical Inc.®) and/or a retrieval balloon catheter (System single use triple lumen stone extraction balloon, Olympus®). When strictly necessary, mechanical lithotripsy (BML-4Q, Olympus; Fusion Lithotripsy Basket, Wilson-Cook Medical®) was performed to fragment the stones prior to extraction from the bile duct. Complete stone removal was documented with a final cholangiogram (Figure 2). If stones were still present, a biliary plastic double pigtail stent was placed and a second ERCP was planned within 4-6 wk.

Outcome measures

Stone size and number were documented on the initial cholangiogram during ERCP. Stone size was assessed by comparing the largest stone diameter with the diameter of the endoscope, measured on the X-ray image.

The primary endpoint was the success rate of complete removal of stones in the initial ERCP session. The secondary endpoints included the number of ERCPs until achievement of complete stone extraction, frequency of mechanical lithotripsy and complications such as bleeding, pancreatitis, cholangitis, and perforation. To assess these complications, blood samples for complete blood count, liver function test, amylase and lipase concentrations and C-reactive protein level were taken 24 h after the procedure. Post-ERCP pancreatitis was defined as persistent abdominal pain of more than 24 h duration associated with elevation of serum amylase more than three times the upper normal limit. Bleeding complications were considered when a decrease in haemoglobin concentration of > 2 g/dL was seen or evidence of clinical bleeding after the procedure, such as melena or hematemesis. Cholangitis was defined as a fever accompanied by jaundice and right upper quadrant pain. All complications were classified and graded according to the 1991 consensus guidelines[14]. After removal of the

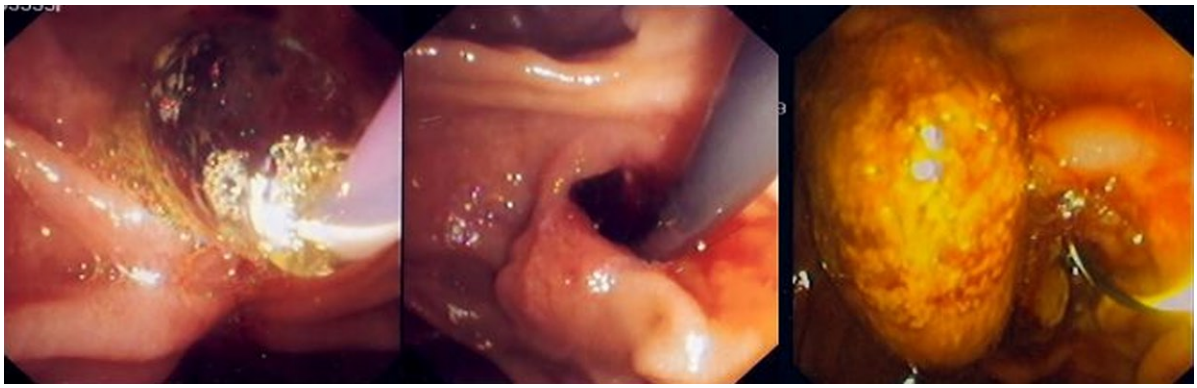


Figure 1 Endoscopic view of papillary large balloon (18 mm) dilation after limited sphincterotomy in a patient with a single large bile duct stone (30 mm, egg shaped).

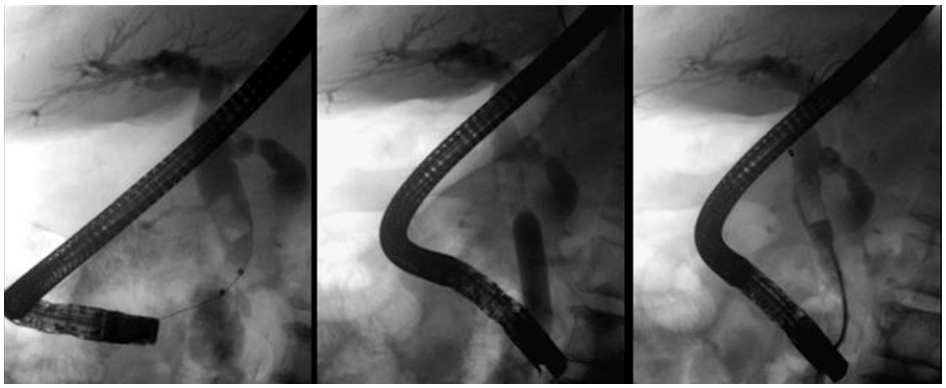


Figure 2 Fluoroscopy sequence showing a dilated common bile duct with a large single stone inside. Balloon inflation until the notch on the waist disappears; clearance of the common bile duct with a Dormia basket.

stones, ductal clearance was confirmed with a balloon catheter cholangiogram at the end of the procedure.

For statistical analysis we used the SPSS for Mac software (version 18.0). Data are presented as the mean ± SD or median with range. Categorical parameters were compared using χ^2 or Fisher's exact tests, while continuous variables were analysed by Student's *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

As described in Table 1, between March/2009 and September/2010, a total of 30 patients with a mean age of 68 ± 10 years, 23 female (77%) and 7 male (23%) were enrolled in the study.

Twenty-six patients (86%) were submitted to EST followed by PBD, 2 required enlargement of previous EST and PBD (7%) and in 2 only PBD (7%) was performed since these patients had a previous EST with adequate dimensions.

In 10 patients a single stone in the CBD (33%) was found and in 20 patients multiple stones (67%) were found. The median diameter of the stones was 17 mm (range 12-30 mm). In 7 cases (23%), the papilla was peridiverticular, although accessible.

The dilations were performed with progressive diameter TTS balloons: 8 up to 12 mm (27%), 9 up to 13.5 mm (30%), 10 up to 15 mm (33%), 2 up to 16.5 mm (7%) and 1 up to 18 mm (3%).

Treatment outcomes

In 29 patients (97%), endoscopic balloon dilation (EBD) of the biliary sphincter was successful and complete retrieval of bile duct stones was achieved. Failure occurred in 1 case (6%) due to impossibility in removing or capturing a 25 mm stone, even with a lithotripsy basket. Successful stone removal in one ERCP session was accomplished in 25 patients (84%). In 4 patients (13%) complete stone removal was possible in a second procedure performed within 4-6 wk. The stone removal rate according to stone size and number is described in Table 2. Mechanical lithotripsy was necessary in six patients (20%), allowing complete stone removal in the same procedure. The use of mechanical lithotripsy according to stone size and number is described in Table 3.

Complications

In our study group, only one patient developed mild-grade post-ERCP pancreatitis that resolved with conservative treatment in 72 h. Haemorrhage did not occur in any of the patients. In 3 cases, minor oozing that spontaneously stopped during the procedure was noted. Fatal

Table 1 Baseline characteristics of the patients

Mean age (yr)	68 ± 10
Gender (M/F)	7/23
Stones	
Single	10 (33%)
Multiple	20 (67%)
Median diameter (mm)	17(12-30)
Periampullary diverticulum	7 (23%)

Table 2 Stone removal after endoscopic balloon dilatation according to stone size and number

		Complete removal (with one ERCP)	Incomplete removal/ failure	*P*
Stones	Single	9 (90%)	1 (10%)	NS
	Multiple	16 (80%)	4 (20%)	
Median diameter (mm)		15	23	0.001

ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant.

complications such as perforation or severe pancreatitis did not occur. An asymptomatic elevation of serum amylase/lipase was noted in 27% (8/30) of the patients and isolated abdominal pain occurred in 3 patients (10%). The elevated serum amylase/lipase usually normalized within 24-48 h after the procedure and did not affect the clinical course of the patients.

DISCUSSION

EBD has been reported to be an effective and safe method to access the bile duct for retrieval of common bile duct stones[13,15-17]. Specifically, EBD is recommended in patients with coagulation defects[13]. However, the use of conventional EBD is restricted to patients with small stones (less than 10 mm in diameter) since balloon dilation does not enlarge the sphincter to the same extent as EST. Concerns surrounding EBD are primarily due to the diameter of the balloon catheter and the associated risk of pancreatitis. EST is the most commonly used technique to access the bile duct in order to treat biliary stones. However, a large EST is associated with complications that in a few cases can be serious, such as perforation or severe haemorrhage[5,15]. Additionally, in difficult bile stones, EST alone does not allow complete stone extraction in some cases. In fact, in difficult cases complete stone extraction is only possible after the use of mechanical lithotripsy and, usually, involving multiple procedures.

To obviate these problems, Ersoz, in 2003, described the combined EST+EBD technique. This was the method performed in our study. The sphincterotomy performed previous to EBD allowed us to control the choledochal direction during dilation, straightening the distal part of the CBD. With this modified EBD procedure, we achieved greater access to the bile duct (12-18 mm) compared to conventional EBD of around 10 mm

Table 3 Use of lithotripsy according to stone size and number

		Use of lithotripsy		*P*
		Yes	No	
Stones	Single	1 (10%)	9 (90%)	0.02
	Multiple	5 (25%)	15 (75%)	
Median diameter (mm)		16	17	NS

NS: Not significant.

in diameter. The combination of these techniques creates a large orifice facilitating removal of large or multiple stones with less chance of impaction in the distal bile duct[15]. In our study, the overall technical success of bile duct stone retrieval was 97%, and the success rate of complete stone retrieval in a single ERCP session (83%) was comparable to previous reports which ranged from 80% to 100%[10-15]. Considering that the average diameter of the bile duct stones was 17 mm, this outcome is clinically acceptable. In addition, mechanical lithotripsy was required in only 6 cases (20%), all of which had stones > 15 mm in diameter.

When assessing the relationship between efficacy, the number of bile duct stones and their median diameter, only the size (larger stones, mean diameter 23 mm) was associated with incomplete removal or failure ($P = 0.001$); the number of stones (single versus multiple) did not influence the success of the technique (Table 2). According to the literature, the use of lithotripsy alone (without balloon dilation) is required in up to 25% of cases of difficult CBD stones[16,17]. In our series, mechanical lithotripsy was required in only 20% of patients who underwent large PBD after EST and it was required in only a few cases of single stones (10%; $P = 0.02$) (Table 3). However, these points of discussion should be validated with larger sized subgroups.

With respect to the complications normally associated with EBD, post-procedural pancreatitis is highly disputed. Even though Disario *et al*[8,9] reported that post-EBD pancreatitis developed in 14% of their patients with 2 fatal cases, other studies have reported that the post-EBD risk of pancreatitis is comparable to the risk associated with conventional EST. In theory, the risk of pancreatitis with EBD seems to be related to the pressure load on the orifice of the main pancreatic duct during balloon dilation. That is why EST prior to EBD could prevent pressure overload on the main pancreatic duct and consequently prevent post-EBD pancreatitis. In this study, we performed EST of the bile duct to control the choledochal direction of balloon dilation and prevent pressure overload on the orifice of the main pancreatic duct and we reported only one case of mild-grade post-ERCP pancreatitis. However, it is still not clear how large the sphincterotomy performed must be in order to achieve the apparent reduction in pancreatitis risk with large balloon dilation[15,17]. Regarding the risk of haemorrhage, this sequential technique has been shown to be as safe as conventional EBD. As in other series[13,15-19], in ours, we did not have any cases of im-

portant haemorrhage. Another issue to consider during EBD with a large balloon is the risk of perforation of the duodenum. However, this risk is controlled, as during the ballooning, the endoscopist is able to monitor the dilation status of the ampulla, both endoscopically and by using fluoroscopy. Additionally, the EST performed previously has the capacity to orientate the correct direction of the dilation and control the impact of its radial force. Hence, the theoretical risk of perforation is very low[13-18]. Again, we had no cases of this complication.

Unlike balloon dilation as a substitute for sphincterotomy, endoscopic papillary large balloon dilation is rapidly catching on as a useful technique for large or difficult bile duct stones in patients with dilated bile ducts, when performed complementary to limited EST.

In conclusion, as reported by other authors[15-19], our study showed that endoscopic papillary large balloon dilation appears to be a safe and effective technique for the removal of large bile duct stones and should be considered in the management of difficult bile duct stones.

COMMENTS

Background

Endoscopy is accepted as a first treatment modality in the management of extrahepatic bile duct. Approximately 10%-15% of large or multiple stones cannot be retrieved individually using conventional means such as balloon, basket, with or without mechanical lithotripsy. Therefore, other endoscopic stone removal methods should be carefully studied and considered as options in these cases.

Research frontiers

It remains a challenge to define the most effective and safe techniques for difficult bile duct stones retrieval.

Innovations and breakthroughs

Endoscopic papillary large balloon dilation after limited endoscopic biliary sphincterotomy (EST) is an alternative technique for the removal of large or difficult stones from the common bile duct; it appears to combine the advantages of EST and papillary balloon dilation (PBD) by increasing the efficacy of stone extraction while minimizing the complications of each technique. Although it was originally described some years ago and a number of studies have been published, the issues concerning this method are still controversial.

Applications

The study showed that endoscopic papillary large balloon dilation appears to be a safe and effective technique for removal of large bile duct stones and should be considered in the management of difficult bile duct stones. Additional major controlled studies should be performed to support this.

Terminology

Endoscopic papillary large balloon dilation is a modified technique that consists of PBD after limited EST. Bile duct stones were considered difficult when they were $\geqslant$ 15 mm in diameter and/or multiple.

Peer review

This is a small retrospective and descriptive study and therefore has its limitations. The authors consider that this technique is a valid option and should be considered in the management of difficult bile duct stones.

REFERENCES

1 **Classen M**, Demling L. [Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl)]. *Dtsch Med Wochenschr* 1974; **99**: 496-497

2 **Kawai K**, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. *Gastrointest Endosc* 1974; **20**: 148-151

3 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918

4 **Staritz M**, Ewe K, Meyer zum Büschenfelde KH. Endoscopic papillary dilation (EPD) for the treatment of common bile duct stones and papillary stenosis. *Endoscopy* 1983; **15** Suppl 1: 197-198

5 **Bergman JJ**, Rauws EA, Fockens P, van Berkel AM, Bossuyt PM, Tijssen JG, Tytgat GN, Huibregtse K. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bileduct stones. *Lancet* 1997; **349**: 1124-1129

6 **Yasuda I**, Tomita E, Enya M, Kato T, Moriwaki H. Can endoscopic papillary balloon dilation really preserve sphincter of Oddi function? *Gut* 2001; **49**: 686-691

7 **May GR**, Cotton PB, Edmunds SE, Chong W. Removal of stones from the bile duct at ERCP without sphincterotomy. *Gastrointest Endosc* 1993; **39**: 749-754

8 **Arnold JC**, Benz C, Martin WR, Adamek HE, Riemann JF. Endoscopic papillary balloon dilation vs. sphincterotomy for removal of common bile duct stones: a prospective randomized pilot study. *Endoscopy* 2001; **33**: 563-567

9 **Bergman JJ**, Tytgat GN, Huibregtse K. Endoscopic dilatation of the biliary sphincter for removal of bile duct stones: an overview of current indications and limitations. *Scand J Gastroenterol Suppl* 1998; **225**: 59-65

10 **Kozarek RA**. Balloon dilation of the sphincter of Oddi. *Endoscopy* 1988; **20** Suppl 1: 207-210

11 **Baron TH**, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. *Am J Gastroenterol* 2004; **99**: 1455-1460

12 **Ersoz G**, Tekesin O, Ozutemiz AO, Gunsar F. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. *Gastrointest Endosc* 2003; **57**: 156-159

13 **Bang S**, Kim MH, Park JY, Park SW, Song SY, Chung JB. Endoscopic papillary balloon dilation with large balloon after limited sphincterotomy for retrieval of choledocholithiasis. *Yonsei Med J* 2006; **47**: 805-810

14 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393

15 **Attam R**, Freeman ML. Endoscopic papillary large balloon dilation for large common bile duct stones. *J Hepatobiliary Pancreat Surg* 2009; **16**: 618-623

16 **Itoi T**, Itokawa F, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Endoscopic sphincterotomy combined with large balloon dilation can reduce the procedure time and fluoroscopy time for removal of large bile duct stones. *Am J Gastroenterol* 2009; **104**: 560-565

17 **Lee DK**, Jahng JH. Alternative methods in the endoscopic management of difficult common bile duct stones. *Dig Endosc* 2010; **22** Suppl 1: S79-S84

18 **Kim HG**, Cheon YK, Cho YD, Moon JH, Park do H, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304

19 **Kochhar R**, Dutta U, Shukla R, Nagi B, Singh K, Wig JD. Sequential endoscopic papillary balloon dilatation following limited sphincterotomy for common bile duct stones. *Dig Dis Sci* 2009; **54**: 1578-1581

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.185

World J Gastrointest Endosc 2012 May 16; 4(5): 185-188
ISSN 1948-5190 (online)

BRIEF ARTICLE

Does capsule endoscopy have an added value in patients with perianal disease and a negative work up for Crohn's disease?

Samuel N Adler, Metzger Yoav, Scapa Eitan, Chowers Yehuda, Rami Eliakim

Samuel N Adler, Metzger Yoav, Scapa Eitan, Chowers Yehuda, Rami Eliakim, Departments of Gastroenterology, Bikur Holim Hospital, Jerusalem, 91104 (ASN, MY), Asaf Harofeh, Zrifin 70300 (ES), and Rambam Health Care Campus, Haifa 31096 (CY, ER), Israel

Author contributions: Adler SN and Eliakim R were the primary investigators; all other authors contributed equally to the article.

Correspondence to: Rami Eliakim, Professor of Medicine, Head, Gastroenterology and Hepatology, Sheba Medical Center, Ramat-Gan 52506, Israel. abraham.eliakim@sheba.health.gov.il

Telephone: +972-3-5302679 Fax: +972-3-53059101
Received: November 8, 2011 Revised: February 22, 2012
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

AIM: To investigate the role of capsule endoscopy in patients with persistent perianal disease and negative conventional work up for Crohn's disease (CD).

METHODS: Patients with perianal disease (abscesses, fistulas, recurrent fissures) were evaluated for underlying CD. Patients who had a negative work up, defined as a negative colonoscopy with a normal ileoscopy or a normal small bowel series or a normal CT/MR enterography, underwent a Pillcam study of the small bowel after signing informed consent. Patients using nonsteroidal anti-inflammatory drugs or who had a history of inflammatory bowel disease or rheumatic disease were excluded.

RESULTS: We recruited 26 patients aged 21-61 years (average 35.6 years), 17 males and 9 females. One case could not be evaluated since the capsule did not leave the stomach. In 6 of 25 (24%) patients with a negative standard work up for Crohn's disease, capsule endoscopy (CE) findings were consistent with Crohn's disease of the small bowel. Family history of CD, white blood cell, hemoglobin, erythrocyte sedimentation rate or C-reactive protein did not predict a diagnosis of CD. Capsule endoscopy findings led to a change in treatment.

CONCLUSION: In patients with perianal disease and a negative conventional work up to exclude CD, CE leads to incremental diagnostic yield of 24%.

Key words: Perianal abscess; Perianal fistula; Ileocolonoscopy; Capsule endoscopy; Crohn's disease

Peer reviewer: István Rácz, MD, PhD, Professor, Head of Internal Medicine, Department of Gastroenterology, Petz Aladár County and Teaching Hospital, Győr, Hungary

Adler SN, Yoav M, Eitan S, Yehuda C, Eliakim R. Does capsule endoscopy have an added value in patients with perianal disease and a negative work up for Crohn's disease? *World J Gastrointest Endosc* 2012; 4(5): 185-188 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/185.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.185

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease that may manifest itself throughout the gastrointestinal tract or by extra intestinal symptoms. The primary presentation of CD may be perianal disease (PD). This presentation is not infrequent. The prevalence of PD in CD ranges between 4% and 80%[1,2]. The large discrepancies in prevalence may be due to the variable defining criteria. In up to 36% of patients, PD precedes the overt intestinal disease, but in the majority of patients, PD occurs

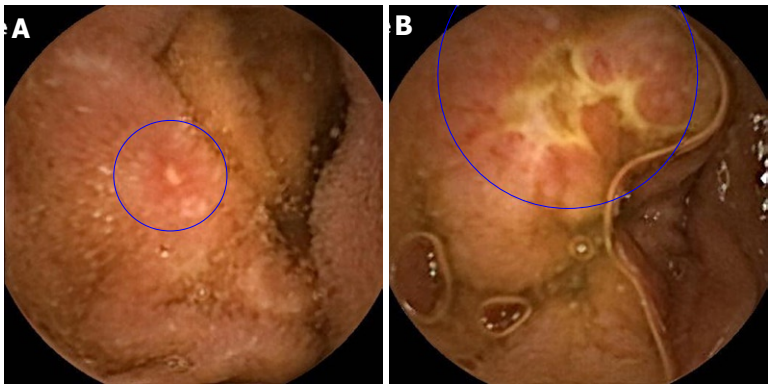


Figure 1 Capsule endoscopy findings in a patient presenting with Perianal disease. A: Apthous ulcer; B: Serpiginous ulcer.

either concurrently or after the diagnosis of small bowel CD[1,3]. Mild manifestations of PD include fissures, skin tags and hemorrhoids, whereas perianal abscesses, rectocutaneous or rectovaginal fistulas, cavitating ulcers and/or anorectal dense strictures are defined as severe PD. Severe PD usually carries a poor prognosis. Many of these patients ultimately will require a proctectomy and a permanent stoma[4]. For many years, PD was considered to be a variant of penetrating CD. According to the Vienna Classification of CD[5], PD at any time in the course of the disease is defined as penetrating disease. This categorization has been challenged and is defined separately in the Montreal classification[6].

Recent studies have shown that perianal CD may be a distinct phenotype, possibly associated with specific susceptibility genes and/or environmental factors, and not related to the "classic" penetrating disease[7-9].

Capsule endoscopy (CE) was introduced in early 2000 and became a very powerful and patient friendly tool to investigate the small bowel. Meta analysis has shown that CE has a significantly higher diagnostic yield for small bowel lesions compared to small bowel follow through exams or CT enterography in patients with either suspected or known CD[10].

The aim of our 3 center study was to investigate whether CE provided any additional diagnostic benefit to patients with PD and a negative standard work-up for CD.

MATERIALS AND METHODS

We recruited patients with "severe" PD, i.e., perianal fistula or rectal abscess, aged 10-80 years in our study. All of these patients had to have had a normal gastrointestinal investigation within the prior 3 mo to qualify for inclusion in this study. A normal gastrointestinal investigation was defined as a normal ileo-colonoscopy, normal colonoscopy and normal small bowel follow through examination or a normal colonoscopy and a normal CT enterography. We excluded patients with a history of established CD or those with nonsteroidal anti-inflammatory drugs (NSAIDs) usage. All patients signed a written informed consent and the study was approved by the local IRBs of the participating hospitals.

The patients were on a clear liquid diet for 24 h and a 12 h fast prior to capsule ingestion (PillCam SB2, Given Imaging, Yoqneam, Israel). They were allowed to drink clear liquids 2 h after ingestion and to eat a light meal 4 h post ingestion. The data recorder 2 was removed when the capsule ceased to transmit images and data was processed by Rapid 6 software and read by 3 investigators (SA, RE, ES). Complete blood count, sedimentation rate, C reactive protein and inflammatory bowel disease (IBD) serology were recorded from patients' files.

RESULTS

Twenty six patients aged 21-61 years were recruited to this study (mean 35.6 years), 17 males and 9 females. One patient was excluded from the study because of gastric capsule retention.

Capsule examination of the small bowel revealed findings compatible with small bowel CD (apthous ulcerations, linear ulcers, circumferential ulcers) in six of the remaining 25 patients (24%) (Figures 1 and 2).

No serious adverse events and no small bowel capsule retention occurred. The observed findings at CE led to change in treatment in all six patients. Statistical analysis of laboratory findings such as CBC, CRP, ESR or family history of IBD, did not reveal any association with CE findings (Table 1).

DISCUSSION

Perianal disease may be the primary manifestation of small bowel CD in up to 36% of cases, or be associated with clinically active small bowel CD[1-3]. The spectrum of PD is wide. The mild form of PD includes fissures, skin tags and hemorrhoids, whereas perianal abscesses, external or rectovaginal fistulas, and/or anorectal strictures are the severe manifestations of PD. Physicians treating patients with PD often order a small bowel follow through examination, an entero-CT or a magnetic resonance enterography or perform an ileo-colonoscopy for the investigation of possible small bowel CD.

CE has gained an important role in the investiga-

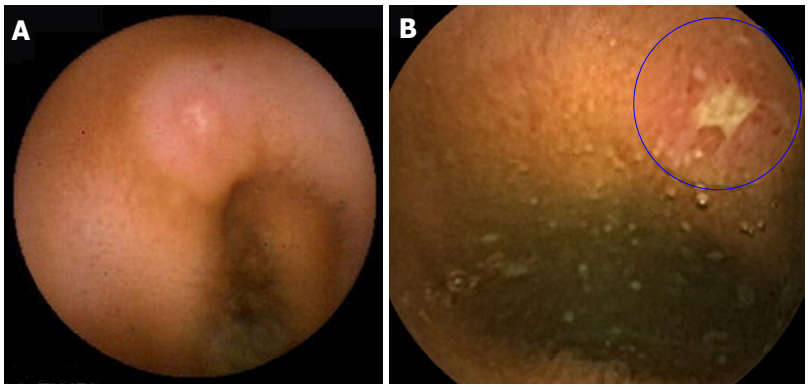


Figure 2 Capsule endoscopy findings (apthous and serpiginous ulcer) in a patient presenting with perianal fistula.

Table 1 Comparison of epidemiological and laboratory parameters in patients with perianal disease with or without small bowel Crohn's disease

	Normal SB	SB CD
Age (yr)	36.05 ± 10.62	34.5 ± 12.07
ESR (mm/h)	16.18 ± 16.19	21.5 ± 15.32
CRP (X upper limit)	3.18 ± 4.11	3.616 ± 1.63
Hemoglobin (mg %)	14.25 ± 1.82	13.96 ± 0.99
WBC (x 10^3/μL)	10.46 ± 8.42	8.11 ± 1.57
Family history of IBD	10.52%	16.60%

SB: Small bowel; CD: Crohn's disease; P: NS for all parameters; IBD: Inflammatory bowel disease; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood cell.

tion of small bowel disease in general and in suspected Crohn's disease specifically[11]. Many studies comparing CE to other radiographic procedures have been performed over the past ten years. A recent meta-analysis found CE to have a significantly higher diagnostic yield for small bowel pathologies compatible with CD than small bowel follow through examinations, entero CT and even ileo-colonoscopy[10]. Moreover, many studies using CE have found proximal small bowel lesions in up to 50% of patients, lesions that were not detected by other modalities[12,13]. Thus, it is logical to assume that in patients with PD and negative conventional investigations, the addition of a CE examination would increase the diagnostic yield, as demonstrated in the present study. The specificity of the capsule findings can be challenged. To avoid the most frequent imitators, we excluded patients who were on NSAIDs or patients who had taken NSAIDs in the 2 mo prior to capsule ingestion. In fact, studies in patients who were not taking NSAIDs for longer than 1 mo did not show any small bowel pathology[14]. Thus, we think our finding truly reflect small bowel CD.

In summary, CE can make the diagnosis of small bowel CD in an additional one quarter of patients presenting with severe PD and who had a negative conventional work up to exclude CD. Future studies are needed to determine whether in fact CE should be the primary investigational tool in such patients.

COMMENTS

Background

Perianal disease such fissure, fistula and abscesses in the ano rectal area can be a manifestation of Crohn's Disease. The diagnosis of Crohn's Disease traditionally has been made using barium follow through studies, computed tomographic (CT) examinations and colonoscopy with ileoscopy. In the past ten years, capsule endoscopy of the small bowel has become available. Capsule endoscopy has been shown to have a higher diagnostic yield in the diagnosis of Crohn's disease compared to barium or CT studies. The question of interest is whether capsule endoscopy is more sensitive in diagnosing Crohn's disease in patients with perianal disease than established traditional methods.

Research frontiers

Capsule endoscopy is a miniature camera that is swallowed and travels through the esophagus, stomach, small intestine and is excreted after passing through the colon. This miniature camera transmits high quality color images from the small bowel to an outside recorder. These images of the surface of the small bowel reveal even minor inflammatory changes such as apthous ulceration and mucosal hemorrhages, which methods such as barium studies and CT examinations cannot appreciate. Capsule endoscopy has proven to be more sensitive in the diagnosis of Crohn's disease.

Innovations and breakthroughs

With the advent of capsule endoscopy of the small bowel, it has become easy to assess the surface of the small bowel. This, in turn, has given doctors and researchers a more sensitive tool to diagnose Crohn's disease of the small bowel. Conventional methods have relied on barium studies of the small bowel, CT examinations of the small bowel and ileo-colonoscopy. The diagnostic sensitivity of these methods is inferior to the diagnostic sensitivity of capsule endoscopy for luminal disease.

Applications

The study results suggests that capsule endoscopy diagnoses Crohn's disease in 24% of patients with perianal disease who were thought not to have Crohn's disease after a conventional work up for Crohn's disease, which included ileo-colonoscopy, CT exam of the small bowel or barium studies of the small bowel.

Terminology

Capsule endoscopy is a capsule containing a miniature camera and a transmission system that sends color images from the intestines of the examinee to an outside recorder. Crohn's disease: chronic inflammatory disease of unknown origin affecting mainly the small bowel and the right colon. Crohn's disease can lead to inflammatory disease of the perianal area with abscesses, fistula formation and severe fissuring.

Peer review

The manuscript is perfectly written, the methodology is correct and the discussion is also informative.

REFERENCES

1 **Sangwan YP**, Schoetz DJ, Murray JJ, Roberts PL, Coller JA.

Perianal Crohn's disease. Results of local surgical treatment. *Dis Colon Rectum* 1996; **39**: 529-535
2 **McClane SJ**, Rombeau JL. Anorectal Crohn's disease. *Surg Clin North Am* 2001; **81**: 169-83, ix
3 **Williams DR**, Coller JA, Corman ML, Nugent FW, Veidenheimer MC. Anal complications in Crohn's disease. *Dis Colon Rectum* 1981; **24**: 22-24
4 **Alexander-Williams J**, Buchmann P. Perianal Crohn's disease. *World J Surg* 1980; **4**: 203-208
5 **Gasche C**, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ, Sutherland LR. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000; **6**: 8-15
6 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus Jr EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5-36
7 **Smith BR**, Arnott ID, Drummond HE, Nimmo ER, Satsangi J. Disease location, anti-Saccharomyces cerevisiae antibody, and NOD2/CARD15 genotype influence the progression of disease behavior in Crohn's disease. *Inflamm Bowel Dis* 2004; **10**: 521-528
8 **Sachar DB**, Bodian CA, Goldstein ES, Present DH, Bayless TM, Picco M, van Hogezand RA, Annese V, Schneider J, Korelitz BI, Cosnes J. Is perianal Crohn's disease associated with intestinal fistulization? *Am J Gastroenterol* 2005; **100**: 1547-1549
9 **Vasiliauskas EA**, Kam LY, Karp LC, Gaiennie J, Yang H, Targan SR. Marker antibody expression stratifies Crohn's disease into immunologically homogeneous subgroups with distinct clinical characteristics. *Gut* 2000; **47**: 487-496
10 **Dionisio PM**, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010; **105**: 1240-128; quiz 1249
11 **Eliakim R**, Suissa A, Yassin K, Katz D, Fischer D. Wireless capsule video endoscopy compared to barium follow-through and computerised tomography in patients with suspected Crohn's disease--final report. *Dig Liver Dis* 2004; **36**: 519-522
12 **Mehdizadeh S**, Chen GC, Barkodar L, Enayati PJ, Pirouz S, Yadegari M, Ippoliti A, Vasiliauskas EA, Lo SK, Papadakis KA. Capsule endoscopy in patients with Crohn's disease: diagnostic yield and safety. *Gastrointest Endosc* 2010; **71**: 121-127
13 **Petruzziello C**, Onali S, Calabrese E, Zorzi F, Ascolani M, Condino G, Lolli E, Naccarato P, Pallone F, Biancone L. Wireless capsule endoscopy and proximal small bowel lesions in Crohn's disease. *World J Gastroenterol* 2010; **16**: 3299-3304
14 **Maiden L**, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. *Gastroenterology* 2005; **128**: 1172-1178

S- Editor Yang XC **L- Editor** Roemmele A **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.189

World J Gastrointest Endosc 2012 May 16; 4(5): 189-193
ISSN 1948-5190 (online)

BRIEF ARTICLE

Anesthetic management for small bowel enteroscopy in a World Gastroenterology Organization Endoscopy Training Center

Somchai Amornyotin, Udom Kachintorn, Siriporn Kongphlay

Somchai Amornyotin, Siriporn Kongphlay, Department of Anesthesiology and Siriraj, Gastrointestinal Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
Udom Kachintorn, Department of Medicine and Siriraj, Gastrointestinal Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
Author contributions: Amornyotin S designed the research; Amornyotin S, Kachintorn U and Kongphlay S performed the research; Amornyotin S wrote the paper.
Correspondence to: Somchai Amornyotin, Associate Professor of Department of Anesthesiology and Siriraj, Gastrointestinal Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. sisam@mahidol.ac.th
Telephone: +66-2-4197990 Fax: +66-2-4113256
Received: October 13, 2011 Revised: December 7, 2011
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

AIM: To study the anesthetic management of patients undergoing small bowel enteroscopy in the World Gastroenterology Organization (WGO) Endoscopy Training Center in Thailand.

METHODS: Patients who underwent small bowel enteroscopy during the period of March 2005 to March 2011 in Siriraj Gastrointestinal Endoscopy Center were retrospectively analyzed. The patients' characteristics, pre-anesthetic problems, anesthetic techniques, anesthetic agents, anesthetic time, type and route of procedure and anesthesia-related complications were assessed.

RESULTS: One hundred and forty-four patients underwent this procedure during the study period. The mean age of the patients was 57.6 ± 17.2 years, and most were American Society of Anesthesiologists (ASA) class Ⅱ (53.2%). Indications for this procedure were gastrointestinal bleeding (59.7%), chronic diarrhea (14.3%), protein losing enteropathy (2.6%) and others (23.4%). Hematologic disease, hypertension, heart disease and electrolyte imbalance were the most common pre-anesthetic problems. General anesthesia with endotracheal tube was the anesthetic technique mainly employed (50.6%). The main anesthetic agents administered were fentanyl, propofol and midazolam. The mean anesthetic time was 94.0 ± 50.5 min. Single balloon and oral (antegrade) intubation was the most common type and route of enteroscopy. The anesthesia-related complication rate was relatively high. The overall and cardiovascular-related complication rates including hypotension in the older patient group (aged ⩾ 60 years old) were significantly higher than those in the younger group.

CONCLUSION: During anesthetic management for small bowel enteroscopy, special techniques and drugs are not routinely required. However, for safety reasons anesthetic personnel need to optimize the patient's condition.

Key words: Anesthetic management; Anesthetic technique; Complication; Developing country; Small bowel enteroscopy; Training center

Peer reviewer: Shuhei Yoshida, MD, PhD, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, United States

Amornyotin S, Kachintorn U, Kongphlay S. Anesthetic management for small bowel enteroscopy in a World Gastroenterology Organization Endoscopy Training Center. *World J Gastrointest Endosc* 2012; 4(5): 189-193 Available from:

URL: http://www.wjgnet.com/1948-5190/full/v4/i5/189.htm
DOI: http://dx.doi.org/10.4253/wjge.v4.i5.189

INTRODUCTION

The small intestine is a difficult area to examine due to its anatomy, location and relative tortuosity. Examination beyond the duodenum is of importance in a number of small bowel disorders. A major breakthrough in imaging of the small bowel came with capsule endoscopy and enteroscopy. However, capsule endoscopy has several limitations such as inability to evaluate a lesion in a to-and fro-manner, inability to provide endoscopic intervention, and inability to obtain tissue for diagnosis[1,2]. Enteroscopy is now the preferred method to examine the small bowel in most situations.

Enteroscopy describes endoscopic examination of the small bowel, extending into the jejunum and/or the ileum. All enteroscopy procedures can be carried out with the processing unit used for standard endoscopy[3]. Many methods such as push enteroscopy, balloon-assisted enteroscopy, and intraoperative enteroscopy have now made observations of the entire small bowel possible. However, enteroscopy is an invasive procedure requiring sedation and/or anesthesia. It usually carries a risk of high morbidity during and in the early post-anesthetic period. The type of anesthesia used is decided according to the patient's medical condition and the anesthesiologist's preference. Intravenous sedation (IVS) can be used, but to ensure better patient and endoscopist comfort during this complicated procedure, general anesthesia (GA) is preferred.

We conducted a retrospective study to report and evaluate the choices and techniques of anesthesia, drug usage and complications in enteroscopy patients during the period of March, 2005 to March, 2011 in the World Gastroenterology Organization (WGO) Endoscopy Training Center in Thailand. This study was also performed in order to adapt and store the data for further research in the near future.

MATERIALS AND METHODS

This was a retrospective study. Data from anesthetic, procedure records and history charts of patients who underwent enteroscopy procedures in Siriraj gastrointestinal Endoscopy Center, World Gastroenterology Organization Endoscopy Training Center, Thailand from March 2005 to March 2011 were reviewed. The general data included sex, age, American Society of Anesthesiologists (ASA) physical status, body weight and indications for endoscopy as well as the type and route of intubation. The anesthetic data encompassed pre-anesthetic problems, anesthetic technique, variety of drugs used, monitoring, anesthetic time, agent and complications which evolved during and immediately after the procedure.

Patients

All patients who underwent small bowel enteroscopy procedures during the study period were enrolled. Inclusion criteria were patients aged ⩾ 17 years old and procedures performed in the endoscopy unit. Exclusion criteria were patients younger than 17 years and procedures performed in the intensive care units and operating rooms.

Enteroscopy procedure

Enteroscopy procedures were performed by senior endoscopists. All procedures were carried out using an Olympus video endoscope compatible with the enteroscopy procedure. After completion of the procedure, all patients were observed in the recovery room for at least two hours prior to discharge. All patients were admitted to the hospital for at least one day. Patients were observed for both anesthesia and/or procedure-related complications. Procedure-related complications were defined as in the guidelines of the British Society of Gastroenterology[4].

Anesthesia-related procedure

The anesthetic agents used depended on the patient's medical condition and the familiarity of the anesthesiologist with the particular case. All anesthetized patients were intubated. A balanced anesthesia technique including analgesic agent, muscle relaxant and inhalation agent was used in the GA group. All sedated patients were given supplemental oxygenation *via* a nasal cannula and were sedated to a deep sedation level, according to the guidelines of the American Society of Anesthesiologists[5] and the American Society for Gastrointestinal Endoscopy[6]. All patients were anesthetized and/or sedated by well trained anesthetic personnel directly supervised by a staff anesthesiologist in the endoscopy room. Anesthetic personnel included residents in anesthesiology and anesthetic nurses who were well trained in the use of the IVS technique and airway management.

Anesthesia-related complications were recorded. Complications were defined as follows: hypertension or hypotension (increase or decrease in blood pressure by 20% from baseline); tachycardia or bradycardia (increase or decrease in heart rate by 20% from baseline); any cardiac arrhythmias; hypoxia (oxygen desaturation, SpO_2 < 90%); airway obstruction. Serious anesthesia-related complications were defined as cardiac arrest and prolonged desaturation or apnea with duration more than 30 s.

Statistical analysis

Results were expressed as mean ± SD or percentage (%), when appropriate. Comparisons of anesthesia-related complications between the patients aged < 60 years and ⩾ 60 years were performed using Chi-square tests (for categorical variables). The statistical software package SPSS for Windows Version 11 (SPSS Inc., Chicago, IL, United States) was used to analyze the data. All statistical comparisons were made at the two-sided 5% level of significance.

Table 1 Patients' characteristics, anesthetic time and technique, and indications for procedure

Variables	Results (n = 154)
Age (yr) (mean, SD; min-max)	57.6 (17.2); 17–92
Gender (male/female; n %)	75/79 (48.7/51.3)
Weight (kg) (mean, SD)	56.3 (11.0); 30-96
ASA physical status (Ⅰ, Ⅱ, Ⅲ, Ⅳ; n %)	15/82/56/1 (9.7/53.2/36.4/0.6)
Anesthetic time (min) (mean, SD; min-max)	94.0 (50.5); 30-290
Anesthetic technique	
GA with endotracheal tube	78 (50.6)
Topical pharyngeal anesthesia and IVS	38 (24.7)
IVS	38 (24.7)
Indications (n %)	
Gastrointestinal bleeding	92 (59.7)
Chronic diarrhea	22 (14.3)
Protein losing enteropathy	4 (2.6)
Others	36 (23.4)

IVS: Intravenous sedation; GA: General anesthesia; ASA: American Society of Anesthesiologists.

Table 2 Endoscopy characteristics and pre-anesthetic problems

	n (%)
Type of enteroscopy	
Single balloon	105 (68.2)
Push	47 (30.5)
Spiral	2 (1.3)
Route of intubation	
Oral (antegrade)	125 (81.2)
Anal (retrograde)	29 (18.8)
Pre-anesthetic problems	
Hematologic disease	114 (74.0)
Hypertension	54 (35.1)
Heart disease	48 (31.2)
Electrolyte imbalance	46 (29.9)
Renal disease	23 (14.9)
Diabetes mellitus	18 (11.7)
Others	43 (27.9)

RESULTS

There were 154 enteroscopy procedures performed during the study period. The majority of the patients were female, with a mean age of 57.6 ± 17.2 years, and ASA physical status Ⅱ-Ⅲ. Mean anesthetic time was 94.0 ± 50.5 min. GA with endotracheal tube was the main anesthetic technique employed. The indications for this procedure are shown in Table 1.

Table 2 shows the endoscopy characteristics and pre-anesthetic problems. Single balloon enteroscopy and antegrade intubation was the most common type and route of procedure. There were 346 pre-anesthetic problems in 154 procedures. They involved mainly hematologic disease; anemia, hypertension and heart disease; coronary artery disease.

Clinical monitoring observed by the anesthetic personnel consisted of non-invasive blood pressure, heart rate, pulse oximetry and electrocardiography. Anesthetic personnel were anesthesiology residents and anesthetic nurses. They sedated and/or anesthetized patients in the endoscopy room outside the operating room directly supervised by a staff anesthesiologist. The anesthetic personnel did not routinely use end-tidal carbon dioxide monitoring. In sedated patients, we did not use end-tidal carbon dioxide monitoring. In comparison, end-tidal carbon dioxide monitoring was used in the majority of intubated patients. Details of the sedative and analgesic agents, inhalation agents and muscle relaxants used are shown in Table 3.

Table 4 demonstrates anesthesia-related complications categorized by age. There was a relatively high complication rate. The most frequent anesthesia-related complication was hypotension which was promptly corrected by the administration of vasopressor and fluid loading. The authors noted that hypotension commonly occurred in the propofol-balanced sedation group after rapid propofol injection. Overall and cardiovascular-related complications including hypotension in the group of patients aged ⩾ 60 years were significantly higher than those in the younger group. One patient who underwent IVS developed cardiac arrest during the procedure due to unresolved airway management. However, the patient was successfully resuscitated. According to ASA physical status, overall and cardiovascular-related complications including hypotension in patients who had ASA physical status Ⅲ-Ⅳ were significantly higher than in patients who had ASA physical status Ⅰ-Ⅱ. However, anesthesia-related complications between gender, anesthetic time (60 min *vs* > 60 min), and anesthetic technique were not significantly different.

DISCUSSION

Enteroscopy is an effective technique for the diagnosis and treatment of small bowel abnormalities with few complications. All enteroscopy procedures require sedation and/or anesthesia except capsule enteroscopy. The most common indication for all enteroscopy procedures is diagnosis and/or therapy of acute or chronic gastrointestinal bleeding. Other indications include Crohn's disease, stricture, ulcer, polyposis syndrome, mass, foreign body, chronic diarrhea, malabsorption, lymphoma and imaging abnormalities[1,7].

All enteroscopes used in our endoscopy unit were Olympus video endoscopes. Therefore, double balloon enteroscopy procedures were not performed. Two spiral enteroscopy procedures were carried out by an expert endoscopist during a workshop demonstration. In addition, our endoscopists were familiar with the single balloon enteroscope. Anesthesiologists had limited experience with this procedure. However, anesthesia for small bowel enteroscopy procedures was relatively safe and effective. No serious adverse events occurred. The authors have used the small bowel enteroscopy procedure since 2005 which has reduced the number of operations, the risk of prolonged anesthesia, and special anesthetic techniques. However, the present study was limited by time, thus the treatment given in certain cases was not

Table 3 Anesthetic agents used (*n*, %)

	n (%)
Sedative and analgesic agents	
Propofol	139 (90.3)
Thiopental	15 (9.7)
Midazolam	88 (57.1)
Fentanyl	150 (97.4)
Muscle relaxation	
Succinyl choline	76 (49.4)
Atracurium	53 (34.4)
Cis-atracurium	21 (13.6)
Rocuronium	5 (3.2)
Vecuronium	4 (2.6)
Inhalation agents	
Isoflurane	43 (27.9)
Sevoflurane	34 (22.1)
Desflurane	5 (3.2)

Table 4 Anesthesia-related complications categorized by age (*n*, %)

Adverse events	< 60 yr (*n* = 75)	≥ 60 yr (*n* = 79)	*P* value
Overall	29 (38.7)	47 (59.5)	0.010[1]
Cardiovascular	25 (33.3)	43 (54.4)	0.008[1]
Hypotension	21 (28.0)	41 (51.9)	0.003[1]
Bradycardia	3 (4.0)	1 (1.3)	0.286
Arrhythmia	0	1 (1.3)	0.328
Cardiac arrest	1 (1.3)	0	0.303
Respiratory	4 (5.3)	4 (5.1)	0.94
Hypoxia (SpO_2 < 90%)	0	1 (1.3)	0.328
Upper airway obstruction	4 (5.3)	3 (3.8)	0.647

[1]Considered to be statistically significant.

completed and further therapy is expected to continue.

There are two basic choices of anesthesia for the enteroscopy procedure, these are the IVS and GA techniques, which have advantages and disadvantages. With the IVS technique, anesthetic agents can be reduced and patients have a rapid recovery, however, control of respiration and the cardiovascular system are more difficult. In addition, there is a high number of procedure- and sedation-related respiratory complications. With the GA technique, the control of respiration and the cardiovascular systems is more reliable. In our center, IVS in the retrograde intubation technique is commonly used due to the reasons given in conjunction with anesthesiologist preference. In comparison, the authors normally use GA with endotracheal tube in antegrade intubation.

Because our center is a tertiary care teaching hospital, more difficult patients are referred for enteroscopy under GA. Additionally, more therapeutic enteroscopy procedures are performed in patients under GA, and these patients have more interventions at the same time compared to patients with IVS[8]. In our hospital, the experience of the endoscopists is not taken into account in the indication to perform enteroscopy under GA. However, it is tempting to speculate that these patients in particular may benefit from the GA technique with less experienced endoscopists. Moreover, cardiopulmonary and other diseases which are more frequent in older patients have been regarded as the major risk factors for complications associated with endoscopy or sedation[9-11]. Old age as an important risk factor for endoscopy, but is not an indication for providing GA more frequently for enteroscopy at our institution. However, this depends on the experience of the anesthesiologists themselves.

The benefits of the higher efficacy and success rate of small bowel enteroscopy under GA compared to IVS were not confirmed in the present study. However, it has been reported that additional time for preparation is required for enteroscopy under GA, with induction of anesthesia and intubation of the patient[12]. In addition, 15-30 min of surveillance in a post-anesthesia care unit need to be added to the additional time required for enteroscopy under GA.

At our center, the most common enteroscopy procedures are single balloon and push enteroscopies. These are normally performed in the left lateral position. When the supine position is preferred to improve visualization in difficult cases, insufficient airway protection may occur during IVS. GA is, therefore, often used at our center to protect the airways during time consuming endoscopy procedures in the supine position.

Propofol is widely used for anesthesia outside the operating room, and has a good safety and efficacy profile due to its quick onset of action, rapid metabolism, significantly shorter recovery time and it has some anti-emetic effects[13,14]. Midazolam is also widely used because of its more rapid onset of action and shorter duration of effect compared with diazepam[15]. Fentanyl has a short half-life and rapid onset of action, and may have an advantage over pethidine in elderly patients. We usually use propofol, midazolam and fentanyl for endoscopic procedures including small bowel enteroscopy. A low dose of midazolam, combined with low dose fentanyl and propofol, was safe and effective, and did not prolong recovery time even in elderly patients[10,11,16,17]. In GA, short-acting muscle relaxants (atracurium and cis-atracurium) and short-acting inhalation agents (isoflurane, sevoflurane and desflurane) are commonly used for short procedures[18].

The present study had a relatively high overall rate of anesthesia-related complications. This rate was higher than that commonly reported, and there may be several explanations for this. We used the following criteria to define complications: hypo/hypertension and brady/tachycardia measured as the changes of blood pressure and heart rate of more than 20% of baseline values. Hypoxia was defined as oxygen saturation < 90%. Moreover, if only serious complications were assessed, the complication rate was only 0.6%, which corresponds to previously published studies[19]. In our study, one serious complication related to IVS was observed.

Small bowel enteroscopy is an invasive endoscopy procedure. This procedure requires not only endoscopists but also anesthetic personnel to observe and take care of the patients. Clinical signs should be carefully

observed because the occurrence of complications has more significance in elderly patients. However, there was no need for special techniques or drugs in anesthesia in this study. For safety reasons anesthetic personnel need to optimize the patients' condition and should be aware of complications.

COMMENTS

Background

Small bowel enteroscopy is the current standard approach for diagnosis and treatment of small bowel abnormalities. It is an invasive and long procedure. Anesthesia is usually used for this endoscopy procedure. However, there are no reports regarding the anesthetic management of patients undergoing small bowel enteroscopy.

Research frontiers

The authors undertook a retrospective study to assess the anesthetic management of patients undergoing small bowel enteroscopy in the World Gastroenterology Organization Endoscopy Training Center in Thailand.

Innovations and breakthroughs

Pre-procedural assessment and preparation is essential for small bowel enteroscopy. Deep sedation and general anesthesia techniques are safe and effective for this procedure. In addition, special anesthetic techniques and drugs are not routinely required.

Applications

General anesthesia with tracheal intubation should be used for antegrade intubation with prolonged procedure time. Retrograde intubation can be performed safely using deep sedation or general anesthesia techniques.

Peer review

The authors have presented a well written documentation of anesthetic management for small bowel enteroscopy.

REFERENCES

1 **Mönkemüller K**, Bellutti M, Fry LC, Malfertheiner P. Enteroscopy. *Best Pract Res Clin Gastroenterol* 2008; **22**: 789-811
2 **Sidhu R**, Sanders DS, Morris AJ, McAlindon ME. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. *Gut* 2008; **57**: 125-136
3 **DiSario JA**, Petersen BT, Tierney WM, Adler DG, Chand B, Conway JD, Coffie JM, Mishkin DS, Shah RJ, Somogyi L, Wong Kee Song LM. Enteroscopes. *Gastrointest Endosc* 2007; **66**: 872-880
4 **British Society of Gastroenterology**. Complications of gastrointestinal endoscopy. *BSG Guidelines in Gastroenterology* 2006; 1-30
5 **American Society of Anesthesiologists**. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; **96**: 1004-1017
6 **Cohen LB**, Delegge MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, Piorkowski JD. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007; **133**: 675-701
7 **Semrad CE**. Small bowel enteroscopy: territory conquered, future horizons. *Curr Opin Gastroenterol* 2009; **25**: 110-115
8 **Chavalitdhamrong D**, Jutabha R. The evolution of enteroscopy to spiral enteroscopy. *Pract Gastroenterol* 2010; 10-18
9 **Amornyotin S**, Na-pomphet S, Wongwathanyoo T, Chalayonnavin V. Anesthesia for endoscopic retrograde cholangiopancreatography (ERCP) from 1999--2003 in Siriraj Hospital: a retrospective study. *J Med Assoc Thai* 2004; **87**: 1491-1495
10 **Amornyotin S**, Kachintorn U, Chalayonnawin W, Kongphlay S. Propofol-based deep sedation for endoscopic retrograde cholangiopancreatography procedure in sick elderly patients in a developing country. *Ther Clin Risk Manag* 2011; **7**: 251-255
11 **Amornyotin S**, Srikureja W, Pausawasdi N, Prakanrattana U, Kachintorn U. Intravenous sedation for gastrointestinal endoscopy in very elderly patients of Thailand. *Asian Biomed* 2011; **5**: 485-491
12 **Lichtenstein DR**, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, Fanelli RD, Gan SI, Harrison ME, Ikenberry SO, Shen B, Stewart L, Khan K, Vargo JJ. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008; **68**: 815-826
13 **Training Committee. American Society for Gastrointestinal Endoscopy.** Training guideline for use of propofol in gastrointestinal endoscopy. *Gastrointest Endosc* 2004; **60**: 167-172
14 **Amornyotin S**, Srikureja W, Chalayonnavin W, Kongphlay S. Dose requirement and complications of diluted and undiluted propofol for deep sedation in endoscopic retrograde cholangiopancreatography. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 313-318
15 **Tolia V**, Peters JM, Gilger MA. Sedation for pediatric endoscopic procedures. *J Pediatr Gastroenterol Nutr* 2000; **30**: 477-485
16 **Amornyotin S**, Chalayonnavin W, Kongphlay S. Propofol-Based Sedation Does Not Increase Rate of Complication during Percutaneous Endoscopic Gastrostomy Procedure. *Gastroenterol Res Pract* 2011
17 **Amornyotin S**, Chalayonnavin W, Kongphlay S. Assisted sedation for percutaneous endoscopic gastrostomy in sick patients in a developing country. *Gastroenterol Insights* 2010; **2**: 17-20
18 **Tonner PH**. Balanced anaesthesia today. *Best Pract Res Clin Anaesthesiol* 2005; **19**: 475-484
19 **Ellett ML**. A literature review of the safety and efficacy of using propofol for sedation in endoscopy. *Gastroenterol Nurs* 2010; **33**: 111-117

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.194

World J Gastrointest Endosc 2012 May 16; 4(5): 194-196
ISSN 1948-5190 (online)

CASE REPORT

Double-balloon endoscopy-diagnosed multiple small intestinal ulcers in a Churg-Strauss syndrome patient

Takayoshi Suzuki, Masashi Matsushima, Yoshitaka Arase, Mia Fujisawa, Ichiro Okita, Muneki Igarashi, Jun Koike, Tetsuya Mine

Takayoshi Suzuki, Masashi Matsushima, Yoshitaka Arase, Mia Fujisawa, Ichiro Okita, Muneki Igarashi, Jun Koike, Tetsuya Mine, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Kanagawa 259-1193, Japan

Author contributions: Suzuki T wrote the paper and performed double-balloon endoscopy; Arase Y, Fujisawa M, Okita I, Igarashi M and Koike J were responsible for data collection; Matsushima M and Mine T reviewed this manuscript.

Correspondence to: Takayoshi Suzuki, MD, PhD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara City, Kanagawa, 259-1193, Japan. takayosh@is.icc.u-tokai.ac.jp

Telephone: +81-463-931121 Fax: +81-463-914175
Received: March 30, 2011 Revised: September 12, 2011
Accepted: March 30, 2012
Published online: May 16, 2012

Abstract

Churg-Strauss syndrome (CSS) is a systemic vascular disorder characterized by severe bronchial asthma, hypereosinophilia, and allergic rhinitis. Small intestinal ulcers associated with CSS are a relatively rare manifestation that causes gastrointestinal bleeding. Multiple deep ulcers with an irregular shape are characteristic of small intestinal involvement of CSS. Video-capsule-endoscopy (VCE), double-balloon endoscopy (DBE) and Spirus assisted enteroscopy have been developed recently and enabled observation of the small intestine. In this case report, we have described a patient with CSS who had multiple deep ulcers in the jejunum detected by oral DBE. Since severe gastrointestinal (GI) involvement has been identified as an independent factor associated with poor outcome, the careful investigation of GI tract must be needed for CSS patients with GI symptoms. We describe the usefulness of DBE for diagnosis of small intestinal ulcers in patient with CSS.

Key words: Churg-Strauss syndrome; Small intestinal ulcers; Double-balloon endoscopy

Peer reviewers: Reena Sidhu, MRCP, MD, Department of Gastroenterology, Royal Hallamshire Hospital, 15 Barncliffe Road, Fulwood, Sheffield S10 4DF, United Kingdom; Sherman M Chamberlain, Associate Professor of Medicine, Section of Gastroenterology, BBR-2538, Medical College of Georgia, Augusta, GA 30912, United States; Sheng-Lei Yan, MD, Division of Gastroenterology, Department of Internal Medicine, Chang Bing Show Chwan Memorial Hospital, No.6, Lugong Rd., Lugang Township, Changhua County 505, Taiwan, China

Suzuki T, Matsushima M, Arase Y, Fujisawa M, Okita I, Igarashi M, Koike J, Mine T. Double-balloon endoscopy-diagnosed multiple small intestinal ulcers in a Churg-Strauss syndrome patient. *World J Gastrointest Endosc* 2012; 4(5): 194-196 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/194.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.194

INTRODUCTION

Churg-Strauss syndrome (CSS), also known as allergic granulomatous angiitis, is a relatively rare systemic vascular disorder. The organ most often affected is the lung, followed by the skin. The gastrointestinal (GI) tract may be involved in approximately 20%-50% of the patients with CSS[1]. The main GI tract symptoms are abdominal pain, diarrhea, and bleeding. However, the involvement of the small intestine is a rare complication, often detected during an emergent operation for treatment of intestinal perforation[2-4]. Previous reports of CSS provided only a few details regarding small intestinal ulcerations.

Double-balloon endoscopy (DBE) is a relatively new endoscopic device designed to visualize the entire small intestine[5]. Observation of the entire small intestine can

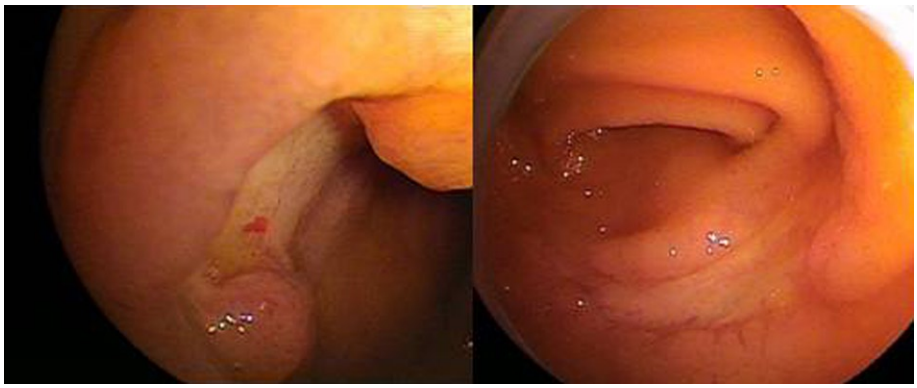


Figure 1 Double- balloon endoscopic examination, showing multiple "punched-out" ulcers in the jejunum.

be performed using an oral and/or anal DBE approach. Endoscopic interventions, such as biopsy, clipping, argon plasma coagulation, balloon dilatation, and endoscopic mucosal resection, can also be performed by DBE. In Japan, DBE is mainly used to find the origin of obscure GI bleeding in cases where the bleeding cause cannot be revealed by the usual methods, such as esophagogastroduodenoscopy, colonoscopy, or radiologic evaluation of small intestine[6].

We report a case of CSS with multiple small intestinal ulcers that were successfully detected by DBE without a surgical procedure.

CASE REPORT

A 79 year-old man with a 2 year history of severe CSS that had been treated by corticosteroids was admitted to Tokai University Hospital because of a 3 d history of tarry stool, edema of the lower extremities and facial swelling. His medical records showed that he had a 7 year history of bronchial asthma and a 2 year history of chronic renal failure. A physical examination revealed severe anemia, facial swelling, and edema of the lower limbs. His blood pressure was 130/60 mmHg, his pulse was 90/min and regular, and his body temperature was 36.3 ℃. No tenderness on palpation of the abdomen was observed; bowel sounds were noted. Digital examination revealed tarry stool. Neurological examination revealed sensory and motor disturbance of both legs, which is compatible with mononeuritis multiplex. Laboratory analyses included the following: white blood cell count, 6400/mm^3 (4000-8000/mm^3) with 0.2% eosinophils (1%-4%); hemoglobin, 4.6 g/dL (13.5-17.5 g/dL); platelet count, 127 000/mm^3 (140 000-400 000/ mm^3); erythrocyte sedimentation rate, 10 mm/h (1- 10 mm/h); C-reactive protein, 0.2 mg/dL (-0.3 mg/dL); IgE, 504 U/mL (-500 U/mL); myeloperoxidase-antineutrophil cytoplasmic antibodies (p-ANCA), 226 EU (< -20 EU). A computed tomographic scan of the abdomen showed no abnormalities. Emergency esophagogastroduodenoscopy showed that there was no bleeding source in the esophagus, duodenum, or stomach, but that gastritis was present. Since 1st DBE consensus meeting in Japan had recommended that DBE with oral approach had been indicated in the cases with overt ongoing bleeding, oral DBE (EN-450T5/20; Fujinon Co, Ltd, Saitama City, Japan) was performed on the 2nd day after his admission; "punched-out" multiple ulcers without visible vessels at the ulcer floor were observed (Figure 1) in the upper jejunum. There were no procedure-related complications. It is quite difficult to diagnose a possible pathological condition from the findings of small intestinal ulcers, because small intestinal ulcers are observed in a number of pathological conditions, such as Crohn's disease, mesenteric ischemia, lymphoma, ulcerated cancer, drug-related injuries, vasculitides, connective tissue disorders, and infections[7]. In this case, biopsy specimens obtained from the ulcerative lesions on DBE did not reveal any specific findings such as eosinophilic infiltration, ischemic change, or malignancy. Because his medical history documented that he had not recently received any medication involving non-steroidal anti-inflammatory drugs or antibiotics, drug-related small intestinal injuries were excluded. Developing tarry stool, edema and mononeuritis multiplex suggested that his condition should be considered a relapse of his CSS. Therefore, prednisolone (30 mg daily) was delivered intravenously for 20 d; the tarry stool improved and gradually tapered off without relapse.

DISCUSSION

CSS is classified as a systemic vasculitis that affects small- to medium- sized vessels associated with bronchial asthma, hypereosinophilia, and allergic rhinitis. The American College of Rheumatology has proposed the following six criteria for defining CSS: asthma; eosinophilia greater than 10% on differential white blood cell count; paranasal sinus abnormality; migratory or transient pulmonary infiltrates detected radiographically; mononeuropathy (including multiplex) or polyneuropathy; and biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas. The presence of four or more of these criteria yields a sensitivity of 85% and a specificity of 99.7% for CSS[8]. In the present case, the diagnosis was arrived at by the presence of five of these six criteria, paranasal sinusitis being the

exception, when he was 77 years old. At that time, a skin biopsy was performed on his left lower extremity, and the section showed marked infiltration of eosinophils at the perivascular and peri-adnexal regions in the dermis.

The clinical elements of CSS occur in three sequential phases: prodromal, eosinophilic, and vasculitic. The prodromal phase is characterized by atopic disease, allergic rhinitis, and asthma. Features of the eosinophilic phase include peripheral blood eosinophilia and eosinophilic infiltration of multiple organs, especially of the lung and GI tract. In the vasculitic phase, a life-threatening systemic vasculitis of the medium and small vessels frequently occurs. The vasculitic phase may be heralded by disparate nonspecific signs and symptoms related to the cardiovascular, gastrointestinal, epidermal, renal, musculoskeletal, and nervous systems. This patient was in the vasculitic phase; he had variety of symptoms, such as GI bleeding, weight loss, malaise, sensory and motor disturbance of both legs, and dyspnea resulting from chronic cardiac failure. A long-term follow-up study conducted by Guillevin *et al*[9] revealed that the presence of renal insufficiency, proteinuria (> 1 g/d), central nervous system or cardiac involvement, and GI disease are indicators of poor prognosis. When the patient in the present case was admitted to our hospital, he already had all these clinical factors, suggesting that his five-year survival rate was approximately 54%.

Among the GI signs reported in a study by Lanham *et al*[10] abdominal pain occurred in 59%, diarrhea in 33%, and bleeding in 18% of patients with CSS. Ulceration, perforation, and stenosis of the GI tract are assumed to be the results of ischemia caused by vasculitis. Although the stomach, duodenum, or colon is often involved in those lesions in patients, the small intestine is rarely involved. A recent report showed video-capsule-endoscopy (VCE) to be a useful tool for diagnosis of GI involvement, especially in the small intestine in a patient with CSS[11]. However this procedure has limitations, such as the unavailability of taking biopsy specimens and of performing therapeutic intervention. There has been no report on an image of small intestinal ulcers associated with CSS detected by balloon-endoscopy. To the best of our knowledge, this is the first report using DBE to show an image of multiple ulcers in the small intestine in a case of CSS. Since typical histological findings such as vasculitis or granuloma could be obtained in approximately one fourth of CSS patients by taking a biopsy from gastrointestinal tissue and therapeutic intervention could subsequently be performed, DBE could represent an important diagnostic and therapeutic tool for small intestinal involvement. In conclusion, DBE in combination with VCE might become a complimentary procedure to diagnose the small intestinal involvement in patients with CSS.

REFERENCES

1 **Chumbley LC**, Harrison EG, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin Proc* 1977; **52**: 477-484

2 **Murakami S**, Misumi M, Sakata H, Hirayama R, Kubojima Y, Nomura K, Ban S. Churg-Strauss syndrome manifesting as perforation of the small intestine: report of a case. *Surg Today* 2004; **34**: 788-792

3 **Nakamura Y**, Sakurai Y, Matsubara T, Nagai T, Fukaya S, Imazu H, Hasegawa S, Ochiai M, Funabiki T, Mizoguchi Y, Kuroda M. Multiple perforated ulcers of the small intestine associated with allergic granulomatous angiitis: report of a case. *Surg Today* 2002; **32**: 541-546

4 **Ahn E**, Luk A, Chetty R, Butany J. Vasculitides of the gastrointestinal tract. *Semin Diagn Pathol* 2009; **26**: 77-88

5 **Yamamoto H**, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, Ido K, Sugano K. Total enteroscopy with a nonsurgical steerable double-balloon method. *Gastrointest Endosc* 2001; **53**: 216-220

6 **Yamamoto H**, Kita H, Sunada K, Hayashi Y, Sato H, Yano T, Iwamoto M, Sekine Y, Miyata T, Kuno A, Ajibe H, Ido K, Sugano K. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. *Clin Gastroenterol Hepatol* 2004; **2**: 1010-1016

7 **Gay G**, Delvaux M, Frederic M. Capsule endoscopy in non-steroidal anti-inflammatory drugs-enteropathy and miscellaneous, rare intestinal diseases. *World J Gastroenterol* 2008; **14**: 5237-5244

8 **Masi AT**, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; **33**: 1094-1100

9 **Guillevin L**, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; **78**: 26-37

10 **Lanham JG**, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore)* 1984; **63**: 65-81

11 **Sánchez R**, Aparicio JR, Baeza T, Calero Y. Capsule endoscopy diagnosis of intestinal involvement in a patient with Churg-Strauss syndrome. *Gastrointest Endosc* 2006; **63**: 1082-1084

S- Editor Yang XC **L- Editor** A **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v4.i5.197

World J Gastrointest Endosc 2012 May 16; 4(5): 197-200
ISSN 1948-5190 (online)

CASE REPORT

Efferent limb of gastrojejunostomy obstruction by a whole okra phytobezoar: Case report and brief review

Thant Zin, Myat Maw, Dinker Ramananda Pai, Rosaini Binti Paijan, Myo Kyi

Thant Zin, Myat Maw, Dinker Ramananda Pai, Department of Surgery, Melaka Manipal Medical College, 75150 Melaka, Malaysia
Rosaini Binti Paijan, Myo Kyi, Department of Surgery, Hospital Pakar Sultanah Fatimah, Muar Johor, Malaysia
Author contributions: Thant Z revised the manuscript and performed data research; Maw M acquired patient information and drafted the manuscript; Pai DR reviewed the manuscript and provided discussion points; Paijan RB and Kyi M helped to obtain patient consent, helped with patient management and amended the manuscript.
Correspondence to: Thant Zin, FRCS, Associate Professor, Department of Surgery, Melaka Manipal Medical College, Jalan Batu Hampar, Bukit Baru, 75150 Melaka, Malaysia. thant.zin@manipal.edu.my
Telephone: +606-2925849 Fax: +606-2925852
Received: April 11, 2011 Revised: January 1, 2012
Accepted: April 27, 2012
Published online: May 16, 2012

Abstract

A phytobezoar is one of the intraluminal causes of gastric outlet obstruction, especially in patients with previous gastric surgery and/or gastric motility disorders. Before the proton pump inhibitor era, vagotomy, pyloroplasty, gastrectomy and gastrojejunostomy were commonly performed procedures in peptic ulcer patients. One of the sequelae of gastrojejunostomy is phytobezoar formation. However, a bezoar causing gastric outlet obstruction is rare even with giant gastric bezoars. We report a rare case of gastric outlet obstruction due to a phytobezoar obstructing the efferent limb of the gastrojejunostomy site. This phytobezoar which consisted of a whole piece of okra (lady finger vegetable) was successfully removed by endoscopic snare. To the best of our knowledge, this is the first case of okra bezoar-related gastrojejunostomy efferent limb obstruction reported in the literature.

Key words: Efferent limb obstruction; Gastrojejunostomy; Okra phytobezoar

Peer reviewer: Makoto Hashizume, MD, PhD, FACS, Professor and Chairman, Department of Advanced Medical Initiatives, Faculty of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Zin T, Maw M, Pai DR, Paijan RB, Kyi M. Efferent limb of gastrojejunostomy obstruction by a whole okra phytobezoar: Case report and brief review. *World J Gastrointest Endosc* 2012; 4(5): 197-200 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i5/197.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i5.197

INTRODUCTION

Gastric bezoars are a form of concretion resulting from the accumulation of ingested materials. They are relatively rare and are found in less than 1% of patients undergoing gastroscopy[1]. The nature of the contents classifies gastric bezoars into many types. Common bezoars are phytobezoars, trichobezoars and pharmacobezoars. Among the various types of bezoars, the most common type is the phytobezoars, which are composed mainly of undigested vegetable materials.

Generally, gastric phytobezoars are common in patients with dentition problems, impaired digestion, decreased gastric motility and previous gastric surgery[2,3]. They usually have a wide range of clinical presentations from abdominal discomfort and weight loss to small bowel obstruction[4]. Gastric outlet obstruction is an uncommon presentation of gastric bezoars even when they occupy the whole stomach. We report a patient who previously underwent gastrectomy and gastrojejunostomy for duodenal ulcer and who presented with signs and symptoms of partial gastric outlet obstruction due to a phytobezoar obstructing the gastrojejunostomy efferent limb.

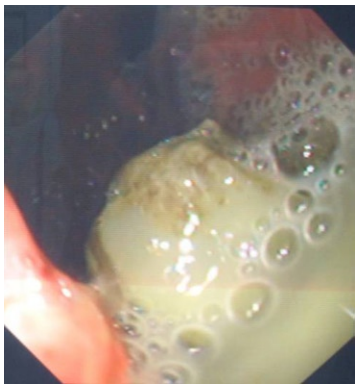


Figure 1 Endoscopic view: Phytobezoar obstructing the efferent limb of gastrojejunostomy.

Figure 2 Whole piece of okra (lady finger vegetable) formed the centre of the phytobezoar.

CASE REPORT

A 67-year-old gentleman presented with intermittent epigastic pain of one month duration. He was suffering from pain associated with vomiting. His vomitus contained old food particles and some bile. He had a history of gastrectomy and gastrojejunostomy for peptic ulcer disease in the previous 30 years. Clinically, he had a distended stomach with a positive succession splash. There was some tooth loss which caused mastication problems. Gastroscopy revealed a distended stomach containing undigested food particles mixed with bile and mucus. The gastrojejunostomy site appeared adequate and no signs of ulceration or stricture were noted. The afferent limb was patent with free flowing bile during intubation. A golf ball-sized phytobezoar was found obstructing the efferent limb area of the gastrojejunostomy (Figure 1). It was successfully removed using an endoscopic snare. Examination of the bezoar after removal revealed an inner core formed from a whole piece of okra (Figure 2). The patient was well following removal of the phytobezoar, and was given appropriate dietary advice upon discharge to prevent recurrence.

DISCUSSION

Gastric bezoars are formed due to the accumulation of ingested materials in the form of concretions. They are rare and found in less than 1% of patients who undergo gastroscopy[1]. The commonest type of bezoar is a phytobezoar which is composed of vegetable material[5]. In our case, the centre of the bezoar was formed by a whole piece of okra; lady finger vegetable. Trichobezoars are composed of swallowed hairs in patients with psychiatric disorders. High fibre persimmon fruits can cause diospyrobezoars, and pharmacobezoars are composed of ingested medications.

The pathogenesis of bezoar formation is usually intricate. It involves many factors such as improper mastication, dentition problems, alterations in the production of acid, pepsin and mucus, previous gastric surgery and impairments in gastric motility[6,7]. Robles *et al*[8] pointed out that 20% of patients have mastication and dentition problems, 70%-94% have had previous gastric surgery and 40% have a history of excessive dietary fibre intake. Most adults with phytobezoars are men between the ages of 40 and 50 years, however, trichobezoars usually occur in young women with psychiatric problems[4,9].

Patients with gastric bezoars may remain asymptomatic for many years. Common symptoms usually include abdominal pain, nausea, vomiting, early satiety, anorexia and weight loss. Some patients present with gastrointestinal bleeding from gastric ulcer formation due to bezoar-induced pressure necrosis[4]. However, gastric outlet obstruction is an uncommon presentation in patients with gastric bezoars, even though some are large enough to fill the whole stomach. Leung *et al*[10] reported a case of bezoar-induced gastric outlet obstruction in a patient who had a previous gastrojejunostomy for peptic ulcer disease in whom they found a stricture at the anastomotic site. In another study, a large bezoar was found to occlude the afferent loop of the gastrojejunostomy, this patient also had afferent loop syndrome which was diagnosed by ultrasound and computed tomography (CT)[11]. In our report, the patient vomited old food indicating a gastric outlet obstruction; however, the presence of bile meant that the afferent loop of the gastrojejunostomy was still patent. Gastric outlet obstruction was due to occlusion of the efferent limb by a whole okra phytobezoar.

Gastric bezoars are usually discovered incidentally in patients with non-specific abdominal symptoms. Abdominal X rays, ultrasound and CT scan can reveal mass or filling defects[12,13]. The current gold standard for diagnosis of a gastric bezoar is upper gastrointestinal endoscopy. It provides not only direct visualization of the bezoar but also allows simultaneous therapeutic intervention.

Many studies have shown successful dissolution of gastric bezoars using agents such as Coca-cola, acetylcystine, cellulase, meat tenderizer and hydrogen peroxide[5,14-19]. However, all available studies are uncontrolled trials and there are no prospective studies evaluating the medical treatment of phytobezoars in the literature.

The majority of gastric bezoars can be removed

endoscopically. Endoscopic removal involves fragmenting the bezoar with a water jet, direct suction, forceps and snares[20]. A variety of other methods have been described in case reports such as Nd:YAG laser, endoscopic drills, and mechanical, electrohydraulic, extracorporeal lithotriopsy and intra-phytozoal Coca-Cola injection[21-26]. Bruzzese *et al*[27] pointed out that any fragments more than one centimetre in size must be extracted after fragmentation to prevent intestinal obstruction.

Surgical removal should be considered in patients who fail conservative therapy, have large bezoars which hinder endoscopic removal or have complications such as obstruction with underlying mechanical problems, as seen in Edmund Leung's study, and associated peptic ulcer bleeding[10]. Laparoscopic removal is a promising option for the removal of gastric as well as intestinal bezoars to avoid conventional surgery which is associated with higher postoperative morbidity[28].

The reported recurrence rate after removal of a gastric bezoar is 14% in some studies, however, this will be higher if underlying risk factors are not corrected[29]. For prevention, it is necessary to educate high risk patients to chew properly, take more fluid and avoid a stringy fibrous diet. Patients with trichobezoars may need to seek psychiatric evaluation to avoid further occurrence. Patients with underlying motility problems also need to be identified and treated as necessary.

Phytobezoars are a rare cause of gastric outlet obstruction, especially in patients with previous gastrojenunostomy. Currently, gastroscopy is the best method for detecting and managing gastric bezoars by endoscopic removal. Some cases require surgical removal, especially those associated with complications. The most important points in the management of a bezoar are identification of the causative factor and prevention of recurrence by counselling.

ACKNOWLEDGMENTS

We thank all the staff at the endoscopic centre; Hospital Pakar Sultanah Fatimah, for help obtaining the necessary information required for this paper and special thanks to the research committee; Melaka Manipal Medical College, who gave training in research paper writing and encouragement for publication.

REFERENCES

1 **Kadian RS**, Rose JF, Mann NS. Gastric bezoars--spontaneous resolution. *Am J Gastroenterol* 1978; **70**: 79-82
2 **Mir AM**, Mir MA. Phytobezoar after vagotomy with drainage or resection. *Br J Surg* 1973; **60**: 846-849
3 **Calabuig R**, Navarro S, Carrió I, Artigas V, Monés J, Puig LaCalle J. Gastric emptying and bezoars. *Am J Surg* 1989; **157**: 287-290
4 **De Bakey M**, Ochsner A. Bezoars and concretions: a comprehensive review of the literature with an analysis of 303 collected cases and a presentation of 8 additional cases. *Surgery* 1939; **5**: 132-160
5 **Holloway WD**, Lee SP, Nicholson GI. The composition and dissolution of phytobezoars. *Arch Pathol Lab Med* 1980; **104**: 159-161
6 **White NB**, Gibbs KE, Goodwin A, Teixeira J. Gastric bezoar complicating laparoscopic adjustable gastric banding, and review of literature. *Obes Surg* 2003; **13**: 948-950
7 **Ahn YH**, Maturu P, Steinheber FU, Goldman JM. Association of diabetes mellitus with gastric bezoar formation. *Arch Intern Med* 1987; **147**: 527-528
8 **Robles R**, Parrilla P, Escamilla C, Lujan JA, Torralba JA, Liron R, Moreno A. Gastrointestinal bezoars. *Br J Surg* 1994; **81**: 1000-1001
9 **Balik E**, Ulman I, Taneli C, Demircan M. The Rapunzel syndrome: a case report and review of the literature. *Eur J Pediatr Surg* 1993; **3**: 171-173
10 **Leung E**, Barnes R, Wong L. Bezoar in gastro-jejunostomy presenting with symptoms of gastric outlet obstruction: a case report and review of the literature. *J Med Case Reports* 2008; **2**: 323
11 **Hui MS**, Perng HL, Choi WM, Chem LK, Yang KC, Chen TJ. Afferent loop syndrome complicated by a duodenal phytobezoar after Billroth-II subtotal gastrectomy. *Am J Gastroenterol* 1997; **92**: 1550-1552
12 **McCracken S**, Jongeward R, Silver TM, Jafri SZ. Gastric trichobezoar: sonographic findings. *Radiology* 1986; **161**: 123-124
13 **Newman B**, Girdany BR. Gastric trichobezoars--sonographic and computed tomographic appearance. *Pediatr Radiol* 1990; **20**: 526-527
14 **Walker-Renard P**. Update on the medicinal management of phytobezoars. *Am J Gastroenterol* 1993; **88**: 1663-1666
15 **Schlang HA**. Acetylcysteine in removal of bezoar. *JAMA* 1970; **214**: 1329
16 **Ladas SD**, Triantafyllou K, Tzathas C, Tassios P, Rokkas T, Raptis SA. Gastric phytobezoars may be treated by nasogastric Coca-Cola lavage. *Eur J Gastroenterol Hepatol* 2002; **14**: 801-803
17 **Kato H**, Nakamura M, Orito E, Ueda R, Mizokami M. The first report of successful nasogastric Coca-Cola lavage treatment for bitter persimmon phytobezoars in Japan. *Am J Gastroenterol* 2003; **98**: 1662-1663
18 **Chung YW**, Han DS, Park YK, Son BK, Paik CH, Jeon YC, Sohn JH. Huge gastric diospyrobezoars successfully treated by oral intake and endoscopic injection of Coca-Cola. *Dig Liver Dis* 2006; **38**: 515-517
19 **Katsinelos P**, Pilpilidis I, Chatzimavroudis G, Katsinelos T, Lazaraki G, Fasoulas K, Zavos C, Kountouras J. Huge gastric bezoar caused by honeycomb, an unusual complication of health faddism: a case report. *Cases J* 2009; **2**: 7077
20 **Zarling EJ**, Thompson LE. Nonpersimmon gastric phytobezoar. A benign recurrent condition. *Arch Intern Med* 1984; **144**: 959-961
21 **Naveau S**, Poynard T, Zourabichvili O, Poitrine A, Chaput JC. Gastric phytobezoar destruction by Nd: YAG laser therapy. *Gastrointest Endosc* 1986; **32**: 430-431
22 **Benes J**, Chmel J, Jodl J, Stuka C, Nevoral J. Treatment of a gastric bezoar by extracorporeal shock wave lithotripsy. *Endoscopy* 1991; **23**: 346-348
23 **Wang YG**, Seitz U, Li ZL, Soehendra N, Qiao XA. Endoscopic management of huge bezoars. *Endoscopy* 1998; **30**: 371-374
24 **Blam ME**, Lichtenstein GR. A new endoscopic technique for the removal of gastric phytobezoars. *Gastrointest Endosc* 2000; **52**: 404-408
25 **Sechopoulos P**, Robotis JF, Rokkas T. Gastric bezoar treated endoscopically with a carbonated beverage: case report. *Gastrointest Endosc* 2004; **60**: 662-664
26 **Gold MH**, Patteson TE, Green GI. Cellulase bezoar injection: a new endoscopic technique. *Gastrointest Endosc* 1976; **22**: 200-202
27 **Bruzzese A**, Chiarini S, Marchegiani C, Corbellini L, Stella S. [Endoscopic fragmentation of gastric phytobezoars as a

valid alternative, in selected cases, to traditional surgery]. *G Chir* 1997; **18**: 485-487
28 **Sharma D**, Srivastava M, Babu R, Anand R, Rohtagi A, Thomas S. Laparoscopic treatment of gastric bezoar. *JSLS* 2010; **14**: 263-267
29 **Krausz MM**, Moriel EZ, Ayalon A, Pode D, Durst AL. Surgical aspects of gastrointestinal persimmon phytobezoar treatment. *Am J Surg* 1986; **152**: 526-530

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Yang XC

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2012 May 16; 4(5): I
ISSN 1948-5190 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Endoscopy*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Endoscopy*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Dirk Domagk, MD, PhD, Department of Medicine B, University of Muenster, Albert-Schweitzer-Str. 33, 48149 Muenster, Germany

Hiroo Imazu, MD, PhD, Department of Endoscopy, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan

Sandeep Nijhawan, Professor, MD, MBBS, Department of Gastroenterology, SMS Medical College, 112, Panchsheel Enclave, Gokul Bhai Bhatt Marg, Durgapura, Jaipur, Rajasthan, India

Konstantinos Antonios Papadakis, MD, PhD, Professor, Associate Professor of Gastroenerolgy, University of Crete, Faculty of Medicine, University Hospital of Heraklion, Gastroenterology Clinic, Building A4, PO Box 1352, Heraklion 71110, Greece

Andrea Riphaus, MD, Medical University Hospital, Miners Hospital, In the Schornau 23-25, Bochum 44892, Germany

David T Rubin, MD, Associate Professor of Medicine, University of Chicago Medical Center, 5841 S. Maryland Ave., MC4076, Chicago, IL 60637, United States

Danny A Sherwinter, MD, FACS, 3rd Floor Department of Surgery, 948 48th Street, Brooklyn, NY 11219, United States

Si-Young Song, MD, PhD, Professor, Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-ku, Seoul 120-752, South Korea

Tomoyuki Tsujikawa, MD, PhD, Associate Professor, Division of Gastroenterology, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga 520-2192, Japan

Jiang-Fan Zhu, MD, Professor of surgery, Department of General Surgery, East Hospital of Tongji University, 150 Ji Mo Road, Pudong 200120, Shanghai, China

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2012 May 16; 4(5): I
ISSN 1948-5190 (online)

Events Calendar 2012

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

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

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

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

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

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

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

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

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

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

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

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

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

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

WJGE World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2012 May 16; 4(5): I-V
ISSN 1948-5190 (online)

GENERAL INFORMATION

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

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

Maximization of personal benefits

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

Aims and scope

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

Columns

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

Name of journal

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

Editor-in-chief

Juan Manuel-Herrerías, MD, PhD, AGAF, Professor, Gastroenterology Service, Hospital Universitario Virgen Macarena, Aparato Digestivo, Avda. Dr. Fedriani, s/n, 41071 Sevilla, Spain

Till Wehrmann, MD, PhD, Professor, FB Gastroenterologie Gastro-enterologie, Deutsche Klinik fuer Diagnostik, Aukammallee 33, 65191 Wiesbaden, Germany

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

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

Published by
Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

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

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

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

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

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

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

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

SUBMISSION OF MANUSCRIPTS

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

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

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

1948-5190office/, or by telephone: +86-10-59080038. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

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

Title page

Title: Title should be less than 12 words.

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

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

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

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

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

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

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

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

Abstract

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

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

Key words

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

Text

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

Illustrations

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

Tables

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

Notes in tables and illustrations

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

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

Acknowledgments

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

REFERENCES

Coding system

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

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

PMID and DOI

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

Style for journal references

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

Style for book references

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

Format

Journals

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

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

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

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

In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Patent (list all authors)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

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

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

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

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

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

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

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

Publication fee
WJGE is an international, peer-reviewed, Open-Access, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. The related standards are as follows. Publication fee: 1300 USD per article. Editorial, topic highlights, original articles, brief articles, book reviews and letters to the editor are published free of charge.