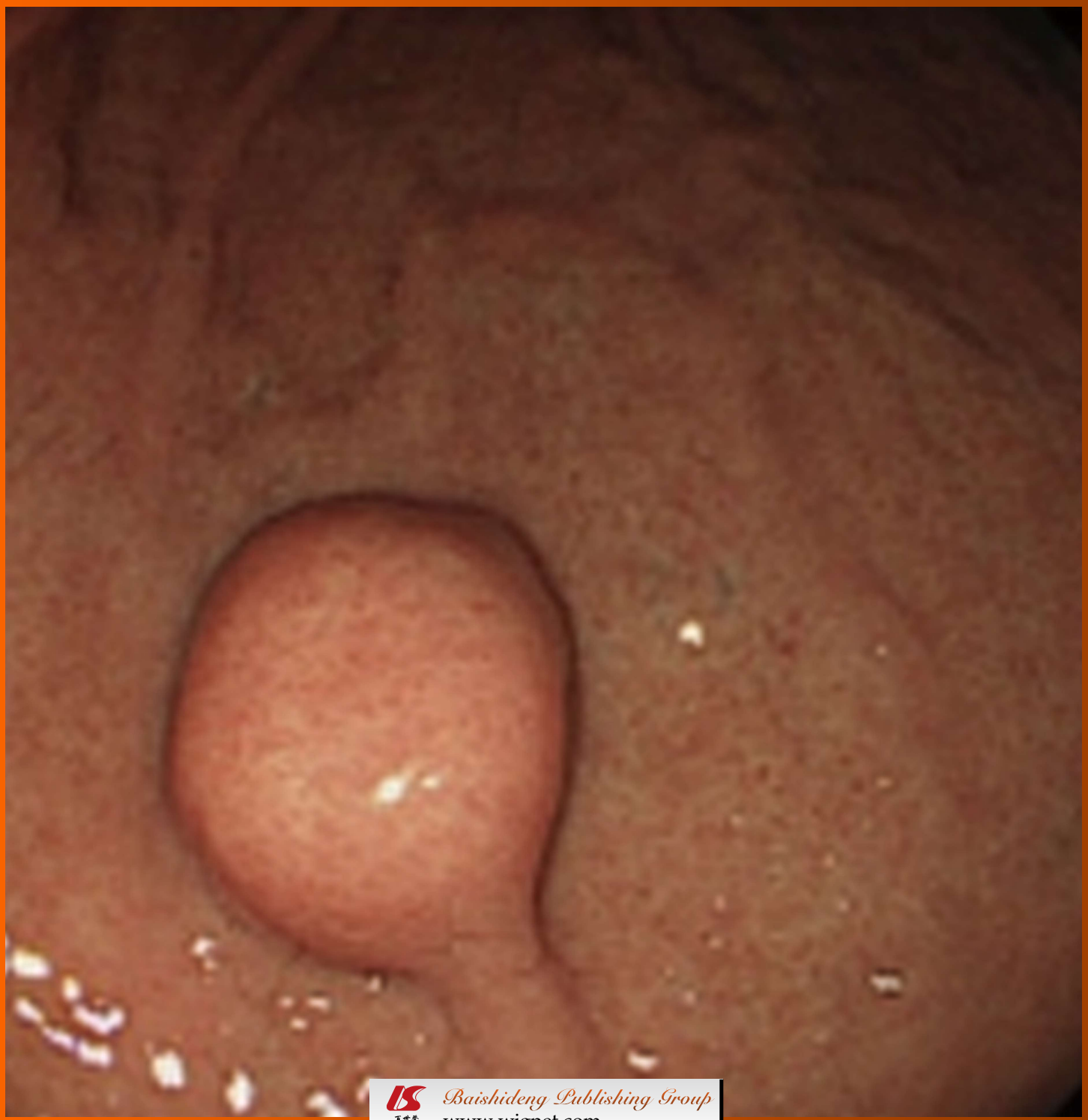
ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2013 April 16; 5(4): 141-202



Baishideng Publishing Group
www.wjgnet.com

WJGE

World Journal of Gastrointestinal Endoscopy

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

Editorial Board

2011-2015

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 402 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 46 countries, including Australia (7), Austria (1), Belgium (6), Brazil (7), Canada (5), Chile (2), China (25), Croatia (2), Cuba (1), Czech Republic (3), Denmark (1), Ecuador (1), Egypt (1), Finland (1), France (10), Germany (28), Greece (11), Hungary (4), India (15), Iran (2), Ireland (2), Israel (6), Italy (37), Japan (62), Lebanon (1), Lithuania (1), Malaysia (2), Mexico (1), Netherlands (5), New Zealand (1), Norway (2), Pakistan (2), Poland (2), Portugal (5), Romania (2), Singapore (2), South Africa (1), South Korea (13), Spain (19), Sweden (3), Switzerland (1), Thailand (5), Turkey (8), United Arab Emirates (1), United Kingdom (17), and United States (68).

Miroslav Zavoral, *Prague*

Denmark

Peter Bytzer, *Koege*

Ecuador

Carlos Robles-Medranda, *Casilla*

Egypt

Nabil Ali Gad El-Hak, *Mansoura*

Finland

Paulina Salminen, *Turku*

France

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

Germany

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

Greece

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

Hungary

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

India

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

Iran

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

Ireland

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

Israel

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

Italy

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

Japan

Mitsuhiro Asakuma, *Osaka*
Hiroki Endo, *Kanagawa*
Shotaro Enomoto, *Wakayama*
Kuang-I Fu, *Chiba prefecture*
Makoto Hashizume, *Fukuoka*
Toru Hiyama, *Higashihiroshima*
Akira Hokama, *Okinawa*
Akira Horiuchi, *Komagane*
Kinichi Hotta, *Nagano*
Atsushi Imagawa, *Kagawa*
Hiroo Imazu, *Tokyo*
Haruhiro Inoue, *Yokohama*
Ryu Ishihara, *Osaka*
Naoki Ishii, *Tokyo*
Hajime Isomoto, *Nagasaki*
Takao Itoi, *Tokyo*
Satoru Kakizaki, *Maebashi*
Hiroshi Kakutani, *Tokyo*
Terumi Kamisawa, *Tokyo*
Yoshihide Kanno, *Sendai*
Mototsugu Kato, *Sapporo*
Takashi Kawai, *Tokyo*
Hirofumi Kawamoto, *Okayama*
Hiroto Kita, *Saitama*
Koga Komatsu, *Akita*
Hitoshi Kondo, *Sapporo*
Hiroaki Kubo, *Fukuoka*
Keiichiro Kume, *Kitakyusyu*
Iruru Maetani, *Tokyo*
Hiroto Miwa, *Nishinomiya*
Akihiro Mori, *Aichi*
Yoshihiro Moriwaki, *Yokohama*
Naoki Muguruma, *Tokushima*
Koichi Nagata, *Chiba*
Shinji Nishiwaki, *Gifu*
Ichiro Oda, *Tokyo*
Kazuichi Okazaki, *Osaka*
Yasuhiro Oono, *Chiba*
Taro Osada, *Tokyo*
Yutaka Saito, *Tokyo*
Yuzo Sakai, *Chiba*
Naoto Sakamoto, *Tokyo*

Nobuyuki Sakurazawa, *Tokyo*
Yasushi Sano, *Hyogo*
Tomoyuki Shibata, *Toyoake*
Takashi Shida, *Chiba*
Atsushi Sofuni, *Tokyo*
Kazuki Sumiyama, *Tokyo*
Nobumi Tagaya, *Saitama*
Hirokazu Takahashi, *Yokohama*
Kyosuke Tanaka, *Mie*
Shinji Tanaka, *Hiroshima*
Gen Tohda, *Fukui*
Tomoyuki Tsujikawa, *Shiga*
Noriya Uedo, *Osaka*
Shuji Yamamoto, *Kyoto*
Takayuki Yamamoto, *Yokkaichi*
Hideo Yanai, *Shimonoseki*
Kenjiro Yasud, *Kyoto*
Naohisa Yoshida, *Kyoto*

Lebanon

Kassem A Barada, *Beirut*

Lithuania

Laimas Virginijus Jonaitis, *Kaunas*

Malaysia

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

Mexico

Oscar T Teramoto-Matsubara, *Chapultepec*

Netherlands

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

New Zealand

Michael PG Schultz, *Dunedin*

Norway

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

Pakistan

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

Poland

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

Portugal

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

Romania

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

Singapore

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

South Africa

Roland N Ndip, *Alice*

South Korea

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

Spain

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

Sweden

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

Switzerland

Valérie Pittet, *Bugnon*

Thailand

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

Turkey

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

United Arab Emirates

Margit Gabriele Muller, *Abu Dhabi*

United Kingdom

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

United States

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

WJGE World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 5 Number 4 April 16, 2013

World Journal of Gastrointestinal Endoscopy
Volume 5 Number 4 April 16, 2013

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

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

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F, Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
April 16, 2013

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

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

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.141

World J Gastrointest Endosc 2013 April 16; 5(4): 141-147
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

Ilaria Tarantino, Assistant Professor, *Series Editor*

Tumors and new endoscopic ultrasound-guided therapies

Silvia Carrara, Maria Chiara Petrone, Pier Alberto Testoni, Paolo Giorgio Arcidiacono

Silvia Carrara, Maria Chiara Petrone, Pier Alberto Testoni, Paolo Giorgio Arcidiacono, Scientific Institute San Raffaele, Vita-Salute San Raffaele University, 20132 Milan, Italy
Author contributions: All the authors gave substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.
Correspondence to: Silvia Carrara, MD, Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Via Olgettina 60, 20132 Milano, Italy. carrara.silvia@hsr.it
Telephone: +39-22-6435509 Fax: +39-22-6435509
Received: September 13, 2012 Revised: February 17, 2013
Accepted: March 8, 2013
Published online: April 16, 2013

Abstract

With the advent of linear echoendoscopes, endoscopic ultrasound (EUS) has become more operative and a new field of oncological application has been opened up. From tumor staging to tissue acquisition under EUS-guided fine-needle aspiration, new operative procedures have been developed on the principle of the EUS-guided puncture. A hybrid probe combining radiofrequency with cryotechnology is now available, to be passed through the operative channel of the echoendoscope into the tumor to create an area of ablation. EUS-guided fine-needle injection is emerging as a method to deliver anti-tumoral agents inside the tumor. Ethanol lavage, with or without paclitaxel, has been proposed for the treatment of cystic tumors in non-resectable cases and complete resolution has been recorded in up to 70%-80%. Many other chemical or biological agents have been investigated for the treatment of pancreatic adenocarcinoma: activated allogenic lymphocyte culture (Cytoimplant), a replication-deficient adenovirus vector carrying the tumor necrosis factor-α gene, or an oncolytic attenuated adenovirus (ONYX-015). The potential advantage of treatment under EUS control is the real-time imaging guidance into a deep target like the pancreas which is extremely difficult to reach by a percutaneous approach. To date there are no randomized controlled trials to confirm the real clinical benefits of these treatments compared to standard therapy so it seems wise to reserve them only for experimental protocols approved by ethics committees.

Key words: Endoscopic ultrasound; Pancreatic cancer; Endoscopic ultrasound guided ablation; Alcohol injection; Anti-tumoral injection

Core tip: New operative procedures have been developed on the principle of the endoscopic ultrasound (EUS)-guided puncture. A hybrid probe combining radiofrequency with cryotechnology is now available, to be passed through the operative channel of the echoendoscope into the tumor to create an area of ablation. The potential advantage of an ablation device employed under EUS control is the real-time imaging guidance into a deep target like the pancreas which is extremely difficult to reach by a percutaneous approach.

Carrara S, Petrone MC, Testoni PA, Arcidiacono PG. Tumors and new endoscopic ultrasound-guided therapies. *World J Gastrointest Endosc* 2013; 5(4): 141-147 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/141.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.141

INTRODUCTION

Endoscopic ultrasound (EUS) has seen significant growth in its applications in oncology in recent years[1-9]. With the advent of linear array therapeutic probes with a large working channel EUS has become more operative. From tumor staging to tissue acquisition under EUS-guided fine-needle aspiration (FNA), new procedures have been

developed on the principle of the EUS-guided puncture: if we can puncture a lesion to acquire a cytological specimen, in the same way we can puncture a tumor to carry chemical, biological, or physical therapy inside it. New accessories have been developed, and clinical research on applications in oncological patients has expanded, especially for pancreatic diseases[10-16].

ABLATIVE TECHNIQUES

Radiofrequency and cryotechnology

Ablative therapies such as radiofrequency (RF) and cryotechnology (CT) are widely used in oncology, though not in the pancreas because of the high operative risks. Retrospective and prospective studies have, however, shown the feasibility of water-cooled monopolar RF ablation in patients with stage Ⅲ pancreatic cancer in an open, percutaneous, or laparoscopic setting[17,18]. They confirmed that ablation in the pancreas is dangerous without additional cooling of adjacent tissue, real-time image control, and currently available ablation systems[19-22]. Italian surgeons applied an RF probe in locally advanced pancreatic cancer during laparotomy, demonstrating the feasibility and safety of the technique[23].

The potential advantage of an ablation device employed under EUS control is the real-time imaging guidance into a deep target like the pancreas which is extremely difficult to reach by a percutaneous approach. A minimally invasive technique to selectively ablate tumor masses could improve the efficacy of neoadjuvant treatments in patients not eligible for any other therapy. The precision of EUS in establishing the location and size of pancreatic masses could be exploited to estimate and follow up the area of ablation and help avoid damage to surrounding structures[24-26].

A new flexible bipolar hybrid ablation system has been developed (ERBE Elektromedizin GmbH, Tübingen, Germany) (Figures 1, 2). This hybrid cryotherm probe (CTP) combines bipolar RF ablation with CT. A bipolar system is believed to create ablations with less collateral thermal damage than monopolar systems but the trade-off is some loss of overall efficiency[27,28]. The CTP combines the advantages of the two technologies and overcomes the loss of efficiency: the more effective cooling by cryogenic gas permits more RF-induced interstitial devitalizing effects than heat alone[29]. Less power (16 W) is needed than with conventional RF ablation systems (30-60 W) to obtain the same result, so there should be less collateral damage.

The CTP has an active electrical part with a diameter of 1.8 mm. The entire probe is covered by a protection tube that can be safely passed through the operative channel of the echoendoscope without any risk for the instrument. Basically this is an internally CO_2-cooled RF-ablation probe which ensures efficient cooling according to the Joule-Thomson effect. The distal tip of the probe is sharp, pointed and stiff in order to penetrate the gut wall and pancreatic parenchyma. Parameters like the power setting of the generator, the pressure of the gas through the expansion vessel, and the duration of application can be set independently.

Total length of the active part = 24 mm (1 + 3 + 2 + 4)
Length of each electrode = 8 mm (1 and 2)
Length of the isolation part = 4 mm (3)
Length of the tip = 4 mm (4)
Diameter of the active part = 1.8 mm
Diameter of the protection tube = 2 mm (5)

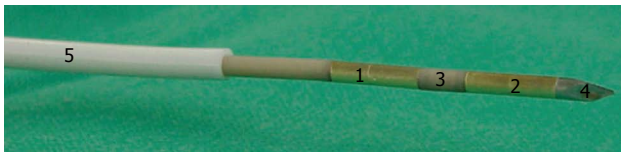


Figure 1 The tip of the ERBE hybrid cryotherm probe with the active electrical part.

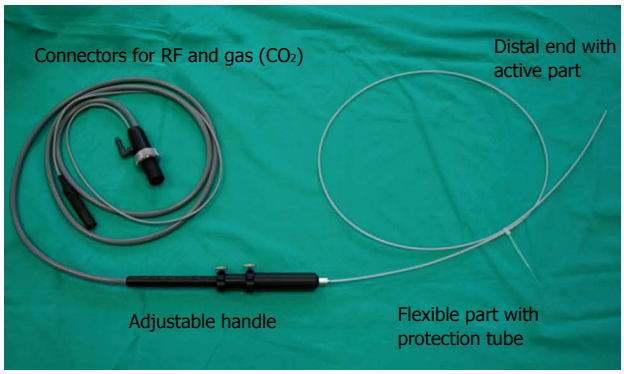


Figure 2 The ERBE flexible probe used for endoscopic ultrasound-guided ablation of the parenchymal organs. The probe, covered with a protection tube, is passed through the operative channel of the echoendoscope.

Transluminal RF ablation in the pancreas under EUS control was feasible in an animal model[30]. The power (16 W) and pressure (650 psi) settings were standardized on the basis of previous experiments. Under real-time EUS-guidance the CTP was clearly visualized as a hyperechoic line moving out of the working channel until it reached its place in the pancreatic parenchyma. During the application a hyperechoic elliptic area appeared around the distal tip of the probe, surrounded by a hypoechoic border (most likely edema) (Figure 3). There was a positive correlation between lesion size and application time: the longer the application time the more the lesion size varied, reflecting the fact that a 900-s application induces high complication rates in a healthy pancreas.

On histological examination a sharp demarcation was visible between the ablated area and the untreated pancreatic parenchyma. Coagulative necrosis was evident in the center of the lesion one week after the ablation; after two weeks the lesions showed less edema and more fibrotic transformation (Figure 4).

After the animal model experiments the efficacy of the CTP was evaluated in an *ex vivo* study for destroying neoplastic tissue of explanted pancreas from patients with resectable pancreatic adenocarcinoma. Again, histological examination found a positive correlation between

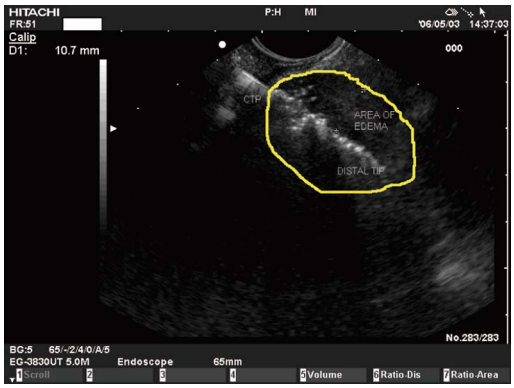


Figure 3 The cryotherm probe applied in the porcine pancreas: the probe is seen as an hyperechoic line. Initially an hyperechoic elliptic area appears around the distal tip of the probe, surrounded by a hypoechoic border (most likely edema).

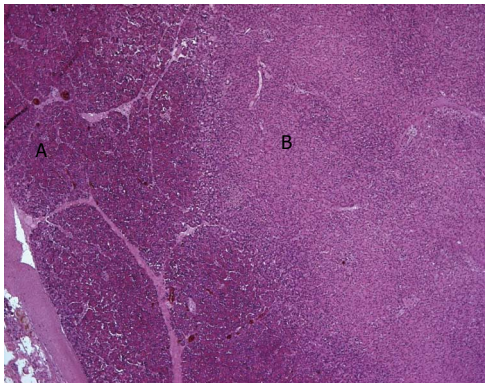


Figure 4 Histopathologic section from the first pig: Normal pancreatic tissue (A) surrounds the central treated area (B).

the size of the ablated area and the application time[31].

In the animal model the complications were related to the ablation time: all but histochemical pancreatitis occurred with ablations longer than 300 s. Pancreatic tissue is very heat-sensitive and the thermal ablation of a normal pancreas usually leads to an inflammatory response with consecutive edema, fibrotic and sometimes cystic transformation. The tissue response should be different and less pronounced in a tumor mass surrounded by a capsule where a desmoplastic reaction limits the damage to the capsule to a certain extent.

Patients with unresectable, locally advanced pancreatic adenocarcinoma were recently enrolled in a prospective case study to investigate the feasibility of EUS-guided CTP application *in vivo* and to assess to what extent progression of the disease was slowed[32]. The inclusion and exclusion criteria are listed in Table 1. From September 2009 to May 2011, 22 patients (11 males and 11 females, mean age 61.9 years) with unresectable stage Ⅲ pancreatic adenocarcinoma were enrolled. The cryotherm ablation was feasible in 16 patients (72.8%). The probe was clearly visible throughout the procedure. No severe complications arose during or immediately after the ablation. Three patients reported post-interventional abdominal pain, which responded well to analgesic drugs. Only one patient experienced a minor bleed in the duodenal lumen after the procedure, which was treated by endoscopic placement of hemostatic clips and did not require blood transfusion. Late complications arose in four cases: three were related mainly to tumor progression. A computed tomography scan was done in all patients but only in 6/16 was it possible to clearly define the tumor margins after ablation. In these patients the tumor seemed smaller than the initial mass ($P = 0.07$).

Table 1 Inclusion and exclusion criteria of patients treated with endoscopic ultrasound-guided cryotherm ablation

Inclusion criteria	Exclusion criteria
Age > 18 yr	Severe alteration of hemostasis
Able to give consent for the procedure	Unwilling or unable to give consent
	Pregnancy
PLT > 100 000/μL	Infection and/or severe leucopenia
INR < 1.5	Acute pancreatitis
Unresectable locally advanced pancreatic adenocarcinoma already treated with neoadjuvant chemotherapy	Distant metastasis

PLT: Platelet count; INR: International normalized ratio.

For experts familiar with the EUS-FNA procedure, the EUS-guided placement of the CTP and the ablation itself should not present any technical challenge.

A hepatocellular carcinoma of the caudate lobe unsuitable for surgery was treated with EUS-guided neodymium: yttrium-aluminium-garnet (Nd:YAG) laser ablation. A 300-μm optical fiber was passed through a 22-G needle which was then positioned in the tumor under EUS guidance. After two months computed tomography scan showed uniform hypo-attenuation without enhancement in the ablated zone[33].

Ablation of cystic lesions

Only few studies have examined the role of ethanol injection in ablation of the lining epithelium of cystic tumors. Pancreatic cystic tumors encompass a wide spectrum of histopathologies and biological behaviors (from benign to borderline to malignant) and can be differentiated essentially as mucinous or non-mucinous. They are often detected by chance in asymptomatic patients during radiological examinations for non-specific gastrointestinal complaints. For the treatment of mucinous cystic tumors, surgical resection is usually the first choice, but EUS-guided ethanol lavage has been proposed as an alternative for patients not suitable for surgery. The rationale for the use of ethanol is that it can sclerose the lining epithelium and reduce the influx of fluid. The cyst is punctured with a 22-G fine needle under EUS-guidance, the fluid is aspirated, then ethanol is injected into the cyst and re-aspirated after 3-5 min (Figure 5). In the initial pilot study the Boston group showed the feasibility and safety of EUS-guided ethanol lavage for pancreatic cystic tumors in 25

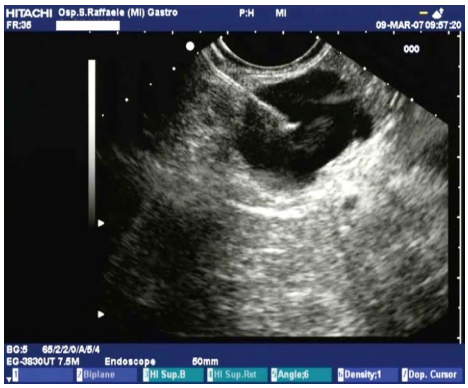


Figure 5 Endoscopic ultrasound-guided puncture of a cystic tumor. The cyst is punctured with a 22-G fine needle under endoscopic ultrasound guidance, the fluid is aspirated, then ethanol is injected into the cyst and re-aspirated after 3-5 min.

patients[34]. They obtained complete resolution of the cysts in eight (33%), with variable degrees of epithelial ablation observed at histological examination of resected specimens in patients who subsequently underwent surgery.

Other studies used taxol for lavage after the ethanol. Paclitaxel is a viscous, hydrophobic chemotherapeutic agent that is believed to have prolonged action in the cyst. In a preliminary study 11 out of 14 patients showed complete cyst resolution after ethanol lavage and paclitaxel injection[35,36].

A more recent cohort study determined the duration of successful cyst resolution after EUS-guided ethanol lavage. Computed tomography scans at a median of 26 mo suggested resolution lasted well[37]. In the Editorial commenting this study, Goodman *et al*[38] suggest that until we have better randomized controlled trials EUS-guided ethanol ablation of pancreatic cysts is best reserved for experimental protocols and for patients who cannot undergo surgery.

EUS-guided injection of anti-tumoral agents

EUS-guided fine-needle injection is emerging as a method to deliver anti-tumoral agents inside pancreatic tumors. Many chemical or biological agents have been investigated for the treatment of pancreatic adenocarcinoma: activated allogenic lymphocyte culture (Cytoimplant)[39], a replication-deficient adenovirus vector carrying the tumor necrosis factor-α gene[40,41], and an oncolytic attenuated adenovirus (ONYX-015)[42]. The procedure was developed on the principle of EUS-guided FNA: the needle is passed through the operative channel of the echoendoscope and is followed in real time while it punctures the tumor and the agent is delivered inside the mass. A Doppler signal helps avoid interposing vessels and makes the procedure safer.

Allogenic mixed lymphocyte culture (Cytoimplant): The first study, by Chang *et al*[40], assessed the technical feasibility and safety of EUS-guided injection of allogenic mixed lymphocyte culture (Cytoimplant) in locally advanced pancreatic adenocarcinoma. Eight patients with unresectable pancreatic cancer were given a single EUS-guided injection of Cytoimplant. The first two received three billion cells, the next three six billion cells and the last three nine billion cells. The procedures were safe and there were no severe complications. The only side effect reported was low-grade fever. Median survival was 13.2 mo. No other studies have followed this first phase I trial.

Replication-deficient adenovirus vector carrying the tumor necrosis factor-α gene: Chang *et al*[40] also tested EUS-guided TNFerade injection in patients with locally advanced pancreatic cancer. TNFerade is a replication-deficient adenovector that contains the human tumor necrosis factor (TNF)-α gene. Patients received five weekly EUS-guided intratumoral injections of TNFerade (4×10^9, 4×10^{10}, and 4×10^{11} particle units in 2 mL). This was combined with *iv* chemotherapy (fluorouracil, 5-FU) and radiation. The rationale for this triple strategy lies in the synergism between the three therapies. 5-FU is directly toxic to malignant cells and is also a radiosensitizer; radiation therapy destroys tumor cells and up-regulates TNF production; and TNFerade, which is also a radiosensitizer, kills the tumor cells. The procedure was well tolerated. Patients who received the higher doses had better locoregional control of the disease, better median survival rates, and a higher percentage of resective surgery after the treatment[41,42].

Adenovirus ONYX-015: Another anti-tumoral viral therapy schedule is ONYX-015, a replication selective adenovirus with a deletion in the E1B-55 kDa gene, which preferentially replicates in tumoral cells and kills them. Twenty-one patients were given EUS-guided injections of ONYX-015 over an eight-week period. Complications were more severe than in the previous studies described: two patients had sepsis and two had duodenal perforation. None showed tumor regression with the ONYX-015 injection alone after five weeks, but two patients had a partial response after the combination with gemcitabine[42].

Although EUS-guided antitumoral injection seems feasible and safe, and the results of these studies seem promising, the efficacy in phase Ⅲ randomized controlled trials has still to be demonstrated and published.

PLACEMENT OF EUS-GUIDED FIDUCIAL MARKERS AND BRACHYTHERAPY

EUS guidance can also be used to place fiducial markers or radioactive seeds inside a tumor. Fiducial markers are radiopaque spheres, coils, or seeds that are implanted in or near the tumor in order to demarcate the borders of the tumor to facilitate image-guided radiation therapy. Many studies have been published on EUS-guided placement of these markers in different tumors[43-47].

The fiducials are passed through a 19-G or 22-G

Table 2 Potential applications of therapeutic endoscopic ultrasound for pancreatic cancer

Ref.	Year of publication	Type of cancer	*n*	Materials	Results	Complications
Arcidiacono *et al*[32]	2012	Adeno-carcinoma	22	Cryotherm probe	Feasible (72%), and safe	Pain (3 pts); minor bleeding (1 pt)
Gan *et al*[34]	2005	Cystic tumors	25	Ethanol lavage	Complete resolution (35%)	No complications
Oh *et al*[36]	2008	Cystic tumors	52	Ethanol lavage + paclitaxel	Complete resolution (62%)	Mild pancreatitis and splenic vein obliteration (1 pt)
Chang *et al*[39]	2000	Adeno-carcinoma	8	Cytoimplant	2 partial responses and 1 minor response	Low-grade fever (86%); GI toxicities (37%)
Hecht	2012	Adeno-carcinoma	50	TNFerade	1 complete response; 3 partial responses; 12 stable diseases	Pancreatitis and cholangitis (3 pts)
Hecht *et al*[42]	2003	Adeno-carcinoma	21	ONYX-015 + *iv* gemcitabine	Partial response (2 pts)	Sepsis (2 pts); duodenal perforation (2 pts)
Jin *et al*[50]	2008	Adeno-carcinoma	22	iodine 125-seeds	Successful implantation in all pts; partial remission (13%); stable disease (45%)	No complications

GI: Gastrointestinal.

needle and deployed with different techniques into the mass, using the stylet, or by injecting sterile water into the needle[46]. The fact that the 19-G needle is stiffer can make it harder to position the fiducials in pancreatic head tumors with the echoendoscope placed in the second portion of the duodenum, while with the smaller-caliber 22-G needle it may be easier to place the fiducials in the deepest portions of the pancreas[48].

Few trials have evaluated EUS-guided implantation of radioactive seeds (iodine-125) in patients with unresectable pancreatic cancer[49,50]. Patients treated with a combination of radioactive seeds and chemotherapy showed tumor regression and reported some relief of pain[50].

CONCLUSION

EUS, born as an extremely accurate imaging technique, is emerging as a tool to guide interventional endoscopy in oncological patients, from EUS-guided FNA, to EUS-guided injection of anti-tumoral agents, to EUS-guided ablation devices. Table 2 summarizes the potential oncological applications of therapeutic EUS.

Many case series and reports have confirmed the feasibility and safety of EUS-guided operative procedures, but there are still no randomized controlled trials to confirm the real clinical benefits of these treatments compared to standard therapy. At the moment it seems wise to reserve them only for experimental protocols approved by ethics committees.

REFERENCES

1 **DeWitt J**, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med* 2004; **141**: 753-763 [PMID: 15545675]

2 **Săftoiu A**. State-of-the-art imaging techniques in endoscopic ultrasound. *World J Gastroenterol* 2011; **17**: 691-696 [PMID: 21390138 DOI: 10.3748/wjg.v17.i6.691]

3 **Barresi L**, Tarantino I, Granata A, Curcio G, Traina M. Pancreatic cystic lesions: How endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle. *World J Gastrointest Endosc* 2012; **4**: 247-259 [PMID: 22720127 DOI: 10.4253/wjge.v4.i6.247]

4 **Krishna SG**, Lee JH. Endosonography in solid and cystic pancreatic tumors. *J Interv Gastroenterol* 2011; **1**: 193-201 [PMID: 22586537 DOI: 10.4161/jig.1.4.19971]

5 **Chong AK**, Caddy GR, Desmond PV, Chen RY. Prospective study of the clinical impact of EUS. *Gastrointest Endosc* 2005; **62**: 399-405 [PMID: 16111959]

6 **Bhutani MS**. Interventional endoscopic ultrasonography: state of the art at the new millenium. *Endoscopy* 2000; **32**: 62-71 [PMID: 10691275]

7 **Fusaroli P**, Kypraios D, Caletti G, Eloubeidi MA. Pancreatico-biliary endoscopic ultrasound: a systematic review of the levels of evidence, performance and outcomes. *World J Gastroenterol* 2012; **18**: 4243-4256 [PMID: 22969187 DOI: 10.3748/wjg.v18.i32.4243]

8 **Tharian B**, Tsiopoulos F, George N, Pietro SD, Attili F, Larghi A. Endoscopic ultrasound fine needle aspiration: Technique and applications in clinical practice. *World J Gastrointest Endosc* 2012; **4**: 532-544 [PMID: 23293723 DOI: 10.4253/wjge.v4.i12.532]

9 **Klapman JB**, Chang KJ. Endoscopic ultrasound-guided fine-needle injection. *Gastrointest Endosc Clin N Am* 2005; **15**: 169-177, x [PMID: 15555959]

10 **Tarantino I**, Barresi L, Fabbri C, Traina M. Endoscopic ultrasound guided biliary drainage. *World J Gastrointest Endosc* 2012; **4**: 306-311 [PMID: 22816011 DOI: 10.4253/wjge.v4.i7.306]

11 **Ashida R**, Chang KJ. Interventional EUS for the treatment of pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2009; **16**: 592-597 [PMID: 19547908 DOI: 10.1007/s00534-009-0129-z]

12 **Perez-Miranda M**, de la Serna C, Diez-Redondo P, Vila JJ. Endosonography-guided cholangiopancreatography as a salvage drainage procedure for obstructed biliary and pancreatic ducts. *World J Gastrointest Endosc* 2010; **2**: 212-222 [PMID: 21160936 DOI: 10.4253/wjge.v2.i6.212]

13 **Tarantino I**, Barresi L. Interventional endoscopic ultrasound: Therapeutic capability and potential. *World J Gastrointest Endosc* 2009; **1**: 39-44 [PMID: 21160649 DOI: 10.4253/wjge.v1.i1.39]

14 **Matthes K**, Mino-Kenudson M, Sahani DV, Holalkere N, Brugge WR. Concentration-dependent ablation of pancreatic tissue by EUS-guided ethanol injection. *Gastrointest Endosc* 2007; **65**: 272-277 [PMID: 17258986 DOI: 10.1016/j.gie.2006.04.043]

15 **Sun S**, Wang S, Ge N, Lei T, Lu Q, Zhou Z, Yang A, Wang Z, Sun M. Endoscopic ultrasound-guided interstitial chemotherapy in the pancreas: results in a canine model. *Endoscopy* 2007; **39**: 530-534 [PMID: 17554649 DOI: 10.1055/s-2007-966353]

16 **Giday SA**, Magno P, Gabrielson KL, Buscaglia JM, Canto MI, Ko CW, Clarke JO, Kalloo AN, Jagannath SB, Shin EJ, Kantsevoy SV. The utility of contrast-enhanced endoscopic ultrasound in monitoring ethanol-induced pancreatic tissue ablation: a pilot study in a porcine model. *Endoscopy* 2007; **39**: 525-529 [PMID: 17554648 DOI: 10.1055/s-2007-966391]

17 **Wu Y**, Tang Z, Fang H, Gao S, Chen J, Wang Y, Yan H. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. *J Surg Oncol* 2006; **94**: 392-395 [PMID: 16967436 DOI: 10.1002/jso.20580]

18 **Spiliotis JD**, Datsis AC, Michalopoulos NV, Kekelos SP, Vaxevanidou A, Rogdakis AG, Christopoulou AN. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. *J Surg Oncol* 2007; **96**: 89-90 [PMID: 17345594 DOI: 10.1002/jso.20764]

19 **Matsui Y**, Nakagawa A, Kamiyama Y, Yamamoto K, Kubo N, Nakase Y. Selective thermocoagulation of unresectable pancreatic cancers by using radiofrequency capacitive heating. *Pancreas* 2000; **20**: 14-20 [PMID: 10630378]

20 **Elias D**, Baton O, Sideris L, Lasser P, Pocard M. Necrotizing pancreatitis after radiofrequency destruction of pancreatic tumours. *Eur J Surg Oncol* 2004; **30**: 85-87 [PMID: 14736529]

21 **Siriwardena AK**. Radiofrequency ablation for locally advanced cancer of the pancreas. *JOP* 2006; **7**: 1-4 [PMID: 16407612]

22 **Spiliotis JD**, Datsis AC, Michalopoulos NV, Kekelos SP, Vaxevanidou A, Rogdakis AG, Christopoulou AN. Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas. *Langenbecks Arch Surg* 2007; **392**: 55-60 [PMID: 17089173 DOI: 10.1007/s00423-006-0098-5]

23 **Girelli R**, Frigerio I, Salvia R, Barbi E, Tinazzi Martini P, Bassi C. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. *Br J Surg* 2010; **97**: 220-225 [PMID: 20069610 DOI: 10.1002/bjs.6800]

24 **Rösch T**, Braig C, Gain T, Feuerbach S, Siewert JR, Schusdziarra V, Classen M. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology* 1992; **102**: 188-199 [PMID: 1727753]

25 **Dewitt J**, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. *Clin Gastroenterol Hepatol* 2006; **4**: 717-25; quiz 664 [PMID: 16675307 DOI: 10.1016/j.cgh.2006.02.020]

26 **Agarwal B**, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol* 2004; **99**: 844-850 [PMID: 15128348 DOI: 10.1111/j.1572-0241.2004.04177.x]

27 **Van Goethem BE**, Rosenveldt KW, Kirpensteijn J. Monopolar versus bipolar electrocoagulation in canine laparoscopic ovariectomy: a nonrandomized, prospective, clinical trial. *Vet Surg* 2003; **32**: 464-470 [PMID: 14569575]

28 **Lee JM**, Han JK, Choi SH, Kim SH, Lee JY, Shin KS, Han CJ, Choi BI. Comparison of renal ablation with monopolar radiofrequency and hypertonic-saline-augmented bipolar radiofrequency: in vitro and in vivo experimental studies. *AJR Am J Roentgenol* 2005; **184**: 897-905 [PMID: 15728615]

29 **Hines-Peralta A**, Hollander CY, Solazzo S, Horkan C, Liu ZJ, Goldberg SN. Hybrid radiofrequency and cryoablation device: preliminary results in an animal model. *J Vasc Interv Radiol* 2004; **15**: 1111-1120 [PMID: 15466798]

30 **Carrara S**, Arcidiacono PG, Albarello L, Addis A, Enderle MD, Boemo C, Campagnol M, Ambrosi A, Doglioni C, Testoni PA. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. *Endoscopy* 2008; **40**: 321-326 [PMID: 18389449 DOI: 10.1055/s-2007-995595]

31 **Petrone MC**, Arcidiacono PG, Carrara S, Albarello L, Enderle MD, Neugebauer A, Boemo C, Doglioni C, Testoni PA. US-guided application of a new hybrid probe in human pancreatic adenocarcinoma: an ex vivo study. *Gastrointest Endosc* 2010; **71**: 1294-1297 [PMID: 20598256 DOI: 10.1016/j.gie.2010.02.014]

32 **Arcidiacono PG**, Carrara S, Reni M, Petrone MC, Cappio S, Balzano G, Boemo C, Cereda S, Nicoletti R, Enderle MD, Neugebauer A, von Renteln D, Eickhoff A, Testoni PA. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. *Gastrointest Endosc* 2012; **76**: 1142-1151 [PMID: 23021160 DOI: 10.1016/j.gie.2012.08.006]

33 **Di Matteo F**, Grasso R, Pacella CM, Martino M, Pandolfi M, Rea R, Luppi G, Silvestri S, Zardi E, Costamagna G. EUS-guided Nd: YAG laser ablation of a hepatocellular carcinoma in the caudate lobe. *Gastrointest Endosc* 2011; **73**: 632-636 [PMID: 21030019 DOI: 10.1016/j.gie.2010.08.019]

34 **Gan SI**, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc* 2005; **61**: 746-752 [PMID: 15855986 DOI: 10.1016/S0016-5107(05)00320-2]

35 **DeWitt J**, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc* 2009; **70**: 710-723 [PMID: 19577745 DOI: 10.1016/j.gie.2009.03.1173]

36 **Oh HC**, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 2008; **67**: 636-642 [PMID: 18262182 DOI: 10.1016/j.gie.2007.09.038]

37 **DeWitt J**, DiMaio CJ, Brugge WR. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. *Gastrointest Endosc* 2010; **72**: 862-866 [PMID: 20883866 DOI: 10.1016/j.gie.2010.02.039]

38 **Goodman AJ**, Gress FG. EUS-guided ethanol lavage for pancreatic cysts: is it ready for prime time? *Gastrointest Endosc* 2010; **72**: 867-869 [PMID: 20883867]

39 **Chang KJ**, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, Granger GA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer* 2000; **88**: 1325-1335 [PMID: 10717613]

40 **Chang KJ**, Irisawa A. EUS 2008 Working Group document: evaluation of EUS-guided injection therapy for tumors. *Gastrointest Endosc* 2009; **69**: S54-S58 [PMID: 19179171 DOI: 10.1016/j.gie.2008.10.057]

41 **Chang KJ**, Lee JG, Holcombe RF, Kuo J, Muthusamy R, Wu ML. Endoscopic ultrasound delivery of an antitumor agent to treat a case of pancreatic cancer. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 107-111 [PMID: 18253139 DOI: 10.1038/ncpgasthep1033]

42 **Hecht JR**, Bedford R, Abbruzzese JL, Lahoti S, Reid TR, Soetikno RM, Kirn DH, Freeman SM. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003; **9**: 555-561 [PMID: 12576418]

43 **Sanders MK**, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, Burton S, McGrath K. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. *Gastrointest Endosc* 2010; **71**: 1178-1184 [PMID: 20362284 DOI: 10.1016/j.gie.2009.12.020]

44 **DiMaio CJ**, Nagula S, Goodman KA, Ho AY, Markowitz AJ, Schattner MA, Gerdes H. EUS-guided fiducial placement for

image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). *Gastrointest Endosc* 2010; **71**: 1204-1210 [PMID: 20598247 DOI: 10.1016/j.gie.2010.01.003]

45 **Ammar T**, Coté GA, Creach KM, Kohlmeier C, Parikh PJ, Azar RR. Fiducial placement for stereotactic radiation by using EUS: feasibility when using a marker compatible with a standard 22-gauge needle. *Gastrointest Endosc* 2010; **71**: 630-633 [PMID: 20189527 DOI: 10.1016/j.gie.2009.11.023]

46 **Pishvaian AC**, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc* 2006; **64**: 412-417 [PMID: 16923491 DOI: 10.1016/j.gie.2006.01.048]

47 **Park WG**, Yan BM, Schellenberg D, Kim J, Chang DT, Koong A, Patalano C, Van Dam J. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. *Gastrointest Endosc* 2010; **71**: 513-518 [PMID: 20189509 DOI: 10.1016/j.gie.2009.10.030]

48 **Ghassemi S**, Faigel DO. EUS-guided placement of fiducial markers using a 22-gauge needle. *Gastrointest Endosc* 2009; **69**: AB337-AB338 [DOI: 10.1016/j.gie.2009.03.980]

49 **Sun S**, Xu H, Xin J, Liu J, Guo Q, Li S. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. *Endoscopy* 2006; **38**: 399-403 [PMID: 16680642 DOI: 10.1055/s-2006-925253]

50 **Jin Z**, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy* 2008; **40**: 314-320 [PMID: 18283622 DOI: 10.1055/s-2007-995476]

P- Reviewers Sahu RP, Izbicki JR, Baba H, Di Matteo F
S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.148

World J Gastrointest Endosc 2013 April 16; 5(4): 148-153
ISSN 1948-5190 (online)

BRIEF ARTICLE

Safety of endoscopic retrograde cholangiopancreatography in pregnancy: Fluoroscopy time and fetal exposure, does it matter?

Ioana Smith, Monica Gaidhane, Allen Goode, Michel Kahaleh

Ioana Smith, Department of Medicine, University of Alabama, Birmingham, AL 35487, United States
Monica Gaidhane, Michel Kahaleh, Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY 10021, United States
Allen Goode, Radiology and Medical Imaging, University of Virginia, Charlottesville, VI 22908, United States
Author contributions: Smith I and Goode A drafted the manuscript, revised the manuscript for important intellectual content; Gaidhane M and Kahaleh M acquired, analysed and interpreted the data and revised the manuscript for important intellectual content.
Correspondence to: Michel Kahaleh, MD, AGAF, FACG, FASGE, Chief of Endoscopy, Division of Gastroenterology and Hepatology, Weill Cornell Medical College, 1305 York Avenue, 4th floor, New York, NY 10021, United States. mkahaleh@gmail.com
Telephone: +1-646-9624000 Fax: +1-646-9620110
Received: September 14, 2012 Revised: December 27, 2012
Accepted: January 23, 2013
Published online: April 16, 2013

Abstract

AIM: To estimate the fetal radiation exposure using thermoluminescent dosimeters (TLD's) in pregnant patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) and assess its relevance.

METHODS: Data on thirty-five therapeutic ERCPs conducted in pregnant patients from 2001 to 2009 were retrieved from a prospective database. Techniques to minimize fluoroscopy time were implemented and the fluoroscopy times captured. TLD's were placed on the mother to estimate the fetal radiation exposure and the results were compared to the maximum allowed dose of radiation to the fetus [0.005 gray (Gy)]. Obstetrics consultations were obtained and the fetus was monitored before and after the ERCP. Fluoroscopy was performed at 75 kVp. ERCP was performed with the patients supine by dedicated biliary endoscopists performing more than 500 cases a year.

RESULTS: A total of 35 pregnant patients underwent ERCP and biliary sphincterotomy (14 in first trimester, 11 in second trimester, and 10 in third trimester). Mean maternal age was 25 years (range 16-37 years) and mean gestational age was 18.9 wk (range 4-35 wk). Mean fluoroscopy time was 0.15 min (range 0-1 min). For 23 women, the estimated fetal radiation exposure was almost negligible (< 0.0001 Gy) while for 8 women, it was within the 0.0001-0.0002 Gy range. Three women had an estimated fetal radiation exposure between 0.0002 and 0.0005 Gy and 1 woman had an estimated fetal radiation exposure greater than 0.0005 Gy. Complications included 2 post-sphincterotomy bleeds, 2 post-ERCP pancreatitis, and 1 fatal acute respiratory distress syndrome. One patient developed cholecystitis 2 d after ERCP.

CONCLUSION: ERCP with modified techniques is safe during pregnancy, and estimating the fetal radiation exposure from the fluoroscopy time or measuring it *via* TLD's is unnecessary.

Key words: Endoscopic retrograde cholangiopancreatography; Pregnancy; Fluoroscopy; Fetal exposure; Pancreaticobiliary disease

Smith I, Gaidhane M, Goode A, Kahaleh M. Safety of endoscopic retrograde cholangiopancreatography in pregnancy: Fluoroscopy time and fetal exposure, does it matter? *World J Gastrointest Endosc* 2013; 5(4): 148-153 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/148.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.148

INTRODUCTION

Choledocholithiasis can occur in as many as 12% of pregnant women and increases with gestational age[1]. It may be associated with cholangitis and/or gallstone pancreatitis, both of which have an increased morbidity for the mother and fetus[2]. Therefore choledocholithiasis is the most common indication for endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy[3]. For pancreaticobiliary diseases in pregnancy, ERCP has been suggested as an effective alternative to surgery[4]. Suggestions have been made that ERCP is likely best performed during the second trimester, though the procedure appears reasonably safe to be performed throughout the entire period of pregnancy[5]. ERCP is currently exclusively indicated for therapeutic reasons in light of the endoscopic risks (such as bleeding, pancreatitis or perforation) as well as the ionizing radiation exposure to the fetus[6]. ERCPs are therapeutic when one or more of the following is performed: endoscopic sphincterotomy, removal of stones, stent placement, dilation of strictures. Efforts to minimize ionizing radiation, measured in rads (radiation absorbed dose)[5] or in rem (radiation equivalent man) or in international units gray (Gy)[7], should be undertaken. During neuron development, the threshold for malformations appears to be 0.001 Gy[5] and the overall maximum allowed dose of radiation to the fetus is 0.005 Gy[7]. The International Commission of Radiological Protections recommends specific calculations of fetal radiation exposure when doses are suspected to exceed the threshold of 0.01 Gy[8]. Our study sought to estimate the fetal radiation exposure using thermoluminescent dosimeters (TLD's) in pregnant women undergoing therapeutic ERCP with modified techniques as well as look at the outcome of the ERCP in those patients.

MATERIALS AND METHODS

All pregnant woman undergoing ERCP between 2001 till 2009 were captured in a dedicated prospective database. A total of thirty-five pregnant women were entered. The records were reviewed to determine the procedure indications and outcome in terms of success and eventual morbidity. Also, existing perinatal records were reviewed. The institutional review board approved the study protocol.

Preprocedure characteristics and evaluation

Pre-ERCP diagnosis included gallstone pancreatitis (17), choledocholithiasis (11), symptomatic cholelithiasis (6) and cholangitis (1). Obstetrics consultations were obtained and the fetus was monitored before and after the ERCP. Antibiotics were administered prophylactically. The modified technique involved the patients being placed supine on the fluoroscopy table, and the lower abdomen and pelvis being shielded with a 0.5- to 1.0-mm thickness of lead or its equivalent[7]. The uterus was positioned outside the primary X-ray beam. Four pairs of TLD's were taped to the skin; one pair on the abdomen over the uterus shielded by lead, one pair on the upper abdomen in the primary beam, one pair on the lower back beneath the uterus shielded by lead and one pair on the upper back in the primary beam[7]. Fluoroscopy was performed at 75 kVp. A TLD reader was used and its readings were converted to milliards (mrads) of dose received at the skin surface by using a calibration curve[7]. TLDs on the upper back in the primary beam recorded the highest dose; about 10% of this dose was estimated to be the fetal dose[7]. The fetus was considered to be 10 cm from the posterior surface, and percentage depth dose at 10 cm was taken as approximately 10%. The depth dose varies with body habitus and gestational age and hence the dose estimation was an approximation[7].

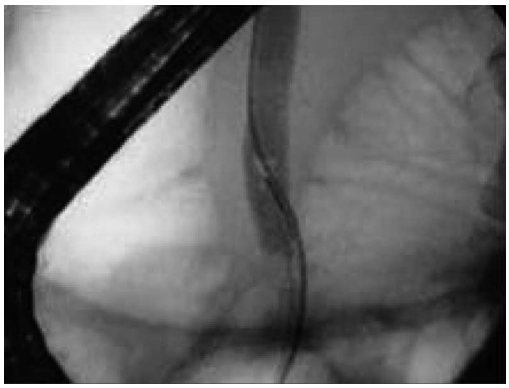


Figure 1 Fluoroscopy view of stone in common bile duct in a pregnant patient.

ERCP techniques

ERCP was performed with the patients supine by dedicated biliary endoscopists performing more than 500 cases a year[7]. Free biliary cannulation was obtained by using a sphincterotome and was confirmed by aspiration of bile, after which a biliary sphincterotomy was performed[7]. An 11.5-mm diameter retrieval balloon was advanced into the bile duct[7]. Contrast medium was injected, and a balloon occlusion cholangiogram was obtained to confirm the presence and location of stones, as well as cystic duct patency, after which the balloon was used to extract stones (Figures 1 and 2)[7].

RESULTS

A total of 35 pregnant patients underwent ERCP and biliary sphincterotomy (14 in first trimester, 11 in second trimester, and 10 in third trimester). Mean maternal age was 25 years (range 16-37 years) and mean gestational age was 18.9 wk (range 4-35 wk). Mean fluoroscopy time was 0.15 min (range 0-1 min). For 23 women, the estimated fetal radiation exposure was negligible (< 0.0001 Gy) while for 8 women, it was within the 0.0001-0.0002 Gy range. Three women had an estimated fetal radiation exposure between 0.0002 and 0.0005 Gy and one woman had an estimated fetal radiation exposure greater than 0.0005 Gy (Figure 3). Mean values for biochemical tests obtained before ERCP were the following: aspartate

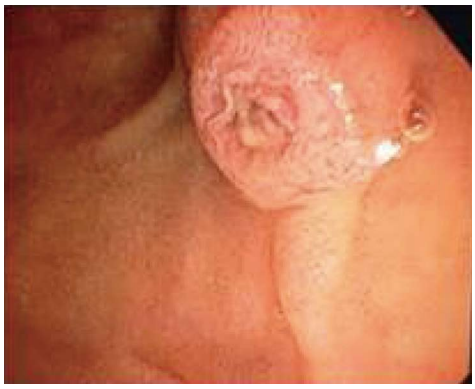


Figure 2 Endoscopic view of impacted stone in a pregnant patient.

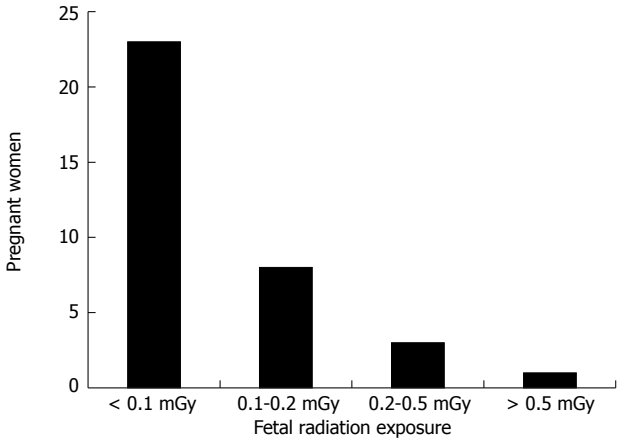


Figure 3 Bar graph representing estimated fetal radiation exposure. Gy: Gray.

aminotransferase 179 IU/L (range: 25-310 IU/L); alanine aminotransferase 210 IU/L (27-561 IU/L); alkaline phosphatase 162 IU/L (44-394 IU/L); and total bilirubin 2.4 mg/dL (0.2-5 mg/dL). Four patients prior to pregnancy had cholecystectomy, one patient had a cholecystectomy during the pregnancy and prior to ERCP, and four patients required cholecystectomy post-ERCP during their pregnancy.

The patients' final diagnosis was made based on ERCP findings, that is, extraction of stone or stone fragments after biliary sphincterotomy. Final diagnosis included the following: choledocholithiasis (18), gallstone pancreatitis (14), cholelithiasis, microlithiasis, and cholestasis. Complications of the ERCP procedure included post-sphincterotomy bleeding in two patients (controlled by hemoclip placement), post-ERCP pancreatitis (pancreatitis that developed within a week after ERCP) in two patients that necessitated one and two days of hospitalization, and acute respiratory distress syndrome in one patient who passed away as a result. One patient had cholecystitis requiring laparoscopic cholecystectomy 2 d post-ERCP. Two patients had contractions post-ERCP that resolved with hydration and terbutaline administration, respectively. Four mothers were at term and 2 mothers were preterm. Labor was induced in 2 mothers with non eventful delivery.

DISCUSSION

The incidence of gallstone disease during pregnancy has been estimated to be between 4.5% to 12%[1,3]. Choledocholithiasis may lead to potentially life-threatening cholangitis and/or gallstone pancreatitis. Given the necessity of treating cholangitis and gallstone pancreatitis during pregnancy[3] with therapeutic ERCP, an estimate of the radiation exposure to the fetus from an uncomplicated ERCP procedure should be known. Several published studies have investigated post-ERCP complications (preterm births, pancreatitis, sphincterotomy bleed) in pregnant women with a few capturing the mean time of fluoroscopy.

The mean fluoroscopy time was 14 s (range 1-48 s) and with use of TLDs the fetal radiation exposure was estimated to be 0.0004 Gy (range 0.0001-0.0018 Gy) in Kahaleh *et al*[7]. Despite there being a correlation between fluoroscopy time and radiation exposure, each fluoroscopy time corresponded with a wide range of radiation exposures. Complications included one post-sphincterotomy bleed and one post-ERCP pancreatitis. Two of the 17 women developed third-trimester preeclampsia, and labor was induced in both. Thirteen of the 15 patients who delivered were contacted and they confirmed that their child was in good health. Similar but limited complications were seen in Jamidar *et al*[9]. Twenty-three pregnant patients underwent a total of 29 ERCPs with one post-ERCP pancreatitis. Also, there was one spontaneous abortion (3 mo after ERCP) and one neonatal death; however, casual relationship to ERCP was not clear.

In Tang *et al*[10] in 2009, the largest retrospective study on ERCP in pregnant women, 68 ERCPs were performed on 65 pregnant women. The median fluoroscopy time was 1.45 min (range 0-7.2 min) and 11 patients (16%) had post-ERCP pancreatitis Term pregnancy was achieved in 53 patients (89.8%). Patients having ERCP in the first trimester had the lowest percentage of term pregnancy (73.3%) and the highest risk of preterm delivery (20.0%) and low-birth-weight newborns (21.4%). None of the 59 patients with long-term follow-up had spontaneous fetal loss, perinatal death, stillbirth, or fetal malformation.

Gupta *et al*[11] reported on one of the longest follow-up periods on fetal outcome after ERCP. Eighteen pregnant women underwent ERCP and sphincterotomy (4 in the first trimester, 6 in the second, and 8 in the third) in which the location of the cannula in the bile duct was confirmed using ultrasound guidance in 5 patients and bile aspiration in 2 patients. Indications included elective ERCP in 14 and symptomatic choledocholithiasis in 4. Complications included a post-sphincterotomy bleed and a mild post-ERCP pancreatitis in another, who also had preterm delivery. Eleven of 18 patients had healthy children without any developmental or congenital abnormalities 11-years post ERCP follow-up.

Tiwari *et al*[12] conducted a systematic review of 19 studies including 214 ERCPs in pregnant women and the procedure related complications included spontaneous abortion (0.9%), fetal distress (0.6%) and post procedure pancreatitis (4.6%). Preterm birth occurred in 4.6% with majority of the APGAR score greater than 8. Post-procedure pancreatitis risk factors include: young age, female sex, history of pancreatitis, sphincter of oddi dysfunction, difficult cannulation and precut sphincterotomy[6]. Thus, post-ERCP pancreatitis does not adversely affect pregnancy-related outcomes, as reported previously[10]. Cholecystectomy was performed in a few of the patients reviewed and most likely does not appear to lead to preterm delivery and low birth weight[10].

In a few studies, biliary stents were placed not only when residual stones or fragments were present, but also in an effort to limit total fluoroscopy time[10]. Farca *et al*[13] placed 10-French biliary stents without sphincterotomy in 10 patients, all of which had uncomplicated pregnancies and deliveries. Daas *et al*[4] in 2009 (17 ERCPs in 10 patients) placed plastic biliary stents when large (> 10 mm) biliary stones were encountered or when there was doubt regarding complete stone clearance. Fluoroscopy was used in 6 cases with mean exposure time of 8 s. Most of the 10 pregnant women in the study required repeat ERCPs with one woman receiving 3 subsequent ERCPs without fluoroscopy and had to return postpartum for a definitive stone extraction.

Barthel *et al*[14] performed biliary sphincterotomy in 3 patients with gallstone pancreatitis despite the absence of choledocholithiasis; one patient had post-ERCP pancreatitis and none had recurrent pancreatitis and all pregnancies had healthy outcome. Tang *et al*[10] showed that prophylactic sphincterotomy during ERCP can effectively reduce the risk of recurrent biliary pancreatitis during pregnancy. Therefore, ERCP with biliary sphincterotomy was performed in all 35 patients in our study.

Some have advocated eliminating radiation exposure by biliary cannulation with a sphincterotome, confirmation of access by bile aspiration[9] followed by sphincterotomy and stone extraction with a balloon catheter[5]. With this technique of using wire-guided cannulation techniques to achieve bile duct access without use of fluoroscopy[15], there is lack of ductal system definition and additional stones may be missed[5]. Importantly, aspiration of bile into the catheter does not necessarily confirm whether the CBD or the cystic duct has been cannulated[5]. Although it is important to minimize radiation exposure during ERCP, without fluoroscopy, residual stones or debris can be left in the CBD and might lead to recurrent cholangitis with more serious effects on both the fetus and mother[5].

In Sharma *et al*[16] in 2008, 11 pregnant women underwent biliary sphincterotomy and stenting without fluoroscopy and had definitive ERCP and stone clearance after pregnancy. One patient with large common bile duct stone required mechanical lithotripsy while another required surgery. Of note, the indication for the ERCP in the study was choledocholithiasis not cholangitis or gallstone pancreatitis which carry an increased mortality to the mother and fetus and likely necessitate definitive ERCP during the pregnancy. Further studies are required to prove that the clinical efficiency of nonradiating ERCP remains at the same level with conventional fluoroscopically guided ERCP[15]. Girotra *et al*[17] described an alternative management strategy to conventional ERCP in pregnant women with choledocholithiasis and cholangitis detected using EUS and choledochoscopy.

Fluoroscopy time can be utilized in ERCPs performed in pregnant patients and limiting fluoroscopy time is one of the most efficient methods to reduce radiation dose[3]. Lead shielding should be used[6] hard copy radiographs should be avoided[5] and anterior posterior beam projection should be used as it results in lower fetal dosing[6,8]. The radiation risks include fetal death, growth retardation especially during organogenesis and malformations[7]. Exposures over 0.001 Gy during neuron development and migration may be associated with microcephaly, mental retardation and childhood cancers[5]. The maximum allowed dose of radiation to the fetus is 0.005 Gy[7].

The International Commission of Radiological Protections recommends specific calculations of fetal radiation exposure when doses are suspected to exceed the threshold of 0.01 Gy[8]. Surprisingly, ERCP-induced fetal radiation exposure from ERCPs carried out in pregnant patients have been reported in the literature to vary from 0.0001 to 0.003 Gy per procedure[1,3,7,9,18,19]. In our study, the ERCP-induced fetal radiation ranged from less than 0.0001 to greater than 0.0005 Gy. For the majority of the women (88.6%), the estimated fetal radiation exposure was no more than 0.0002 Gy; while only one woman's estimated fetal radiation exposure was greater than 0.0005 Gy. The fetal radiation exposure values in our study are below the threshold established by the International Commission of Radiological Protections needing specific calculations of fetal radiation exposure and the maximum allowed dose of radiation to the fetus.

Thus, for a routine ERCP with modified techniques, estimating the fetal radiation exposure from the fluoroscopy time and measuring it with the use of TLD's is unnecessary. The threshold may be exceeded in complicated long-lasting ERCPs[3] and in these complicated long-lasting ERCPs, dosimetry may be used to estimate the fetal radiation exposure, such as patients with altered anatomy, failed prior ERCP or complex bile leak. By placing TLD's on the pregnant patient over and above the uterus, one can obtain a good estimate of the fetus doses from calculations based on a TLD reading. The value is an approximation, probably an underestimate of the real value, as the principal source of radiation to the fetus during the ERCP comes from scattered radiation absorbed within the mother's body[3]. Tham *et al*[1] attempted to attain a better estimate using nonanthopomorphic phantom to estimate the entrance skin dose and estimated the fetal dose exposure at 0.003 Gy.

The safety and efficacy of therapeutic ERCP has been

demonstrated in many studies[1,7,9.11,13,20-31]. For a routine ERCP, the reported fetal radiation exposure falls below the maximum allowed dose of radiation to the fetus of 0.005 Gy[7], therefore estimating the fetal radiation exposure from the fluoroscopy time or by measuring it from the use of TLD's is unnecessary.

COMMENTS

Background

For pancreaticobiliary diseases in pregnancy, endoscopic retrograde cholangiopancreatography (ERCP) has been suggested as an effective alternative to surgery. ERCPs are therapeutic when one or more of the following is performed: endoscopic sphincterotomy, removal of stones, stent placement, dilation of strictures.

Research frontiers

Fluoroscopy time can be utilized in ERCPs performed in pregnant patients and limiting fluoroscopy time is one of the most efficient methods to reduce radiation dose.

Innovations and breakthroughs

The fetal radiation exposure values in the authors' study are below the threshold established by the International Commission of Radiological Protections needing specific calculations of fetal radiation exposure and the maximum allowed dose of radiation to the fetus.

Peer review

The aim of the present article is the estimation of the fetal radiation exposure using TLD's in pregnant women undergoing ERCPs. The article is sound and deserves publication.

REFERENCES

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

2 **Scott LD**. Gallstone disease and pancreatitis in pregnancy. *Gastroenterol Clin North Am* 1992; **21**: 803-815 [PMID: 1478736]

3 **Samara ET**, Stratakis J, Enele Melono JM, Mouzas IA, Perisinakis K, Damilakis J. Therapeutic ERCP and pregnancy: is the radiation risk for the conceptus trivial? *Gastrointest Endosc* 2009; **69**: 824-831 [PMID: 19243762 DOI: 10.1016/j.gie.2008.05.068]

4 **Daas AY**, Agha A, Pinkas H, Mamel J, Brady PG. ERCP in pregnancy: is it safe? *Gastroenterol Hepatol (N Y)* 2009; **5**: 851-855 [PMID: 20567530 DOI: 10.1007/s11894-012-0294-0]

5 **Al-Hashem H**, Muralidharan V, Cohen H, Jamidar PA. Biliary disease in pregnancy with an emphasis on the role of ERCP. *J Clin Gastroenterol* 2009; **43**: 58-62 [PMID: 19020461 DOI: 10.1097/MCG.0b013e31818acf80.]

6 **Baron TH**, Schueler BA. Pregnancy and radiation exposure during therapeutic ERCP: time to put the baby to bed? *Gastrointest Endosc* 2009; **69**: 832-834 [PMID: 19327473 DOI: 10.1016/j.gie.2008.07.010]

7 **Kahaleh M**, Hartwell GD, Arseneau KO, Pajewski TN, Mullick T, Isin G, Agarwal S, Yeaton P. Safety and efficacy of ERCP in pregnancy. *Gastrointest Endosc* 2004; **60**: 287-292 [PMID: 15278066 DOI: 10.1016/S0016-5107(04)01679-7]

8 **International Commission on Radiological Protection**. Pregnancy and medical radiation. *Ann ICRP* 2000; **30**: iii-viii, 1-43 [PMID: 11108925]

9 **Jamidar PA**, Beck GJ, Hoffman BJ, Lehman GA, Hawes RH, Agrawal RM, Ashok PS, Ravi TJ, Cunningham JT, Troiano F. Endoscopic retrograde cholangiopancreatography in pregnancy. *Am J Gastroenterol* 1995; **90**: 1263-1267 [PMID: 7639227]

10 **Tang SJ**, Mayo MJ, Rodriguez-Frias E, Armstrong L, Tang L, Sreenarasimhaiah J, Lara LF, Rockey DC. Safety and utility of ERCP during pregnancy. *Gastrointest Endosc* 2009; **69**: 453-461 [PMID: 19136111 DOI: 10.1016/j.gie.2008.05.024]

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

12 **Tiwari P**, Khan AS, Nass JP, Rivera RE, Romero RV, Antillon MR, Roy PK. Mo1578 ERCP in Pregnancy: A Systematic Review. *Gastrointest Endosc* 2011; **73**: AB392-AB393 [DOI: 10.1016/j.gie.2011.03.877]

13 **Farca A**, Aguilar ME, Rodriguez G, de la Mora G, Arango L. Biliary stents as temporary treatment for choledocholithiasis in pregnant patients. *Gastrointest Endosc* 1997; **46**: 99-101 [PMID: 9260726]

14 **Barthel JS**, Chowdhury T, Miedema BW. Endoscopic sphincterotomy for the treatment of gallstone pancreatitis during pregnancy. *Surg Endosc* 1998; **12**: 394-399 [PMID: 9569356 DOI: 10.1007/s004649900689]

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

16 **Sharma SS**, Maharshi S. Two stage endoscopic approach for management of choledocholithiasis during pregnancy. *J Gastrointestin Liver Dis* 2008; **17**: 183-185 [PMID: 18568140]

17 **Girotra M**, Jani N. Role of endoscopic ultrasound/SpyScope in diagnosis and treatment of choledocholithiasis in pregnancy. *World J Gastroenterol* 2010; **16**: 3601-3602 [PMID: 20653072 DOI: 10.3748/wjg.v16.i28.3601]

18 **Axelrad AM**, Fleischer DE, Strack LL, Benjamin SB, al-Kawas FH. Performance of ERCP for symptomatic choledocholithiasis during pregnancy: techniques to increase safety and improve patient management. *Am J Gastroenterol* 1994; **89**: 109-112 [PMID: 8273776]

19 **Howden JK**, Robuck-Mangum G, Jowell PS, Branch MS, Yoshizumi T, Swartz KL, Baillie J. Endoscopic management of symptomatic choledocholithiasis (CDL) during pregnancy: Safety and efficacy of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES). *Gastrointest Endosc* 2001; **53**: AB96 [DOI: 10.1016/S0016-5107(01)80140-1]

20 **Baillie J**, Cairns SR, Putman WS, Cotton PB. Endoscopic management of choledocholithiasis during pregnancy. *Surg Gynecol Obstet* 1990; **171**: 1-4 [PMID: 2360143]

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

22 **Cappell MS**. The fetal safety and clinical efficacy of gastrointestinal endoscopy during pregnancy. *Gastroenterol Clin North Am* 2003; **32**: 123-179 [PMID: 12635415 DOI: 10.1016/S0889-8553(02)00137-1]

23 **Swisher SG**, Hunt KK, Schmit PJ, Hiyama DT, Bennion RS, Thompson JE. Management of pancreatitis complicating pregnancy. *Am Surg* 1994; **60**: 759-762 [PMID: 7944038]

24 **Qureshi WA**, Rajan E, Adler DG, Davila RE, Hirota WK, Jacobson BC, Leighton JA, Zuckerman MJ, Hambrick RD, Fanelli RD, Baron T, Faigel DO. ASGE Guideline: Guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2005; **61**: 357-362 [PMID: 15758903 DOI: 10.1016/S0016-5107(04)02780-4]

25 **Tarnasky PR**, Simmons DC, Schwartz AG, Macurak RB, Edman CD. Safe delivery of bile duct stones during pregnancy. *Am J Gastroenterol* 2003; **98**: 2100-2101 [PMID: 14499796 DOI: 10.1016/S0002-9270(03)00621-X]

26 **Simmons DC**, Tarnasky PR, Rivera-Alsina ME, Lopez JF, Edman CD. Endoscopic retrograde cholangiopancreatogra-

phy (ERCP) in pregnancy without the use of radiation. *Am J Obstet Gynecol* 2004; **190**: 1467-1469 [PMID: 15167871 DOI: 10.1016/j.ajog.2004.02.030]

27 **Sungler P**, Heinerman PM, Steiner H, Waclawiczek HW, Holzinger J, Mayer F, Heuberger A, Boeckl O. Laparoscopic cholecystectomy and interventional endoscopy for gallstone complications during pregnancy. *Surg Endosc* 2000; **14**: 267-271 [PMID: 10741447 DOI: 10.1007/s004640000037]

28 **Howden JK**, Baillie J. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate pancreatitis: a prospective randomized trial. *Gastrointest Endosc* 2001; **53**: 834-836 [PMID: 11414240]

29 **Akcakaya A**, Ozkan OV, Okan I, Kocaman O, Sahin M. Endoscopic retrograde cholangiopancreatography during pregnancy without radiation. *World J Gastroenterol* 2009; **15**: 3649-3652 [PMID: 19653343 DOI: 10.3748/wjg.15.3649]

30 **Chong VH**, Jalihal A. Endoscopic management of biliary disorders during pregnancy. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 180-185 [PMID: 20382591]

31 **García-Cano J**, Pérez-Miranda M, Pérez-Roldán F, González-Carro P, González-Huix F, Rodríguez-Ramos C, Naranjo A, González-Martín JÁ, de la Serna C. ERCP during pregnancy. *Rev Esp Enferm Dig* 2012; **104**: 53-58 [PMID: 22372797 DOI: 10.4321/S1130-01082012000200002]

P- Reviewers Arcidiacono PG, Sudhoff H **S- Editor** Zhai HH
L- Editor A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.154

World J Gastrointest Endosc 2013 April 16; 5(4): 154-159
ISSN 1948-5190 (online)

BRIEF ARTICLE

Accuracy of community based video capsule endoscopy in patients undergoing follow up double balloon enteroscopy

David Tenembaum, Cristina Sison, Moshe Rubin

David Tenembaum, Cristina Sison, Moshe Rubin, Department of Medicine, New York Hospital Queens, Weill Cornell Medical College, New York, NY 11355, United States
Author contributions: All authors contributed equally to this work.
Correspondence to: David Tenembam, MD, Department of Medicine, New York Hospital Queens, Weill Cornell Medical College, 56-45 Main Street, Flushing, New York, NY 11355, United States. royaltbaum@aol.com
Telephone: +1-718-6617203 Fax:+1-718-6702456
Received: September 13, 2012 Revised: February 7, 2013
Accepted: February 28, 2013
Published online: April 16, 2013

Abstract

AIM: To determine the test characteristics of community based video capsule endoscopy (VCE) in patients undergoing sequential VCE and double balloon enteroscopy (DBE).

METHODS: Eighty-nine patients (34 females, 55 males, mean age 66) who underwent both VCE and DBE from 2008-2010 were retrospectively reviewed. Lesions detected at VCE were categorized. Capsule directed DBE followed and included 44 antegrade, 11 retrograde and 34 combined antegrade and retrograde procedures. Lesions detected were compared utilizing the McNemar's test.

RESULTS: Angioectasia detection with VCE was 25% and with DBE 35% ($P < 0.03$) with a calculated sensitivity and specificity of 58% and 93% respectively. Polyps were detected by VCE in 22% and in DBE 20%, ($P = 0.6$), with a sensitivity and specificity for VCE of 61% and 87%. Small bowel diverticula were only seen in 1% of VCE but in 12% of DBE patients ($P < 0.002$) with a calculated sensitivity and specificity of VCE of 9% and 100%.

CONCLUSION: VCE would be moderately sensitive and specific overall with considerable variation by lesion. Furthermore, VCE cannot be relied upon to diagnose small bowel diverticula.

Key words: Video capsule endoscopy; Double balloon enteroscopy; Angioectasia; Diverticulosis; Obscure gastrointestinal bleeding

Core tip: Advances in endoscopic technology have revolutionized the evaluation of small intestinal disorders. Non-invasive imaging utilizing video capsule endoscopy (VCE) offers the potential to safely visualize the entire small bowel with a high diagnostic yield. It is limited by a lack of therapeutic ability, imprecise localization, failure to reach the colon in all cases and inconsistent visualization of the entire small bowel. Deep enteroscopy, utilizing double balloon enteroscopy (DBE), enables diagnostic and therapeutic endoscopy of the small bowel. Although total enteroscopy can be accomplished, it typically requires antegrade and retrograde approaches. In most clinical situations, VCE is performed initially. By using DBE as the criterion (gold) standard, the sensitivity and specificity of community based VCE can be assessed for individual lesions, offering a more informative comparison than diagnostic yield.

Tenembaum D, Sison C, Rubin M. Accuracy of community based video capsule endoscopy in patients undergoing follow up double balloon enteroscopy. *World J Gastrointest Endosc* 2013; 5(4): 154-159 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/154.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.154

INTRODUCTION

Advances in endoscopic technology have revolutionized

the evaluation of small intestinal disorders. Non-invasive imaging utilizing video capsule endoscopy (VCE) offers the potential to safely visualize the entire small bowel with a high diagnostic yield[1,2]. It is limited by a lack of therapeutic ability, imprecise localization, failure to reach the colon in all cases and inconsistent visualization of the entire small bowel[3]. Deep enteroscopy, utilizing double balloon enteroscopy (DBE), enables diagnostic and therapeutic endoscopy of the small bowel. Limitations of DBE include its invasive nature, limited availability and the need for anesthesia[4]. Although total enteroscopy can be accomplished, it typically requires antegrade and retrograde approaches. The rate of total enteroscopy varies between 11%-66%[5,6]. In most clinical situations, VCE is performed initially[3]. The results can then be used to determine the need for deep enteroscopy as well as the entry route (antegrade or retrograde)[7,8]. Studies comparing the relative abilities of VCE and DBE, are based on "diagnostic yield" which refers to the proportion of examinations in which any abnormality is detected. Two recent meta-analyses of studies comparing VCE and DBE have demonstrated comparable diagnostic yields[1,2]. Few studies, however, compared the individual abnormalities detected at VCE with those subsequently confirmed at DBE[9]. We propose to evaluate the test characteristics of VCE for each type of lesion by comparing the results of community based VCE to the findings at follow up DBE for each patient. By using DBE as the criterion (gold) standard, the sensitivity and specificity of community based VCE can be assessed for individual lesions, offering a more informative comparison than diagnostic yield.

MATERIALS AND METHODS

Patients

Eighty-nine patients, 34 females and 55 males with a mean age of 66, who underwent sequential VCE and DBE exams between 2008-2010 were retrospectively reviewed (Table 1). The study was approved by the New York Hospital Queens institutional review board. All VCE studies but one were performed with the Given Imaging Pillcam SB2® system. VCE studies were read by both community and full-time academic gastroenterologists in the New York metropolitan area. A formal second review of VCE studies by a single expert was not performed. Preparation for VCE was variable and depended on the preferences of the referring physician. Findings were not correlated with use and type of preparation. No attempt was made to correlate VCE findings with pre-procedure preparation since the effect of preparation on diagnostic yield remains controversial[10-12]. All patients undergoing antegrade DBE were NPO for eight hours prior to the exam. All patients undergoing retrograde DBE were prepped with a combination of 2 L of polyethylene glycol and Bisacody l20 mg.

DBE

DBE studies were performed with the Fujinon EN-450T5 enteroscope with a methodology described previously[13].

Table 1 Demographics *n* (%)

Total patients	89
Male	55 (62)
Female	34 (38)
Median days from VCE to DBE	29 (8-64)
Age (range) (yr)	66 (19-93)
Antegrade DBE	44 (49)
Retrograde DBE	11 (12)
Antegrade and retrograde DBE	34 (38)

VCE: Video capsule endoscopy; DBE: Double balloon enteroscopy.

All DBE procedures were performed by one attending (MR) and a gastroenterology fellow at New York Hospital Queens Weill-Cornell Medical College. The approach to DBE was guided by VCE findings. Patients with positive VCE findings in the proximal and mid small-bowel underwent antegrade DBE initially. If the lesion was not found, a retrograde procedure was then performed. Patients with lesions seen in the distal small bowel at VCE underwent a retrograde DBE as the initial procedure. If the lesion was not found, an antegrade procedure was then performed. In total 44 patients underwent antegrade DBE, 11 retrograde DBE and 34 underwent both. Sixteen of the 34 had complete enteroscopy[5,6]. In patients with obscure gastrointestinal bleeding (OGIB) and negative VCE exams, DBE was guided by the patient's history. A second DBE was only performed if no lesion was found. The median time interval between the performance of VCE and the initial DBE was 29 d.

Descriptive statistics such as means, SD, medians and interquartile range were used to characterize the age distribution and time between VCE and DBE. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), along with their corresponding 95% confidence intervals, were calculated to evaluate the accuracy of VCE for identification of lesions using DBE as criterion standard. McNemar's test for paired data was used to compare detection rates between VCE and DBE. In addition to investigating detection rates for the overall presence of any lesion, separate analyses were also performed according to the type of lesion (angioectasia, diverticula, mass, polyps, ulcers/erosions). All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A result was considered statistically significant at the $P < 0.05$ level of significance.

Statistical analysis

Abnormalities identified by VCE and DBE were categorized into 5 groups to facilitate the comparison of VCE to DBE by lesion type. These groups include: (1) Angioectasia; (2) Diverticula; (3) Mass; (4) Polyps; and (5) Ulcers/Erosions.

RESULTS

Indication

Indications for VCE included OGIB (n = 78, 88%), suspicion of Crohn's disease (n = 10, 11%), and suspicion

Table 2 Diagnostic yield by lesion

	VCE	DBE	*P* value
Angioectasia	25%	35%	0.03
Diverticula	1%	12%	0.002
Mass	2%	2%	NA
Polyps	22%	20%	0.62
Ulcers	17%	14%	0.44
All Lesions	64%	66%	0.72

VCE: Video capsule endoscopy; DBE: Double balloon enteroscopy; NA: Not available.

of Whipples disease (n = 1, 1%).

Diagnostic yield

The overall diagnostic yields of VCE and DBE were 64% and 66% respectively (P = 0.72). Diagnostic yield by lesion type showed a significantly higher detection rate for DBE in the detection of angioectasia and diverticula. Angioectasia detection by VCE was 25% compared to 35% for DBE (P = 0.03, Table 2). By location, 35% of angioectasias identified at VCE were in the first tertile, 43% in the second tertile and 22% in the third tertile. The vast majority of angioectasias (11/13) seen at DBE but not at VCE were in the proximal to mid-small bowel. Small bowel diverticula were seen in 1% of all VCE patients compared to 12% of DBE patients (P = 0.002). Diverticula were identified in the duodenum in 2 patients, jejunum in 7 patients and the ileum in 4 patients. Mass lesions were seen in two patients with VCE and both were confirmed at DBE. No additional mass lesions were discovered by DBE. Small bowel polyps were seen in 22% of VCE patients compared to 20% of DBE patients (P = 0.62). Small bowel ulcers were seen in 17% of VCE patients compared to 14% of DBE patients (P = 0.44) (Table 2).

Test characteristics of VCE

Comparison of VCE and DBE findings by lesion type: (1) Angioectasia: Angioectasias were found by both VCE and DBE in 18 patients. They were found only in VCE in 4 patients and in DBE alone in 13 patients; and (2) Diverticula: Small bowel diverticula were seen in both VCE and DBE in only 1 patient but were seen at DBE in 10 additional patients (Figure 1).

Two masses were seen by both VCE and DBE. Polyps were found by both VCE and DBE in eleven patients, at VCE and not DBE in 9 patients, and were seen at DBE and not VCE in 7 patients. Ulcers were found in both VCE and DBE in 6 patients, at VCE but not DBE in 9 patients, and were seen at DBE and not VCE in 6 patients (Table 3).

The sensitivity and specificity of VCE using DBE as the criterion standard varied by lesion type (Figure 2). Overall, the sensitivity of VCE was 65% and the specificity was 66%. VCE was most sensitive and specific for masses (100%). It was moderately sensitive (58%) but highly specific (93%) for angioectasia. The sensitivity for ulcers/erosions was 50% and the specificity was 88%. For polyps, the sensitivity and specificity was 61% and 87%. Importantly, VCE had very low sensitivity for detecting diverticulosis (9%) (Figure 2, Table 3).

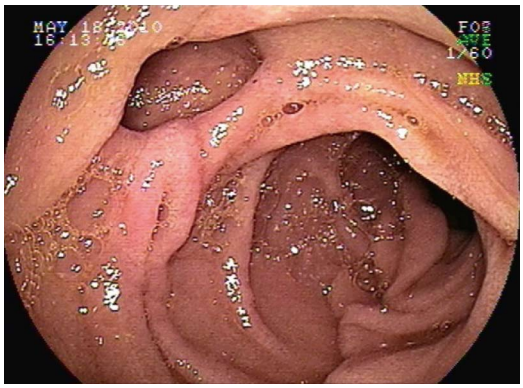


Figure 1 Small bowel diverticula.

The positive and NPV of VCE by lesion were; Angioectasia 82% and 81% respectively; Diverticula 100% and 89% respectively; Mass 100% positive and NPV; Polyps 55.0% and 90% respectively; Ulcers/erosions 40% and 92% respectively (Figure 3, Table 3).

DISCUSSION

In our study of patients undergoing sequential VCE and DBE, the overall diagnostic yield of these two procedures was equivalent. This is consistent with prior studies[1,2]. However, when diagnostic yield was compared by lesion type, we found significant differences between VCE and DBE. DBE had a higher diagnostic yield for both diverticula and angioectasia.

Duodenal diverticula are reported in 5% of upper abdominal radiographs and up to 25% in patients undergoing ERCP or at autopsy[14]. Small bowel diverticula are less common but have been found in 0.5% to 5% of radiographs and autopsies[15,16]. In our study, 11 patients (12%) who were referred for DBE were found to have diverticula. However, only 1 of 11 was detected on VCE. The failure of VCE to diagnose small bowel diverticula has been noted previously. In 2008, Hussain *et al*[17] reported finding multiple diverticula in a patient undergoing DBE, which was not detected by VCE. In 2009, Fukumoto *et al*[18] reported finding an ileal diverticulum on DBE that was missed by VCE. Marmo *et al*[19] reported two missed jejunal diverticula that were later seen on subsequent DBE. Similarly, Arakawa *et al*[20] reported 2 cases of diverticulosis of the small bowel that were missed at previous VCE. In this larger series, the sensitivity of VCE for detecting diverticula was only 9%, confirming that VCE cannot be relied upon to make this diagnosis.

The diagnostic yield for angioectasia at DBE was significantly higher than VCE (35% *vs* 25%). Differences in angioectasia detection by VCE and DBE have been reported. Some studies found a higher detection rate at VCE while others found a higher rate at DBE. Fukumoto

Table 3 Test characteristics of video capsule endoscopy using double balloon enteroscopy as the Criterion Standard

Lesions	VCE+/DBE+	VCE+/DBE+	VCE+/DBE+	VCE+/DBE+	Sensitivity of VCE	Specificity of VCE	PPV	NPV
Angioectasia	18	4	13	54	58%	93%	82%	81%
Diverticula	1	0	10	78	9%	100%	100%	89%
Mass	2	0	0	87	100%	100%	100%	100%
Polyps	11	9	7	62	61%	87%	55%	90%
Ulcers/erosions	6	9	6	68	50%	88%	40%	92%

VCE: Video capsule endoscopy; DBE: Double balloon enteroscopy; PPV: Positive predictive value; NPV: Negative predictive value.

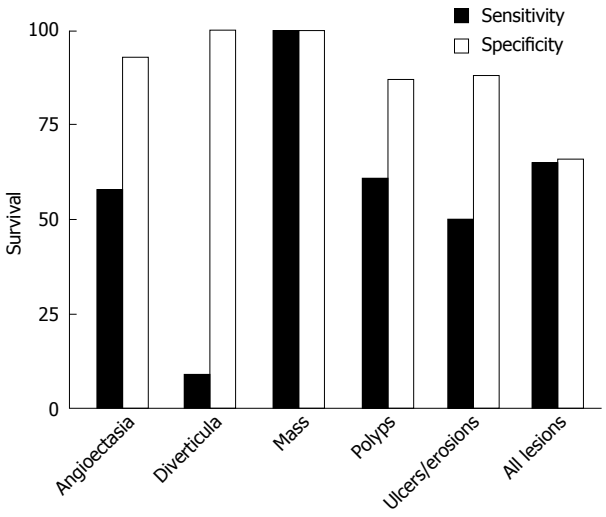


Figure 2 Sensitivity and specificity of video capsule endoscopy.

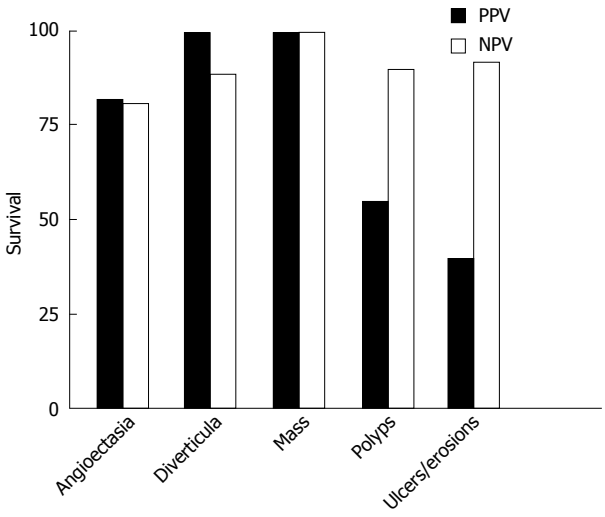


Figure 3 Positive and negative predictive value of capsule. PPV: Positive predictive value; NPV: Negative predictive value.

et al[18] described 2 patients that had angioectasia at VCE that were missed at subsequent DBE. Similarly, Arakawa reported 3 cases with missed angioectasia at DBE. Both studies attributed the missed lesions to incomplete DBE[18,20]. Angioectasia detected at DBE but not at VCE has also been described. Arakawa and Marmo each reported 2 VCE-negative DBE-positive cases[19,20]. None of these studies, however, assessed the test characteristics of VCE using DBE as the criterion standard. In our study, we found that VCE is highly specific but only moderately sensitive for detecting angioectasia (93% and 58% respectively). Since DBE detects a greater number of angioectasia, a negative capsule should not be viewed as conclusive. However, since not all red spots identified at DBE are true angioectasia, the clinical significance of the detection rate differences between VCE and DBE remains uncertain.

The diagnostic yield for polyp detection at VCE and DBE was statistically equivalent (22% and 20% respectively). However, using DBE as the criterion standard, the actual sensitivity of VCE was only 61% and the specificity was 87%. The low sensitivity implies that a significant number of lesions were missed at VCE. Alternatively some lesions thought to be polyps at VCE that were not confirmed at DBE may have been due to over interpretation of bulges and folds at VCE. The limitation of DBE however, was a lack of complete enteroscopy in all patients. Our approach of VCE directed deep enteroscopy is consistent with standard practice[3]. Nevertheless, these findings illustrate the limitation of relying on diagnostic yield as an overall measure of test accuracy. The same findings holds true for ulcers and erosions.

The limitations of our study include its retrospective design, interobserver variability in community based VCE interpretation[21], reliance on capsule directed deep enteroscopy rather than attempting complete enteroscopy in all patients and the likelihood of false positive and false negative results at DBE. Correlation of VCE findings with pre-procedure preparation was not assessed since the effect of preparation on diagnostic yield remains controversial[10-12]. Despite these limitations, we believe this data is significant and reflects the actual clinical practice of referring patients to specialized centers for deep enteroscopy based on the findings of community read VCE studies. Thus, the test characteristics described in this study may be unique to patients undergoing community based VCE followed by expert DBE and may not reflect the test characteristics of VCE in patients undergoing both studies at a tertiary care referral center. However, our study is reflective of real world practice and adds to our understanding of the benefits and limitations of these modalities.

In summary, our results suggest that comparing the diagnostic yield of VCE and DBE as a measure of test accuracy is misleading. By assessing the test characteris-

tics of VCE utilizing deep enteroscopy as the criterion standard, we have demonstrated that VCE is moderately sensitive and specific in the diagnosis of patients with small bowel disease. VCE cannot, however, be relied upon to rule out small bowel diverticula. Furthermore, based on our findings, the currently accepted algorithm for the evaluation of patients with obscure bleeding[22] which currently recommends observation alone in patients with a negative VCE should be reconsidered.

COMMENTS

Background

Studies comparing video capsule endoscopy (VCE) and deep enteroscopy have shown equivalent diagnostic yields. Although both procedures yield similar numbers of abnormalities, the accuracy of VCE by lesion type utilizing double balloon enteroscopy (DBE) as the criterion standard has not been well defined.

Research frontiers

The aim of this study is to determine the test characteristics of community based VCE in patients undergoing subsequent DBE and define the accuracy of VCE by individual lesion type.

Innovations and breakthroughs

The results of this study show that the detection rates for DBE and VCE were equivalent overall (66% *vs* 64%). However, detection rates were not equivalent when comparing individual lesions. DBE had a significantly greater detection rate for AVM's (35% *vs* 25%, $P = 0.03$) and diverticulosis (12% *vs* 1%, $P = 0.002$). The sensitivity and specificity of VCE varies by lesion type.

Applications

VCE and DBE are complimentary procedures. In the community setting, VCE is typically performed initially in patients with obscure gastrointestinal bleeding and will help guide subsequent DBE. However, VCE has a low sensitivity for certain lesions, especially small bowel diverticula. Therefore, patients with negative VCE and obscure bleeding should undergo subsequent deep enteroscopy.

Terminology

Diagnostic yield refers to the number of positive findings in each exam.

Peer review

The manuscript is very valuable presenting a comparison of VCE with DBE in real life setting. Although the review is retrospective it offers a lot of new information mostly for the daily endoscopy practice.

REFERENCES

1 **Teshima CW**, Kuipers EJ, van Zanten SV, Mensink PB. Double balloon enteroscopy and capsule endoscopy for obscure gastrointestinal bleeding: an updated meta-analysis. *J Gastroenterol Hepatol* 2011; **26**: 796-801 [PMID: 21155884 DOI: 10.1111/j.1440-1746.2010.06530.x]

2 **Pasha SF**, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, Sharma VK. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2008; **6**: 671-676 [PMID: 18356113 DOI: 10.1016/j.cgh.2008.01.005]

3 **Leighton JA**. The role of endoscopic imaging of the small bowel in clinical practice. *Am J Gastroenterol* 2011; **106**: 27-36; quiz 37 [PMID: 20978483 DOI: 10.1038/ajg.2010.410]

4 **May A**, Nachbar L, Ell C. Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. *Gastrointest Endosc* 2005; **62**: 62-70 [PMID: 15990821 DOI: 10.1016/S0016-5107(05)01586-5]

5 **Domagk D**, Mensink P, Aktas H, Lenz P, Meister T, Luegering A, Ullerich H, Aabakken L, Heinecke A, Domschke W, Kuipers E, Bretthauer M. Single- vs. double-balloon enteroscopy in small-bowel diagnostics: a randomized multicenter trial. *Endoscopy* 2011; **43**: 472-476 [PMID: 21384320 DOI: 10.1055/s-0030-1256247]

6 **May A**, Färber M, Aschmoneit I, Pohl J, Manner H, Lotterer E, Möschler O, Kunz J, Gossner L, Mönkemüller K, Ell C. Prospective multicenter trial comparing push-and-pull enteroscopy with the single- and double-balloon techniques in patients with small-bowel disorders. *Am J Gastroenterol* 2010; **105**: 575-581 [PMID: 20051942 DOI: 10.1038/ajg.2009.712]

7 **Pasha SF**, Hara AK, Leighton JA. Diagnostic evaluation and management of obscure gastrointestinal bleeding: a changing paradigm. *Gastroenterol Hepatol (N Y)* 2009; **5**: 839-850 [PMID: 20567529]

8 **Raju GS**, Gerson L, Das A, Lewis B. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. *Gastroenterology* 2007; **133**: 1697-1717 [PMID: 17983812 DOI: 10.1053/j.gastro.2007.06.007]

9 **Li X**, Dai J, Lu H, Gao Y, Chen H, Ge Z. A prospective study on evaluating the diagnostic yield of video capsule endoscopy followed by directed double-balloon enteroscopy in patients with obscure gastrointestinal bleeding. *Dig Dis Sci* 2010; **55**: 1704-1710 [PMID: 19672712 DOI: 10.1007/s10620-009-0911-4]

10 **Chen HB**, Huang Y, Chen SY, Song HW, Li XL, Dai DL, Xie JT, He S, Zhao YY, Huang C, Zhang SJ, Yang LN. Small bowel preparations for capsule endoscopy with mannitol and simethicone: a prospective, randomized, clinical trial. *J Clin Gastroenterol* 2011; **45**: 337-341 [PMID: 20871410 DOI: 10.1097/MCG.0b013e3181f0f3a3]

11 **Pons Beltrán V**, González Suárez B, González Asanza C, Pérez-Cuadrado E, Fernández Diez S, Fernández-Urién I, Mata Bilbao A, Espinós Pérez JC, Pérez Grueso MJ, Argüello Viudez L, Valle Muñoz J, Carballo Alvarez F, Muñoz-Navas M, Llach Vila J, Ramírez Armengol JA, Balanzó Tintoré J, Sala Felis T, Menchen Fernández-Pacheco P. Evaluation of different bowel preparations for small bowel capsule endoscopy: a prospective, randomized, controlled study. *Dig Dis Sci* 2011; **56**: 2900-2905 [PMID: 21479818 DOI: 10.1007/s10620-011-1693-z]

12 **de Franchis R**, Avgerinos A, Barkin J, Cave D, Filoche B. ICCE consensus for bowel preparation and prokinetics. *Endoscopy* 2005; **37**: 1040-1045 [PMID: 16189787 DOI: 10.1055/s-2005-870327]

13 **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 [PMID: 11174299 DOI: 10.1067/mge.2001.112181]

14 **Løtveit T**, Skar V, Osnes M. Juxtapapillary duodenal diverticula. *Endoscopy* 1988; **20** Suppl 1: 175-178 [PMID: 3139398 DOI: 10.1055/s-2007-1018171]

15 **Baskin RH**, Mayo CW. Jejunal diverticulosis; a clinical study of 87 cases. *Surg Clin North Am* 1952; 1185-1196 [PMID: 14950695]

16 **Rosedale RS**, Lawrence HR. Jejunal diverticulosis. *Am J Surg* 1936; **34**: 369-373 [DOI: 10.1016/S0002-9610(36)90820-6]

17 **Hussain SA**, Esposito SP, Rubin M. Identification of small bowel diverticula with double-balloon enteroscopy following non-diagnostic capsule endoscopy. *Dig Dis Sci* 2009; **54**: 2296-2297 [PMID: 19051015 DOI: 10.1007/s10620-008-0607-1]

18 **Fukumoto A**, Tanaka S, Shishido T, Takemura Y, Oka S, Chayama K. Comparison of detectability of small-bowel lesions between capsule endoscopy and double-balloon endoscopy for patients with suspected small-bowel disease. *Gastrointest Endosc* 2009; **69**: 857-865 [PMID: 19136103 DOI: 10.1016/j.gie.2008.06.007]

19 **Marmo R**, Rotondano G, Casetti T, Manes G, Chilovi F, Sprujevnik T, Bianco MA, Brancaccio ML, Imbesi V, Benvenuti S, Pennazio M. Degree of concordance between double-balloon enteroscopy and capsule endoscopy in obscure gas-

trointestinal bleeding: a multicenter study. *Endoscopy* 2009; **41**: 587-592 [PMID: 19588285 DOI: 10.1055/s-0029-1214896]

20 **Arakawa D**, Ohmiya N, Nakamura M, Honda W, Shirai O, Itoh A, Hirooka Y, Niwa Y, Maeda O, Ando T, Goto H. Outcome after enteroscopy for patients with obscure GI bleeding: diagnostic comparison between double-balloon endoscopy and videocapsule endoscopy. *Gastrointest Endosc* 2009; **69**: 866-874 [PMID: 19136098 DOI: 10.1016/j.gie.2008.06.008]

21 **Zheng Y**, Hawkins L, Wolff J, Goloubeva O, Goldberg E. Detection of lesions during capsule endoscopy: physician performance is disappointing. *Am J Gastroenterol* 2012; **107**: 554-560 [PMID: 22233695 DOI: 10.1038/ajg.2011.461]

22 **Mergener K**, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy* 2007; **39**: 895-909 [PMID: 17968807 DOI: 10.1055/s-2007-966930]

P- Reviewers Racz I, Swaminath A **S- Editor** Wen LL
L- Editor A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.160

World J Gastrointest Endosc 2013 April 16; 5(4): 160-164
ISSN 1948-5190 (online)

BRIEF ARTICLE

Endoscopic retrograde cholangiopancreatography under moderate sedation and factors predicting need for anesthesiologist directed sedation: A county hospital experience

Saurabh Chawla, Ariel Katz, Bashar M Attar, Benjamin Go

Saurabh Chawla, Bashar M Attar, Benjamin Go, Division of Gastroenterology, Department of Medicine, Cook County-John H Stroger Jr Hospital, Chicago, IL 60612, United States
Ariel Katz, Department of Medicine, Cook County-John H Stroger Jr Hospital, Chicago, IL 60612, United States
Bashar M Attar, Department of Medicine, Rush Medical College, Chicago, IL 60612, United States
Author contributions: Chawla S contributed to study design, literature search, data collection, data analysis and manuscript writing; Katz A contributed to study design, data analysis and manuscript writing; Attar BM contributed to study design and manuscript writing; Go B contributed to data collection and manuscript writing.
Correspondence to: Saurabh Chawla, MD, Division of Gastroenterology, Department of Medicine, Cook County-John H Stroger Jr Hospital, Room No. 1435, 14th Floor, 1900 W Polk Street, Chicago, IL 60612, United States. schawla2@gmail.com
Telephone: +1-312-8647955 Fax: +1-312-8647955
Received: July 30, 2012 Revised: December 22, 2012
Accepted: January 5, 2013
Published online: April 16, 2013

Abstract

AIM: To evaluate variables associated with failure of gastroenterologist directed moderate sedation (GDS) during endoscopic retrograde cholangiopancreatography (ERCP) and derive a predictive model for use of anesthesiologist directed sedation (ADS) in selected patients.

METHODS: With institutional review board approval, we retrospectively analyzed consecutive records of all patients who underwent ERCPs between July 1, 2009 to October 1, 2011 to identify patient related and procedure related factors which could predict failure of GDS. For patient related factors, we abstracted and analyzed data regarding the age, gender, ethnicity, alcohol and illicit drug use habits. For procedure related factors, we abstracted data regarding initial or repeat procedures, indication for performing ERCP, the interventions performed during ERCP, and the grade d difficulty of cannulation as defined in the American Society for Gastrointestinal Endoscopy guidelines. Our outcome of interest was procedural success. If the procedure was not successful, the reasons for failure of procedures were recorded along with immediate post procedure complications. Multivariate analysis was then performed to define factors associated with failure of GDS and a model constructed to predict requirement of ADS.

RESULTS: Fourteen percent of patients undergoing GDS could not complete the procedure due to intolerance and 2% due to cardiovascular complications. Substance abuse, male gender, black race and alcohol use were significant predictors of failure of GDS on univariate analysis and substance abuse and higher grade of procedure remained significant on multivariate analysis. Using our predictive model where the presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3, only 12% patients with a score of 1 would require ADS due to failure of GDS, compared to 50% with a score of 3 or higher.

CONCLUSION: We conclude that ERCP under GDS is safe and effective for low grade procedures, and ADS should be judiciously reserved for procedures which have a higher risk of failure with moderate sedation.

Key words: Cholangiopancreatography; Endoscopic retrograde/methods; Conscious sedation/utilization; Deep sedation/utilization; Adult; Endoscopy

Chawla S, Katz A, Attar BM, Go B. Endoscopic retrograde cholangiopancreatography under moderate sedation and factors predicting need for anesthesiologist directed sedation: A county hospital experience. *World J Gastrointest Endosc* 2013; 5(4): 160-164 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/160.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.160

INTRODUCTION

Endoscopic procedures have routinely been performed under moderate sedation administered by the gastroenterologist in the United States[1]. In recent years there has been an increasing trend towards using deep sedation or general anesthesia provided by a trained anesthesia professional. Given the high volume of endoscopic procedures and the high volume performed under anesthesia guidance, the spending on such procedures is estimated to increase into the billions of dollars over the next few years[2]. Endoscopic retrograde cholangiopancreatography (ERCP) is considered an advanced endoscopic procedure which has evolved from a diagnostic procedure to a predominantly therapeutic one of increasing duration and complexity. No guidelines specifically recommend the use of deep sedation or general anesthesia for ERCPs though the American Society of Gastrointestinal Endoscopy (ASGE) suggests considering deep sedation for increasing length or complexity of procedure[1]. Over the years, the spectrum of interventions performed during ERCPs have also increased tremendously, requiring various societies to grade the ERCP procedure into different grade s of complexity (Grade 1-3 by ASGE)[3]. The more challenging and higher grade of ERCPs are now performed at tertiary centers by dedicated advanced endoscopists, while lower grade interventions are routinely performed in various community hospitals and practices.

Increasingly, high volume centers are now routinely performing ERCPs with anesthesiologist directed sedation (ADS) while moderate to low volume centers usually perform ERCPs under gastroenterologist directed moderate sedation (GDS). Anesthesia support is usually sought if prior attempts with GDS have failed.

In this era of increasing health care costs and resource limitations, it is important to establish the role of ADS in ERCP.

The objective of our study was to evaluate variables associated with failure of moderate sedation administered by gastroenterologists (GDS) during ERCP and derive a predictive model for use of ADS in selected patients.

MATERIALS AND METHODS

The study was approved by the local institutional review board of our hospital. We retrospectively analyzed consecutive records of all patients who underwent ERCPs between July 1, 2009 to October 1, 2011 to identify patient related and procedure related factors which could predict failure of GDS. The type of sedation use was documented as GDS which is administered with an opioid (meperidine or fentanyl) and a benzodiazepine (midazolam); or ADS which was administered as monitored anesthesia care with propofol or general anesthesia requiring intubation. If the ADS was administered after failure of GDS, it was abstracted as secondary ADS and if it was administered because the patient did not meet our institution's criteria for administration of GDS it was abstracted as elective or primary ADS. The exclusion criteria for administering GDS in our institution include patients who are American Society of Anesthesiologists (ASA) Grade 3 or more, history of anesthesia or sedation complication/difficulty, history of difficulty with tracheal intubation, compromised airway, morbid obesity, hemodynamic instability and pregnant patients. For patient related factors, we abstracted and analyzed data regarding the age, gender, ethnicity, alcohol and illicit drug use habits. For procedure related factors, we abstracted data regarding initial or repeat procedures, indication for performing ERCP, the interventions performed during ERCP, and the one word-graded difficulty of procedure as defined in the ASGE guidelines Table 1[3].

Table 1 Endoscopic retrograde cholangiopancreatography-degree of difficulty

Grade	Diagnostic	Therapeutic
Grade 1: standard	Deep cannulation, diagnostic sampling	Biliary sphincterotomy, stones < 10 mm, stents for leaks and low tumors.
Grade 2: advanced	Billroth II diagnostics, minor papilla cannulation	Stones > 10 mm, hilar tumor stent placement, benign biliary strictures
Grade 3: tertiary	Manometry, Whipple, Roux en Y, intraductal endoscopy	Billroth II therapeutics, intrahepatic stones, pancreatic therapies

The date was quoted by the reference of 3.

Outcome measures

Our outcome of interest was procedural success. A procedure was deemed successful if deep cannulation had been obtained and the objective of the procedure accomplished. If the procedure was not successful, the reasons for failure of procedures were recorded along with immediate post procedure complications. In order to limit selection bias in patients who elected for primary ADS, we compared the cannulation rates of patients receiving primary ADS to the rest of the patients.

Statistical analysis

The results were expressed as mean plus or minus standard deviation and range. Univariate analysis was performed using logistic regression. To evaluate the association between related factors and intolerance to sedation, multivariable models were constructed that included terms to adjust for age, race, gender, alcohol and substance use and included in the final model if they

Table 2 Patient demographics

Demographic	*n* (%)
Gender	
Males	234 (48)
Females	252 (52)
Race	
Hispanic	189 (39)
Non hispanic black	179 (37)
White	91 (19)
Asian	20 (4)
Unspecified	7 (1.5)
Alcohol use	225 (46)
Other illicit substance use	79 (16)

significantly contributed to the outcome variable ($P < 0.05$). From these multivariable models, odds ratios were estimated using the logistic regression. All data was analyzed using STATA version 10.1 (College Station, TX).

RESULTS

Five hundred ninety-one ERCP procedures done in 392 patients were reviewed. One hundred and five of 591 procedures (18%) were performed electively with primary ADS and were excluded. Four hundred eighty-six procedures were included for our analysis. One hundred thirty-nine patients had more than 1 procedure during the study period. Patient demographics are presented in Table 2. Substance abuse was documented in 14% patients (24% of men, 4% of women).The mean dose of medications administered were 5.9 milligrams of midazolam, and 115 micrograms of fentanyl or 100 milligrams of meperidine. Most common indication for performing ERCP was choledocholithiasis (40%) followed by strictures (26%). The majority of procedures were Grade 1, with one fifth of the procedures Grade 2 or 3. The cannulation rates were similar in the patients with primary ADS (91%) to the rest of the patients (92%). Reasons for failure with GDS are presented in Table 3.

In our univariate analysis, substance abuse, male gender, black race and alcohol use were significant predictors of failure of GDS. However, after adjusting for substance abuse, these variables were no longer significant predictors. Hispanic race was a significant predictor for success of GDS after adjusting for substance abuse (Table 4) although most of the procedures were grade 1 procedures. ERCPs for strictures and pancreatic interventions were the most likely procedures to convert to ADS (Table 5). On multivariate analysis, substance abuse and higher grade of intervention remained the most significant predictors of need for monitored/general anesthesia (Table 6). A predictive model for requirement of monitored anesthesia for ERCP was derived. Presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the procedure. Using this model, 12% of procedures with a score of 1, 25% with score of 2 and 50% with score of 3 or higher required monitored anesthesia.

Table 3 Causes of endoscopic retrograde cholangiopancreatography failure with gastroenterologist directed sedation *n* (%)

Cause	
Total number of patients undergoing GDS	486
Patient intolerance	68 (14)
Cardiopulmonary complications	10 (2)
Hypertension	6 (1.2)
Hypoxia, hypotension, bradycardia or tachycardia	4 (0.8)
Failure to cannulate	40 (8)
Food/contrast in lumen	8 (1.6)
Roux en Y anatomy	2 (0.4)
Esophageal bleeding on entry	1 (0.2)

GDS: Gastroenterologist directed sedation.

DISCUSSION

Based on our analysis, most patients at moderate volume ERCP centers do not require anesthesia service use for ERCPs. Our results indicate that less than 20% of patients failed moderate sedation provided as GDS. On multivariate analysis, the most important predictors of failure of gastroenterologist directed moderate sedation included substance abuse and the grade of the procedure. Using our predictive model where the presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the procedure, less than one in eight procedures with a score of 1 would require monitored anesthesia compared to half of patients with a score of 3 or higher.

To our knowledge, this is the first study that has attempted to define factors predicting the failure of GDS for ERCPs. Our study population is unique in that most of our low risk patients undergo GDS for ERCPs. Since anesthesia resources are limited, only those patients who meet strict criteria for monitored anesthesia based on their ASA scores or other co-morbidities are scheduled for elective anesthesia service use.

Most of the previously published studies evaluating the use of anesthesia in ERCP conclude that ERCPs with gastroenterologist directed sedation have similar cannulation and complication rates to those with ADS[4-6]. However none of these studies was designed to specifically study the factors predicting the failure of GDS.

In some studies, ADS has been associated with higher physician satisfaction and slightly higher completion rates[7,8]. These studies have been uncontrolled or limited by lack of blinding. Furthermore, routine anesthesia service use for ERCP has other limitations. Aside from increasing the cost of the procedure, it may also increase the peri-procedure time. Additionally, it may make the procedure more difficult to schedule if anesthesia support outside the operating rooms is not readily available.

Our study may have several limitations. First, as a retrospective study, we cannot be certain that are results are confirmed from chance alone (verification bias). Care was taken to a priori assess only the variable thought to be directly related to success of GDS. Further prospective studies are needed to determine if these two variables

Table 4 Patient variables predicting failure with gastroenterologist directed sedation for endoscopic retrograde cholangiopancreatog raphies

Patient variables	MS	MS failure	*P* value	Patient variables[1]	MS	MS failure	*P* value
Substance abuse	31	13	0.003				
Male	131	25	0.01	Male[1]	104	14	0.09
Female	157	12		Female[1]	153	10	
Race				Race[1]			
AA	79	22	0.001	AA	61	10	0.06
White	42	6	0.8	White	38	6	0.2
Hispanic	142	8	0.001	Hispanic	134	7	0.04
Asian	15	1	0.5	Asian	15	1	0.7
> 65 yr	37	2	0.15	> 65 yr[1]	33	1	0.16
⩽ 65 yr	251	35		⩽ 65 yr[1]	224	23	
Alcohol use	113	21	0.04	Alcohol use[1]	87	11	0.24
No alcohol use	175	16		No alcohol use[1]	170	13	
Bilirubin-elevated	252	44	0.03	Bilirubin-elevated[1]	222	34	0.45
Bilirubin-normal	146	43		Bilirubin-normal[1]	126	24	

[1]Adjusted for substance abuse. MS: Moderate sedation.

Table 5 Odds ratios for failure with gastroenterologist directed sedation by indication of the procedure

Indication	*n* (%)	OR (95%CI)	Adjusted OR (95%CI)[1]
Gallstones/cholangitis	231 (38)	0.6 (0.4, 1.0)	0.7 (0.4, 1.3)
All strictures	125 (20)	1.5 (0.9, 2.4)	1.6 (0.9, 2.9)
Benign strictures	53 (9)	2.2 (1.2, 4.2)	2.7 (1.2, 5.7)
Suspected malignancy	72 (12)	0.9 (0.5, 1.8)	0.9 (0.4, 2.0)
Abn LFTs	36 (6)	0.6 (0.2, 1.6)	0.5 (0.12, 2.3)
Pancreatic	11 (2)	2.7 (0.8, 9.4)	3.7 (0.9, 16)
Other	7 (1)	1.8 (0.4, 9.7)	2.5 (0.5, 12.9)
Post cholecystectomy stone/leak	24 (4)	0.4 (0.1, 1.7)	0.3 (0.0, 2.0)
Exchange/incomplete	51 (8)	2.1 (1.1, 4.0)	0.9 (0.3, 2.5)
	485		

[1]Adjusted to substance abuse. OR: Odds ratio.

Table 6 Multivariate analysis of predictors of failure with gastroenterologist directed sedation

Variable	β coefficient	*P* value	OR (95%CI)
Grade of procedure (1-3)[1]	0.75	0.002	2.1 (1.3, 3.4)
Substance abuse[1]	1.03	0.001	2.8 (1.5, 5)
Indication			
Strictures	0.13	0.687	1.1 (0.6, 2.1)
Gallstone	-0.18	0.563	0.8 (0.5, 1.5)
Alcohol use	0.33	0.267	1.4 (0.8, 2.5)
Female gender	-0.29	0.33	0.7 (0.4, 1.3)

[1]Significant variables in the multivariate model.

(substance use and procedure grade) can determine the likelihood of GDS success. Second, while the procedures were deemed successful, we did not identify delayed complications which may have occurred after the patient left the endoscopy unit. Third, our ERCPs are initially attempted by gastroenterology trainees and only later taken over by the supervising physician. This may increase the procedure time and lead to patient intolerance especially in patients under gastroenterologist directed moderate sedation. High dose of benzodiazepines and opioids may convert moderate sedation to deep sedation, which has been demonstrated in previous studies that advocated the use of capnography during sedation[9]. While we did not use capnography to gauge the respiratory depression, our mean doses of sedating agents used was 6 mg of midazolam and 115 mg of fentanyl suggesting a reasonably conservative approach with medication administration.

Recent data suggests an increased utilization of anesthesia services for low risk endoscopic significantly increases the cost of the procedures and may potentially affect the cost effectiveness of procedures like screening colonoscopies[2].

Although, no cost benefit analysis have been done for use of anesthetist administered sedation or anesthesia for ERCPs, our study suggests that most of the ERCPs can be safely performed and completed under gastroenterologist directed sedation.

We conclude that ERCP under GDS is safe and effective for low grade procedures, and anesthesia service use should be judiciously reserved for procedures which have a higher risk of failure with moderate sedation.

COMMENTS

Background

In recent years there has been an increasing trend towards utilizing anesthesiologist directed sedation (ADS) in patients undergoing endoscopic procedures. Factors predicting failure of gastroenterologist directed moderate sedation (GDS) during endoscopic retrograde cholangiopancreatography (ERCP) have not been well studied.

Research frontiers

Evaluate variables associated with failure of GDS during ERCP and derive a predictive model for use of ADS in selected patients.

Innovations and breakthroughs

Gastroenterologist directed sedation is safe and effective for low grade ERCP procedures. Higher grade ERCPs and/or those performed in patients with substance abuse have a higher risk of failure with moderate sedation and therefore anesthesiologist directed deep sedation should be considered for these procedures. A predictive model for requirement of monitored anesthesia for ERCP was derived. Presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the pro-

cedure. Using this model, 12% of procedures with a score of 1, 25% with score of 2 and 50% with score of 3 or higher required monitored anesthesia.

Applications

Based on the analysis, most patients at moderate volume ERCP centers do not require anesthesia service use for ERCPs. The results indicate that less than 20% of patients failed moderate sedation provided as GDS. On multivariate analysis, the most important predictors of failure of gastroenterologist directed moderate sedation included substance abuse and the grade of the procedure. Using the predictive model where the presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the procedure, less than one in eight procedures with a score of 1 would require monitored anesthesia compared to half of patients with a score of 3 or higher.

Terminology

The type of sedation use was documented as GDS which is administered with an opioid (meperidine or fentanyl) and a benzodiazepine (midazolam); or ADS which may be administered as general anesthesia or intravenous anesthesia administered with propofol.

Peer review

With this study, the authors conclude that that ERCP under GDS is safe and effective for low grade procedures, and anesthesia service use should be judiciously reserved for procedures which have a higher risk of failure with moderate sedation.

REFERENCES

1 **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 [PMID: 18984096 DOI: 10.1016/j.gie.2008.09.029]

2 **Liu H**, Waxman DA, Main R, Mattke S. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. *JAMA* 2012; **307**: 1178-1184 [PMID: 22436958 DOI: 10.1001/jama.2012.270]

3 **Baron TH**, Petersen BT, Mergener K, Chak A, Cohen J, Deal SE, Hoffinan B, Jacobson BC, Petrini JL, Safdi MA, Faigel DO, Pike IM. Quality indicators for endoscopic retrograde cholangiopancreatography. *Am J Gastroenterol* 2006; **101**: 892-897 [PMID: 16635233 DOI: 10.1111/j.1572-0241.2006.00675.x]

4 **Mehta PP**, Vargo JJ, Dumot JA, Parsi MA, Lopez R, Zuccaro G. Does anesthesiologist-directed sedation for ERCP improve deep cannulation and complication rates? *Dig Dis Sci* 2011; **56**: 2185-2190 [PMID: 21274625 DOI: 10.1007/s10620-011-1568-3]

5 **Salminen P**, Grönroos JM. Anesthesiologist assistance in endoscopic retrograde cholangiopancreatography procedures in the elderly: is it worthwhile? *J Laparoendosc Adv Surg Tech A* 2011; **21**: 517-519 [PMID: 21524233 DOI: 10.1089/lap.2010.0527]

6 **Raymondos K**, Panning B, Bachem I, Manns MP, Piepenbrock S, Meier PN. Evaluation of endoscopic retrograde cholangiopancreatography under conscious sedation and general anesthesia. *Endoscopy* 2002; **34**: 721-726 [PMID: 12195330 DOI: 10.1055/s-2002-33567]

7 **Berzin TM**, Sanaka S, Barnett SR, Sundar E, Sepe PS, Jakubowski M, Pleskow DK, Chuttani R, Sawhney MS. A prospective assessment of sedation-related adverse events and patient and endoscopist satisfaction in ERCP with anesthesiologist-administered sedation. *Gastrointest Endosc* 2011; **73**: 710-717 [PMID: 21316669 DOI: 10.1016/j.gie.2010.12.011]

8 **Lordan JT**, Woods J, Keeling P, Paterson IM. A retrospective analysis of benzodiazepine sedation vs. propofol anaesthesia in 252 patients undergoing endoscopic retrograde cholangiopancreatography. *HPB (Oxford)* 2011; **13**: 174-177 [PMID: 21309934 DOI: 10.1111/j.1477-2574.2010.00266.x]

9 **Qadeer MA**, Vargo JJ, Dumot JA, Lopez R, Trolli PA, Stevens T, Parsi MA, Sanaka MR, Zuccaro G. Capnographic monitoring of respiratory activity improves safety of sedation for endoscopic cholangiopancreatography and ultrasonography. *Gastroenterology* 2009; **136**: 1568-1576; quiz 1568-1576 [PMID: 19422079]

P- Reviewer Wehrmann T **S- Editor** Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.165

World J Gastrointest Endosc 2013 April 16; 5(4): 165-168
ISSN 1948-5190 (online)

BRIEF ARTICLE

Polyethylene glycol 3350 based colon cleaning protocol: 2 d *vs* 4 d head to head comparison

Rotem Elitsur, Lisa Butcher, Lund Vicki, Yoram Elitsur

Rotem Elitsur, Lisa Butcher, Lund Vicki, Yoram Elitsur, Department of Pediatrics, Section of Gastroenterology, Marshall University School of Medicine, Huntington, WV 25701, United States
Author contributions: Elitsur R, Butcher L, Vicki L and Elitsur Y contributed equally to the paper.
Correspondence to: Yoram Elitsur, MD, Professor in Pediatrics, Department of Pediatrics, Section of Gastroenterology, Marshall University School of Medicine, 1600 Medical Center Drive, Huntington, WV 25701, United States. elitsur@marshall.edu
Telephone: +1-304-6911300 Fax: +1-304-6911375
Received: October 9, 2012 Revised: October 26, 2012
Accepted: January 5, 2013
Published online: April 16, 2013

Abstract

AIM: To compare between 2 and 4 d colon cleansing protocols.

METHODS: Children who were scheduled for colonoscopy procedure (2010-2012) for various medical reasons, were recruited from the pediatric gastroenterology clinic at Marshall University School of Medicine, Huntington, WV. Exclusion criteria were patients who were allergic to the medication used in the protocols [polyethylene glycol (PEG) 3350, Bisacodyl], or children with metabolic or renal diseases. Two PEG 3350 protocols for 4 d (A) and 2 d (B) were prescribed as previously described. A questionnaire describing the volume of PEG consumed, clinical data, and side effects were recorded. Colon preparation was graded by two observers according to previously described method. Main outcome measurements: Rate of adequate colon preparation.

RESULTS: A total of 78 patients were considered for final calculation (group A: 40, group B: 38). Age and stool consistency at the last day was comparable in both groups, but the number of stools/day was significantly higher in group B (P = 0.001). Adequate colon preparation was reached in 57.5% (A) and 73.6% (B), respectively (P = 0.206). Side effects were minimal and comparable in both groups. There was no difference in children's age, stool characteristics, or side effects between the children with adequate or inadequate colon preparation. Correlation and agreement between observers was excellent (Pearson correlation = 0.972, kappa = 1.0).

CONCLUSION: No difference between protocols was observed, but the 2 d protocol was superior for its shorter time. Direct comparison between different colon cleansing protocols is crucial in order to establish the "gold standard" protocol for children.

Key words: Colonoscopy; Polyethylene glycol 3350; Cleansing protocol; Children

Elitsur R, Butcher L, Vicki L, Elitsur Y. Polyethylene glycol 3350 based colon cleaning protocol: 2 d *vs* 4 d head to head comparison. *World J Gastrointest Endosc* 2013; 5(4): 165-168 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/165.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.165

INTRODUCTION

Colon cleansing protocols have been one of the limiting factors in preparing children for diagnostic colonoscopy procedures needed for various medical reasons. Due to bad palatability and the quantity needed, the commonly used liquids in adult patients are not accepted by children and compliance is unacceptable[1-3]. In the last decade, polyethylene glycol (PEG) 3350 has been introduced to children and was found to be palatable and acceptable by children for the treatment of various medical conditions, mainly constipation. Several studies have shown that children will accept this PEG based solution and the compli-

ance rate was very good even for long term therapy[4-7]. In the past, we showed that PEG 3350 is an excellent solution for colon cleansing protocol in children reaching adequate colon preparation in up to 92% of the children examined[8]. Moreover, we reported that following the number of defecation and stool consistency in the last days of preparation may be used as indicators for the colon condition, and would reduce the number of failed procedures due to an unprepared colon. In recent years a similar PEG 3350 based protocol was reported that suggested similar results with a shorter preparation[9]. In that protocol, a higher dose of PEG 3350 with daily dose of 5 mg Bisacodyl resulted in an excellent colon condition for colonoscopy reaching up to 92%[9].

An unprepared colon in adults is considered one of the limiting factors for achieving an adequate rate of polyp detection during colonoscopy procedures[10,11]. In children, the rate of the unprepared colon during colonoscopy is high and was reported between 5%-30%[12-15]. The different colon cleansing protocols used by different centers was never standardized and the "optimal" protocol has never been established. We believe that a head to head comparison between protocols in children is needed in order to standardize clinical practice and to find the best available protocol. Such protocol would limit the rate of the unprepared colon and established the gold standard protocol for colonoscopy procedures in children.

In the present study, in a head to head analysis, we prospectively compare two different PEG 3350 based protocols in order to establish the better cleansing protocol in children.

MATERIALS AND METHODS

Children who were scheduled for colonoscopy procedure (2010-2012) for various medical reasons, were recruited from the pediatric gastroenterology clinic at Marshall University School of Medicine, Huntington, WV. Exclusion criteria were patients who were allergic to the medication used in the protocols (PEG 3350, Bisacodyl), or children with metabolic or renal diseases. One of the two different colon protocols was prescribed to the participating patients. A computer generated random list assigned the children to each protocol. The parents/caregivers (or child when appropriate) were asked to complete a clinical questionnaire during the colon preparation as previously described[8]. Briefly, the questionnaire included the amount of PEG 3350 consumed per day, number of stools per day, consistency of stool (scale: 1-5), and various side effects (abdominal pain, vomiting). Informed consent was obtained from all participants and the study was approved by the IRB Committee at Marshall University School of Medicine, Huntington, WV.

Colon cleansing protocols

Two PEG 3350 protocols for 4 and 2 d were prescribed as previously described[8,9]. The 4 dy protocol (protocol A) included PEG 3350 at 1.5 g/kg per day (up to a limit of 100 g/d) for 4 d. Patients were allowed to eat regular food until the day before procedure and clears only at the last day of protocol. The 2 d protocol (protocol B) included PEG 3350 at 2 g/kg per day (up to a limit of 136 g/d) plus 5 mg/d Bisacodyl for 2 d. Patients were allowed to eat regular food on day 1 and clears on day 2. No adjunct medication or enema was allowed in any of the protocols. The parents/caregivers were required to complete a simple questionnaire as previously described[8]. The questionnaires were returned to the physicians on the day of procedure and reviewed with the parents to ensure compliance and accuracy. Patients who did not follow the protocol for various reasons including: inadequate PEG 3350 dose, missed clinical data on the questionnaire, or other protocol violations, were excluded from the final calculation.

Colon preparation assessment

Colonoscopy procedure was performed under propofol sedation given by certified anesthesiologists. The colon was assessed according to previous methodology as previously described[8]. Briefly, the colon preparation was graded according to 5 different levels (Grade 1 to 5) as follows: G1: unacceptable (large amount of solid stool covering the mucosa); G2: poor preparation (enough stool that much of intra-procedural cleaning was required); G3: fair preparation (some liquid stool, easily removed); G4: good preparation (successful visualization of the colon mucosa); G5: Excellent preparation (Crystal clear colonic mucosa). For the current study, colon preparation at grade $\geqslant$ 4 was considered as adequate colon preparation. The investigators were allowed to incorporate 0.5 grade per their discretion. Grading of colon preparation was performed within 5-10 min of procedure completion. To reduce bias, the grading was performed simultaneously and separately by the endoscopist (Elitsur Y), and the assisting endoscopy nurse who participate in the procedure (Butcher L). The grading was documented on a separate page where both persons were blinded to the documentation of the other. Once documentation was done, both grades became final and no change of grading was allowed. A correlation between physician's grade and the nurse's grade was calculated.

Statistical analysis

Comparison between the two protocols was performed using two-tailed χ^2 analysis, and nonparametric analysis (Wilcoxon Signed Rank Test) using the IBM-SSPS statistics 19 program. Correlation analysis was performed using Pearson correlation. Significant analysis was set at P value < 0.05.

RESULTS

A total of 93 children enrolled (period 2010-2012), of whom 48 were assigned to protocol A and 45 to protocol B. A total of 15 patients were not included in the study due to a protocol violation, 8 in protocol A and 7 in pro-

Table 1 Clinical data

Protocol	4 d	2 d	*P* value[1]
No patients	40	38	
Age (yr, mean ± SD)	10.10 ± 4.6	9.91 ± 4.7	0.792
Male/female ration	1.0:1.0	0.8:1.0	0.811[4]
No stools/d (mean ± SD)[2]	5.15 ± 2.6	7.88 ± 4.1	0.001
Consistency (mean ± SD)[2]	5.65 ± 0.8	5.49 ± 0.9	0.904
Colon grade (mean ± SD)	3.50 ± 1.1	4.01 ± 1.0	0.140
Colon grade (≥ 4)[3]	23 (57.5%)	28 (73.6%)	0.206[4]

[1]*P* value: wilcoxon signed rank test; [2]At the last day of protocol; [3]Grade ≥ 4 considered adequate preparation; [4]*P* value: χ^2 analysis.

tocol B. The major clinical diagnoses were gastrointestinal bleeding of unknown origin, and follow up colonoscopy in inflammatory bowel disease patients. Overall, a total of 78 patients were considered for final calculation, 40 in protocol A and 38 in protocol B. In both protocols, the number of stools per day increased from the first day to the last day of protocol (data not shown). The age, male/female ratio, and stool consistency at the last day in either protocol was comparable for both groups, but the number of stools per day was significantly higher in group B compared to group A (Table 1). Adequate colon preparation (defined as grade ≥ 4) was reach in 57.5% and 73.6% of children from protocol A and protocol B, respectively (P = 0.206, Table 1). Side effects were minimal and comparable in both groups (abdominal pain: 26%-32%, vomiting: 2%). None of the children discontinued his protocol due to side effects. The cecum was successfully reached in 76 (98%) children, and when attempted, the terminal ileum was visualized in 68 (87%) children (32 children in protocol A and 36 children in protocol B). There was no difference in children's age, stool frequency, stool consistency, or side effect between the children who had adequate colon preparation (grade > 4.0) and those with inadequate colons (grade < 4.0) (data not shown). The correlation and agreement between colonoscopy grading between physician and the endoscopy nurse for both groups was excellent (P = 0.972, kappa = 1.0).

DISCUSSION

Preparing the colon for colonoscopy procedure for children has been a difficult task for many years, and various colon cleansing protocols have been suggested and used. In fact, there is no one pediatric protocol that has been accepted as the "gold standard" and different medical centers are using different protocols. In some centers, the adult protocol is used for teenage children and young adults. After we confirmed the excellent results with a 4 d PEG 3350 protocol, it became the preferred colon cleansing protocol in our clinic[8]. In 2011, Phatak *et al*[9] presented a similar PEG 3350 based colon preparation protocol that was shorter. In the present study, we present for the first time a true head to head comparison between 2 different colon cleansing protocols in order to establish the better protocol for children. Results showed that both protocols were comparable with regard to the rate of adequate colon preparation, stool characteristics, side effects, or patients' compliance. The number of stools per day at the last day of the shorter protocol (protocol B) was significantly higher compared to protocol A (P = 0.001), but no difference in the colon grading was noted between the groups. In fact, the adequate colon preparation, as defined in our study (grade ≥ 4), was higher in protocol B but did not reach a statistical significance (57.5% *vs* 73.6%, P = 0.206). We believe that the addition of a stimulant laxative (Bisacodyl), and the higher dose of PEG 3350 prescribed in protocol B (1.5 g/kg *vs* 2.0 g/kg) were the reasons for those results. We suggest that the 2 d protocol is at least as good as the 4 d protocols while having the advantage of being a shorter protocol.

We acknowledge the few differences existed in our study. (1) When compared with previous reports, our study showed a lower rate of adequate colons in both groups (57.5% and 73.6% for protocols A and B, respectively). In the present study we followed a stricter definition for adequate colon preparation (grade ≥ 4.0) that may reduce the rate of success in our population. When the definition of adequate preparation dropped to grade ≥ 3.5, our success rate increased to 63% and 79%, respectively (P = 0.17). Similarly, when a higher degree of preparation (excellent preparation) was considered in Phatak's study[9], a comparable rate of adequate colon was achieved between both studies; (2) Compared with previous study[9], a second observer (gastrointestinal nurse), blinded to the grading of the first observer, was utilized to grade the colons. The agreement between both observers was excellent (Spearman correlation = 0.972, kappa = 1.0); and (3) The number of participants in our study was lower than in previous studies, a fact that could explained the lack of statistical significance noted between the protocols[8,9]. We suggest that those methodological differences may explain the lower rate of adequate colon preparation reported in our study.

In conclusion, we prospectively compared two PEG 3350 based cleansing protocol for children who were scheduled for diagnostic colonoscopy. Our results showed that both protocol were acceptable to children, but the 2 d protocol is superior to the 4 d protocol at least for its shorter course. Further comparison between different cleansing protocols in children is needed in order to establish the best protocol for colonoscopy procedure in children.

COMMENTS

Background

Colon cleansing protocols have been the major obstacle in successful colonoscopy in children. Of the polyethylene glycol (PEG) 3350 protocols published, none has been recommended as the best protocol.

Research frontiers

In the last decade, PEG 3350 has been introduced to children and was found to be palatable and acceptable by children for the treatment of various medical

conditions, mainly constipation. Several studies have shown that children will accept this PEG based solution and the compliance rate was very good even for long term therapy.

Innovations and breakthroughs

In recent years a similar PEG 3350 based protocol was reported that suggested similar results with a shorter preparation. In that protocol, a higher dose of PEG 3350 with daily dose of 5 mg Bisacodyl resulted in an excellent colon condition for colonoscopy reaching up to 92%.

Applications

In the present study, in a head to head analysis, the authors prospectively compare two different PEG 3350 based protocols in order to establish the better cleansing protocol in children.

Peer review

The number of stools per day at the last day in each protocol, and the mean colon grading was significantly higher in the shorter protocol (protocol B). This is a randomized controlled trial and an interesting and important paper for colonoscopy procedures in children.

REFERENCES

1 **Vanner SJ**, MacDonald PH, Paterson WG, Prentice RS, Da Costa LR, Beck IT. A randomized prospective trial comparing oral sodium phosphate with standard polyethylene glycol-based lavage solution (Golytely) in the preparation of patients for colonoscopy. *Am J Gastroenterol* 1990; **85**: 422-427 [PMID: 2183591]

2 **Hookey LC**, Depew WT, Vanner SJ. A prospective randomized trial comparing low-dose oral sodium phosphate plus stimulant laxatives with large volume polyethylene glycol solution for colon cleansing. *Am J Gastroenterol* 2004; **99**: 2217-2222 [PMID: 15555005 DOI: 10.1111/j.1572-0241.2004.40482.x]

3 **Pinfield A**, Stringer MD. Randomised trial of two pharmacological methods of bowel preparation for day case colonoscopy. *Arch Dis Child* 1999; **80**: 181-183 [PMID: 10325738 DOI: 10.1136/adc.80.2.181]

4 **Youssef NN**, Peters JM, Henderson W, Shultz-Peters S, Lockhart DK, Di Lorenzo C. Dose response of PEG 3350 for the treatment of childhood fecal impaction. *J Pediatr* 2002; **141**: 410-414 [PMID: 12219064 DOI: 10.1067/mpd.2002.126603]

5 **Pashankar DS**, Bishop WP. Efficacy and optimal dose of daily polyethylene glycol 3350 for treatment of constipation and encopresis in children. *J Pediatr* 2001; **139**: 428-432 [PMID: 11562624 DOI: 10.1067/mpd.2001.117002]

6 **Loening-Baucke V**, Krishna R, Pashankar DS. Polyethylene glycol 3350 without electrolytes for the treatment of functional constipation in infants and toddlers. *J Pediatr Gastroenterol Nutr* 2004; **39**: 536-539 [PMID: 15572895 DOI: 10.1097/00005176-200411000-00016]

7 **Pashankar DS**, Uc A, Bishop WP. Polyethylene glycol 3350 without electrolytes: a new safe, effective, and palatable bowel preparation for colonoscopy in children. *J Pediatr* 2004; **144**: 358-362 [PMID: 15001943 DOI: 10.1016/j.jpeds.2003.11.033]

8 **Safder S**, Demintieva Y, Rewalt M, Elitsur Y. Stool consistency and stool frequency are excellent clinical markers for adequate colon preparation after polyethylene glycol 3350 cleansing protocol: a prospective clinical study in children. *Gastrointest Endosc* 2008; **68**: 1131-1135 [PMID: 18950761 DOI: 10.1016/j.gie.2008.04.026]

9 **Phatak UP**, Johnson S, Husain SZ, Pashankar DS. Two-day bowel preparation with polyethylene glycol 3350 and bisacodyl: a new, safe, and effective regimen for colonoscopy in children. *J Pediatr Gastroenterol Nutr* 2011; **53**: 71-74 [PMID: 21694539 DOI: 10.1097/MPG.0b013e318210807a]

10 **Radaelli F**, Meucci G, Sgroi G, Minoli G. Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. *Am J Gastroenterol* 2008; **103**: 1122-1130 [PMID: 18445096 DOI: 10.1111/j.1572-0241.2007.01778.x]

11 **Ibáñez M**, Parra-Blanco A, Zaballa P, Jiménez A, Fernández-Velázquez R, Fernández-Sordo JO, González-Bernardo O, Rodrigo L. Usefulness of an intensive bowel cleansing strategy for repeat colonoscopy after preparation failure. *Dis Colon Rectum* 2011; **54**: 1578-1584 [PMID: 22067188 DOI: 10.1097/DCR.0b013e31823434c8]

12 **Gremse DA**, Sacks AI, Raines S. Comparison of oral sodium phosphate to polyethylene glycol-based solution for bowel preparation for colonoscopy in children. *J Pediatr Gastroenterol Nutr* 1996; **23**: 586-590 [PMID: 8985850 DOI: 10.1097/00005176-199612000-00013]

13 **Barrish JO**, Gilger MA. Colon cleanout preparations in children and adolescents. *Gastroenterol Nurs* 1993; **16**: 106-109 [PMID: 8286425 DOI: 10.1097/00001610-199312000-00004]

14 **Dahshan A**, Lin CH, Peters J, Thomas R, Tolia V. A randomized, prospective study to evaluate the efficacy and acceptance of three bowel preparations for colonoscopy in children. *Am J Gastroenterol* 1999; **94**: 3497-3501 [PMID: 10606310 DOI: 10.1111/j.1572-0241.1999.01613.x]

15 **da Silva MM**, Briars GL, Patrick MK, Cleghorn GJ, Shepherd RW. Colonoscopy preparation in children: safety, efficacy, and tolerance of high- versus low-volume cleansing methods. *J Pediatr Gastroenterol Nutr* 1997; **24**: 33-37 [PMID: 9093983 DOI: 10.1097/00005176-19970]

P- Reviewer Ikematsu H **S- Editor** Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.169

World J Gastrointest Endosc 2013 April 16; 5(4): 169-173
ISSN 1948-5190 (online)

BRIEF ARTICLE

Malpractice claims for endoscopy

Lyndon V Hernandez, Dominic Klyve, Scott E Regenbogen

Lyndon V Hernandez, Department of Gastroenterology, Aurora Medical Center and GI Associates, LLC, Kenosha, WI 53142, United States
Dominic Klyve, Department of Mathematics, Central Washington University, Ellensburg, WA 98926, United States
Scott E Regenbogen, Division of Colorectal Surgery, University of Michigan Health System, Ann Arbor, MI 48103, United States
Author contributions: Hernandez LV study design; Hernandez LV and Regenbogen SE data analysis; Hernandez LV wrote the manuscript; Regenbogen SE edited manuscript; Klyve D performed statistical analysis.
Correspondence to: Lyndon V Hernandez, MD, MPH, Department of Gastroenterology, Aurora Medical Center and GI Associates, LLC, 10400 75th, Suite 208, Kenosha, WI 53142, United States. lhernan@mcw.edu
Telephone: +1-414-9086624 Fax: +1-414-7611829
Received: October 20, 2012 Revised: December 20, 2012
Accepted: January 23, 2013
Published online: April 16, 2013

Abstract

AIM: To summarize the magnitude and time trends of endoscopy-related claims and to compare total malpractice indemnity according to specialty and procedure.

METHODS: We obtained data from a comprehensive database of closed claims from a trade association of professional liability insurance carriers, representing over 60% of practicing United States physicians. Total payments by procedure and year were calculated, and were adjusted for inflation (using the Consumer Price Index) to 2008 dollars. Time series analysis was performed to assess changes in the total value of claims for each type of procedure over time.

RESULTS: There were 1901 endoscopy-related closed claims against all providers from 1985 to 2008. The specialties include: internal medicine (n = 766), gastroenterology (n = 562), general surgery (n = 231), general and family practice (n = 101), colorectal surgery (n = 87), other specialties (n = 132), and unknown (n = 22). Colonoscopy represented the highest frequencies of closed claims (n = 788) and the highest total indemnities ($54 093 000). In terms of mean claims payment, endoscopic retrograde cholangiopancreatography (ERCP) ranked the highest ($374 794) per claim. Internists had the highest number of total claims (n = 766) and total claim payment ($70 730 101). Only total claim payments for colonoscopy and ERCP seem to have increased over time. Indeed, there was an average increase of 15.5% per year for colonoscopy and 21.9% per year for ERCP after adjusting for inflation.

CONCLUSION: There appear to be differences in malpractice coverage costs among specialties and the type of endoscopic procedure. There is also evidence for secular trend in total claim payments, with colonoscopy and ERCP costs rising yearly even after adjusting for inflation.

Key words: Complications; Endoscopy; Colonoscopy; Endoscopic retrograde cholangiopancreatogram; Medical malpractice

Hernandez LV, Klyve D, Regenbogen SE. Malpractice claims for endoscopy. *World J Gastrointest Endosc* 2013; 5(4): 169-173 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/169.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.169

INTRODUCTION

Endoscopies are being performed at an increasing rate for the last decade[1]. Endoscopic procedures are also becoming more complicated as interventional techniques are used more widely. Despite increasing national awareness of medical errors, and the high costs of associated malpractice, there is a lack of data sources from which to understand the incidence and trends of errors resulting in major injuries during endoscopic procedures.

Traditionally, the main source of information on endoscopy-related errors comes from institutional morbidity and mortality conferences. However, this and other

self-reporting methods are known to underestimate the true incidence of complications[2]. In general and vascular surgery, the National Surgical Quality Improvement Program has become a platform for validated, risk-adjusted outcome comparisons between institutions, however, only a select minority of hospitals have implemented the program, and similar registries have not been as widely accepted in other interventional subspecialties.

Aligned with value-based purchasing by the Centers for Medicare and Medicaid Services, the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy have advocated for measuring endoscopy quality indicators. As preventing errors is linked to quality, endoscopists increasingly are recognizing the importance of understanding and benchmarking endoscopic errors at a national level.

Claims in malpractice litigation offer an opportunity to study major iatrogenic injuries. In a study by Studdert *et al*[3], trained reviewers examined 1500 closed claims of alleged medical injuries from negligence and found that 97% of closed claims involved injury, of which 63% resulted from error. In another study of surgical claims[4], technical errors accounted for about half of the cases. A study by Conklin *et al*[5] focusing on gastroenterologists showed that 25% of claims were due to improper performance of an endoscopic procedure, but further information such as type of endoscopies were not described. In addition, endoscopies in the United States are also performed by non-gastroenterologists, and there have been no studies to our knowledge that have looked into malpractice information in this population.

Our aim is to provide a synopsis of the magnitude and time trends of endoscopy-related claims and to compare total malpractice indemnity according to specialty and procedure.

MATERIALS AND METHODS

We obtained summary-level data from a comprehensive database of closed claims against physicians who are members of the Physicians Insurers Association of America (PIAA), which is a trade association of professional liability companies owned by physicians, hospitals, and other health care providers. PIAA, which has the largest database of malpractice claims in the nation, insures over 300 000 doctors and 1300 hospitals, representing over 60% of United States doctors and underwrites 46% or $5.2 billion of the total medical liability industry premium. The closed claims represented data from all 50 states from January 1985 up to December 2008.

Due to confidentiality agreements with member companies, the PIAA is unable to provide specific geographic information. The de-identified data is therefore not traceable to the provider. PIAA collects data based on information provided by the member liability insurance company which covered the physician. The professional coder from the liability insurance company codes the condition, care rendered, and outcome by complying with PIAA guidelines. Inclusion criteria were all endoscopic procedures (esophagogastroduodenoscopy, EGD; colonoscopy, flexible sigmoidoscopy; rigid proctosigmoidoscopy; endoscopic retrograde cholangiopancreatography, ERCP; and percutaneous endoscopic gastrostomy, PEG) that resulted in closed claims during the study period. There was no identifiable code available for endoscopic ultrasound at the time of the study.

Etiologies of claims were categorized by PIAA coders according to a priori definition of errors. Improper performance is defined as an endoscopic procedure that was done incorrectly. An example is an ERCP with improperly placed stent that led to a fatal complication. Diagnosis error is resulted from failure to diagnose or providing an incorrect diagnosis. Data on total and average payment to plaintiffs for claims were provided according to specialty but not to type of procedure.

A claim is a written demand for compensation for medical injury within the statute of limitations of a jurisdiction. A claim can be closed in one of four possible ways: (1) at the end of a trial by final judgment; (2) at any point before the end of the trial when the case is settled with a payment; (3) when the case is voluntarily dropped by the plaintiff; or (4) if the defendant successfully files a motion to dismiss the case when there is a valid legal basis to do so. Thus, a claim may be closed with or without indemnity payment, which is defined as the sum of money paid in compensation for injury.

Statistical analysis

Total payments by procedure and year were calculated, and were adjusted for inflation (using the consumer price index) to 2008 dollars. We then focused on time series analysis to see how the total value of claims for each type of procedure changed over time. Two models were used: a linear least-squares regression model, which will show the average absolute growth in total claims (in adjusted dollars) per year; and an exponential least-squares regression model, which will derive the average percent growth. The ability of these models to describe the data is captured in the value of R^2. A value of zero means that the model has no explanatory power, while a value of one indicates that the total claim value can be perfectly deduced from the year.

RESULTS

There were 1901 endoscopy-related closed claims against all providers from 1985 to 2008. The specialties include: internal medicine (n = 766), gastroenterology (n = 562), general surgery (n = 231), general and family practice (n = 101), colorectal surgery (n = 87), other specialties (n = 132), and unknown (n = 22). Over 98% resulted in physical injury, which was generally severe (25.8% resulted in deaths and 40.7% resulted in significant or major disability). Close to 70% of all cases were dropped by the plaintiff or dismissed by the court before the trial was concluded. An additional 5% of cases were won by the defendant at trial.

Closed claims against gastroenterologists from 1985

Table 1 Endoscopy claims against gastroenterologists (1985 to 2006) *n* (%)

Etiology of claims	Frequency (*n* = 341)
Improper performance	175 (51.3)
Diagnosis error (failure, incorrect)	59 (17.3)
Meritless (no clear evidence)	35 (10.3)
Failure to supervise or monitor	17 (4.9)
Not indicated/contraindicated	14 (4.1)
Failure to recognize complication	12 (3.5)
Failure to communicate with patient	6 (1.8)
Delay in performance	4 (1.2)
Others	19 (5.6)

to 2006 that involve endoscopies are shown in Table 1. The majority resulted from improper performance of an endoscopic procedure, followed by diagnosis error. Right and left-sided colon cancers were almost equally represented. Closed claims involving colon cancer according to location were as follows: cecum (n = 3), hepatic flexure (n = 2), transverse colon (n = 2), rectosigmoid junction (n = 6), rectum (n = 3), and unspecified location (n = 5).

Colonoscopy, followed by sigmoidoscopy (flexible and rigid) represented the highest frequencies of closed claims and the highest total indemnities (Table 2). In terms of average cost per claim, ERCP ranked the highest.

Table 2 shows the average and total indemnity comparing the various specialties that perform endoscopies. Internists had the highest number of total claims and total claim payment. Figure 1 shows the total claim payments over time according to procedure. For procedures such as EGD which sometimes have only one or two closed claims per year, one very large payment can skew these averages. Colonoscopy and ERCP have had many more paid claims, and for these procedures there is a clear increase in average claim payment. Indeed, there appears to have been an average increase of 15.5% per year for colonoscopy and 21.9% per year for ERCP after adjusting for inflation.

In the time period covered, closed claims for PEG procedures were recorded during only six of the years studied, thus there was insufficient data for analysis. For the other procedures, an exponential model fit the data better than a linear model in three of the four cases. Table 3 shows both the absolute and percentage increase (in real dollars) of the average value of claims. Of note, the total sigmoidoscopy claims have been declining on average since 1985. The data from which these regression figures were calculated is shown in Figure 1.

DISCUSSION

Our study shows that from the standpoint of insurers, internists who perform endoscopies had the highest total claim payment, costing over twice than gastroenterologists in terms of compensation for negligence. The largest total indemnities resulted from colonoscopies and sigmoidoscopies, but only colonoscopy and ERCP have been increasing over time. This could reflect the increasing number of colonoscopies performed per year and the increasing number of endoscopists who perform ERCPs.

Table 2 Endoscopy claims by specialty against all providers according to procedure, ranked according to total claims payment to plaintiffs (1985-2008) (*n* = 1901)

Procedure	Closed claims	Total paid claims	Total claim payments ($)	Mean claim payments ($)
Colonoscopy	788	216	54 093 000	250 430.56
Flexible sigmoidoscopy	513	182	28 674 000	157 549.45
ERCP	217	67	25 207 000	376 223.88
Rigid proctoscopy	125	51	15 726 000	308 352.94
EGD	209	47	9 666 000	205 659.57
PEG	49	7	2 598 000	371 142.86
Internal medicine	766	-	70 730 101	261 963
Gastroenterology	562	-	30 841 008	250 740
General surgery	231	-	13 305 060	187 395
General/family practice	101	-	7 288 674	186 889
Colorectal surgery	87	-	6 593 000	286 652
Other specialties	154	-	7 206 157	163 776

ERCP: Endoscopic retrograde cholangiopancreatography; EGD: Esophago gastroduodenoscopy; PEG: Percutaneous endoscopic gastrostomy.

The annual cost of the United States medical liability system is estimated to be $55.6 billion[6]. According to the United States Government Accountability Office, the primary driver in medical liability insurance industry economics is the rising average cost of indemnity, which leads to rising premiums that has affected gastroenterologists and non-gastroenterologists alike. Although the specialty of gastroenterology has always been viewed as low-risk for medical malpractice lawsuit, a recent seminal study[7] has shown that gastroenterology ranks six out of 25, before obstetrics and gynecology, in terms of proportion of physicians facing malpractice claims.

Our data have several limitations. PIAA produces summary data making us unable to cross-reference variables and to assess inter-relationships between any predictors. There is no information on individuals who do not sue. However, these claims represent the most significant injuries that merit attention. Also, no chart validation studies were performed to confirm robustness of findings. The denominator, or the total number of physicians per specialty who perform endoscopies is unknown, so our data reflect frequencies and not proportions. Internists had higher cost per claim, but we do not know if there is higher cost per insured internist because the denominator is not available. It is possible that gastroenterologists were misclassified as internists, but sued doctors self-classified themselves, of which the PIAA coders used in data collecting. Thus, we believe a gastroenterologist would have no incentive to classify him or herself as an internist.

There are also several factors other than legal merit that determines whether claims are paid in litigation, such as severity of injury. Thus, we realize that the legal definition of negligence (or failure to use reasonable care) is not necessarily synonymous with genuine error in all instances. Typically, there is a hierarchy as to what people

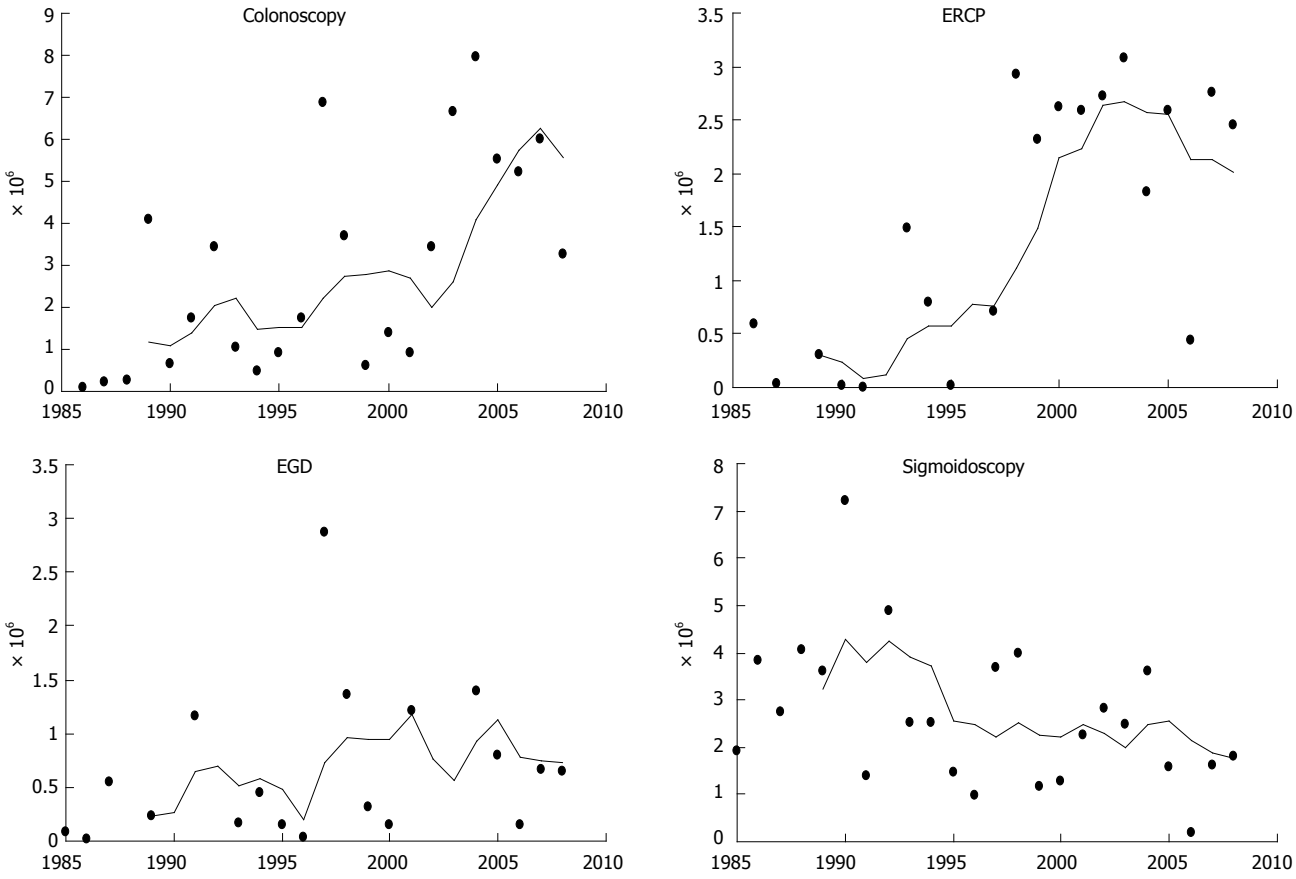


Figure 1 Total claim payments by procedure type, adjusted to 2008 dollars, together with 5-year moving averages (y-axis, total claim payments in dollars; X-axis, years), showing an increasing temporal trend for colonoscopy and endoscopic retrograde cholangiopancreatography. EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Absolute percentage increase of average closed claims

	Linear increase/ yr ($)	Model R^2	Expon increase/ yr, %	Model R^2
Colonoscopy	229 000	0.3976	12.59	0.4874
ERCP	122 000	0.5098	19.06	0.4076
EGD	23 000	0.0567	7.53	0.1697
Sigmoidoscopy	-93 000	0.1873	-4.6	0.1938

ERCP: Endoscopic retrograde cholangiopancreatography; EGD: Esophago gastroduodenoscopy.

consider preventable injury-there are those caused by error, of which some involved negligence, but usually all negligence involves error.

However despite our limited data resource, our study provides useful, unprecedented information on litigations related to endoscopy. All closed claims are likely captured by the collaborative PIAA database. Because of the economics of litigation, these cases typically represent those involving serious injuries.

In summary, closed malpractice claims data yielded important information on alleged injuries resulting from endoscopy. We found discrepancies in malpractice costs among specialties and the type of procedure. There is also evidence for secular trend in total claim payments, with colonoscopy and ERCP costs rising yearly after adjusting for inflation.

Malpractice insurers might use this information to scale their premiums according to both specialty and type of endoscopy performed, allowing a risk differential payment structure. They may also incentivize simulation training, credentialing, or other regulatory strategies, and to sponsor safety improvement efforts to reduce their exposure. Gastroenterologists are to be held accountable for managing risks of errors[8] in endoscopy by adhering to standards of practice, especially when performing ERCP[9,10] (adequate training and yearly volume) or colonoscopy[11] (minimize colon cancer miss rates and ensure proper documentation). The limitations of our retrospective data highlight the need for a comprehensive, perhaps even a prospective, nationwide database at an individual level to capture the incidence rates of major adverse events and errors, and to design interventions that can reduce iatrogenic injuries resulting from substandard endoscopy.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Atul Gawande of the Harvard School of Public Health (HSPH) in Boston, MA who facilitated our collaboration at HSPH. We also thank

Ms. Jacque Dresen for assisting in the manuscript.

COMMENTS

Background

Little is known about major endoscopy-related errors categorized by procedure and specialty, and time trends.

Research frontiers

In general and vascular surgery, the National Surgical Quality Improvement Program has become a platform for validated, risk-adjusted outcome comparisons between institutions, however only a select minority of hospitals have implemented the program, and it has not been highly developed for other fields that involve procedures.

Innovations and breakthroughs

Authors obtained summary-level data from a comprehensive database of closed claims against physicians who are members of the Physicians Insurers Association of America (PIAA), which is a trade association of professional liability companies owned by physicians, hospitals, and other health care providers.

Applications

Their study provides useful, unprecedented information on litigations related to endoscopy. All closed claims are likely captured by the collaborative PIAA database. Because of the economics of litigation, these cases typically represent those involving serious injuries.

Peer review

In this study the investigators compare and contrast major endoscopy-related errors for which insurance claims were filed, categorized by procedure and specialty, and time trends. They also compared total malpractice indemnity by specialty and procedure. The data was acquired from a database of closed claims from a trade association of professional liability insurance carriers, and covers approximately 60% of United States physicians in all 50 states. A total of 1901 endoscopy-related closed claims were found against all providers from 1985 to 2008. Colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) had highest dollar value per claim. Internists had the highest number of total claims and total claim payment. Corrected for inflation, only total claim payments for colonoscopy and ERCP seem to have increased over time. The study was retrospective and showed rates, not proportions.

REFERENCES

1 National Center for Health Statistics. Available from: URL: http://www.cdc.gov/nchs/data/databriefs/db32.htm
2 **Hutter MM**, Rowell KS, Devaney LA, Sokal SM, Warshaw AL, Abbott WM, Hodin RA. Identification of surgical complications and deaths: an assessment of the traditional surgical morbidity and mortality conference compared with the American College of Surgeons-National Surgical Quality Improvement Program. *J Am Coll Surg* 2006; **203**: 618-624 [PMID: 17084322 DOI: 10.1016/j.jamcollsurg.2006.07.010]
3 **Studdert DM**, Mello MM, Gawande AA, Gandhi TK, Kachalia A, Yoon C, Puopolo AL, Brennan TA. Claims, errors, and compensation payments in medical malpractice litigation. *N Engl J Med* 2006; **354**: 2024-2033 [PMID: 16687715 DOI: 10.1056/NEJMsa054479]
4 **Regenbogen SE**, Greenberg CC, Studdert DM, Lipsitz SR, Zinner MJ, Gawande AA. Patterns of technical error among surgical malpractice claims: an analysis of strategies to prevent injury to surgical patients. *Ann Surg* 2007; **246**: 705-711 [PMID: 17968158 DOI: 10.1097/SLA.0b013e31815865f8]
5 **Conklin LS**, Bernstein C, Bartholomew L, Oliva-Hemker M. Medical malpractice in gastroenterology. *Clin Gastroenterol Hepatol* 2008; **6**: 677-681 [PMID: 18456572 DOI: 10.1016/j.cgh.2008.02.047]
6 **Mello MM**, Chandra A, Gawande AA, Studdert DM. National costs of the medical liability system. *Health Aff (Millwood)* 2010; **29**: 1569-1577 [PMID: 20820010 DOI: 10.1377/hlthaff.2009.0807]
7 **Jena AB**, Seabury S, Lakdawalla D, Chandra A. Malpractice risk according to physician specialty. *N Engl J Med* 2011; **365**: 629-636 [PMID: 21848463 DOI: 10.1056/NEJMsa1012370]
8 **Floyd TK**. Medical malpractice: trends in litigation. *Gastroenterology* 2008; **134**: 1822-1825, 1825.e1 [PMID: 18482584 DOI: 10.1053/j.gastro.2008.05.001]
9 **Baron TH**, Petersen BT, Mergener K, Chak A, Cohen J, Deal SE, Hoffinan B, Jacobson BC, Petrini JL, Safdi MA, Faigel DO, Pike IM. Quality indicators for endoscopic retrograde cholangiopancreatography. *Am J Gastroenterol* 2006; **101**: 892-897 [PMID: 16635233 DOI: 10.1111/j.1572-0241.2006.00675.x]
10 **Cotton PB**. Analysis of 59 ERCP lawsuits; mainly about indications. *Gastrointest Endosc* 2006; **63**: 378-382; quiz 464 [PMID: 16500382 DOI: 10.1016/j.gie.2005.06.046]
11 **Rex DK**, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006; **101**: 873-885 [PMID: 16635231]

P- Reviewers Vivas S, Ciaccio EJ **S- Editor** Gou SX
L- Editor A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.174

World J Gastrointest Endosc 2013 April 16; 5(4): 174-179
ISSN 1948-5190 (online)

BRIEF ARTICLE

Endocytoscopic visualization of squamous cell islands within Barrett's epithelium

Nicholas Eleftheriadis, Haruhiro Inoue, Haruo Ikeda, Manabu Onimaru, Akira Yoshida, Toshihisa Hosoya, Roberta Maselli, Shin-ei Kudo

Nicholas Eleftheriadis, Haruhiro Inoue, Haruo Ikeda, Manabu Onimaru, Akira Yoshida, Toshihisa Hosoya, Roberta Maselli, Shin-ei Kudo, Digestive Disease Center, Showa University, Northern Yokohama Hospital, Tsuzuki-ku, Yokohama 224-8503, Japan
Author contributions: Eleftheriadis N wrote the manuscript; Inoue H performed the procedure, designed the study, analyzed and interpreted the data, corrected the manuscript; Ikeda H, Onimaru M, Yoshida A, Hosoya T and Maselli R participated in the procedure and contributed to the analysis and interpretation of data; Kudo S design the study, analyzed and interpreted the data.
Correspondence to: Nicholas Eleftheriadis, MD, Digestive Disease Center, Showa University, Northern Yokohama Hospital, 35-1 Chigasakichuo, Tsuzuki-ku, Yokohama 224-8503, Japan. nikoseleftheriadis@yahoo.com
Telephone: +81-45-9497641 Fax: +81-45-9497263
Received: May 24, 2012 Revised: March 11, 2013
Accepted: March 15, 2013
Published online: April 16, 2013

Abstract

AIM: To study the endocytoscopic visualization of squamous cell islands within Barrett's epithelium.

METHODS: Endocytoscopy (ECS) has been studied in the surveillance of Barrett's esophagus, with controversial results. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for the staining of Barrett's mucosa. Integrated type endocytoscopes (GIF-Q260 EC, Olympus Corp, Tokyo, Japan) have been recently developed, with the incorporation of a high-power magnifying endocytoscope into a standard endoscope together with narrow-band imaging (NBI). Moreover, double staining with a mixture of 0.05% crystal violet and 0.1% of methylene blue (CM) during ECS enables higher quality images comparable to conventional hematoxylin eosin histopathological images.

RESULTS: *In vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported. Conventional white light endoscopy showed typical long-segment Barrett's esophagus, with small squamous cell islands within normal Barrett's mucosa, which were better visualized by NBI endoscopy. ECS after double CM staining showed regular Barrett's esophagus, while higher magnification (× 480) revealed the orifices of glandular structures better. Furthermore, typical squamous cell papillary protrusion, classified as endocytoscopic atypia classification (ECA) 2 according to ECA, was identified within regular glandular Barrett's mucosa. Histological examination of biopsies taken from the same area showed squamous epithelium within glandular Barrett's mucosa, corresponding well to endocytoscopic findings.

CONCLUSION: To our knowledge, this is the first report of *in vivo* visualization of esophageal papillary squamous cell islands surrounded by glandular Barrett's epithelium.

Key words: Endocytoscopy; Barrett's esophagus; Surveillance; Endocytoscopic atypia classification; Crystal violet; Methylene blue; Hematoxylin eosin stain

Core tip: Endocytoscopy has been also studied in surveillance of Barrett's esophagus, with controversial results. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for staining of Barrett's mucosa. In the present study, *in vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported.

Eleftheriadis N, Inoue H, Ikeda H, Onimaru M, Yoshida A, Hosoya T, Maselli R, Kudo S. Endocytoscopic visualization of squamous cell islands within Barrett's epithelium. *World J Gastrointest Endosc* 2013; 5(4): 174-179 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/174.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.174

INTRODUCTION

Endocytoscopy (ECS) with ultra-high magnification (× 400-1100) represents the most recent innovation in endoscopic imaging, permitting *in vivo* cellular imaging of gastrointestinal (GI) mucosa and visualization of nuclear atypia in neoplastic lesions during routine endoscopic examination[1-5]. Not only structural atypia, but also cellular atypia, with observation of lumens and nuclei, is achieved by recent advances in ECS[5-9].

Two different integrated type endocytoscopes (GIF-Q260, Olympus Medical Systems Corp, Tokyo, Japan) have been recently developed[2,6]. The first is a dual charged couple device (CCD) integrated type (CIF-Y0001, EC1 Olympus, Tokyo, Japan) and the other is a single CCD integrated type (CIF-Y0002, EC2 Olympus).

The dual CCD prototype carries both conventional magnification (× 80) and ultra-high magnification (× 480) abilities, which can be easily interchanged by pushing a button on the endocytoscope[2,6].

The single CCD prototype endocytoscope (CIF-Y0002, EC2 Olympus) has only one lens that can consecutively increase the magnification power from the conventional magnification power to × 380 using a hand lever. The video processor (prototype, Olympus CV-260X) with a light source (Olympus CLV-260) allows narrow-band imaging (NBI)[2].

Methylene blue or toluidine blue single staining was initially used for endocytoscopic evaluation of esophageal lesions[6,10,11]. Recently, however double staining with a mixture of 0.05% crystal violet and 0.1% methylene blue (CM) has been also proposed during ECS[2,3]. Crystal violet alone effectively stains the cytoplasm, while methylene blue single staining dyes both nuclei and cytoplasm, revealing details of cell structure[11,12]. Double CM staining enables well balanced staining of both cytoplasm and nuclei, resulting in improved endocytoscopic visualization of GI lesions, comparable to conventional hematoxylin eosin histopathological images[1].

Minami *et al*[2] has recently described a five type endocytoscopic atypia classification (ECA) of esophageal squamous cell lesions based on size and uniformity of nuclei, number of cells and regularity of cellular arrangement. ECA-1 to ECA-3 lesions correspond to histological categories 1 to 3, according to the revised Vienna[13,14] histological classification of gastrointestinal epithelial neoplasia, while ECA-4 to ECA-5 lesions correspond to Vienna categories 4 to 5 (Table 1). According to the results of Minami *et al*[2], overall accuracy of ECS in evaluation of esophageal squamous cell lesions was 91.3%, providing images similar to conventional hematoxylin and eosin staining[2]. Other endocytoscopic atypia classification systems of esophageal lesions based on "nuclear density" and "nuclear abnormality" have also been studied, with promising results[15].

Endocytoscopy has also been studied in surveillance of Barrett's esophagus, with controversial results[16,17]. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for staining of Barrett's mucosa[16,17]. Although a standardized endocytoscopic atypia classification system for Barrett's esophageal glandular lesions has not been yet described, endocytoscopically, dysplasia was diagnosed on the basis of polarity of cells and nuclei (spacing, orientation); size, shape and uniformity of nuclei; chromatin; nucleoli; and nucleus to cytoplasm ratio[17].

In the present study, *in vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported.

MATERIALS AND METHODS

The dual CCD integrated prototype endocytoscope (CIF-Y0001, EC1 Olympus, Tokyo, Japan) was used for evaluation of long-segment Barrett's esophagus in the present study. In order to compare endocytoscopic images to histological images, biopsies were taken from the same area of ECS by an experienced endoscopist.

Conventional magnifying endoscopy and ECS was performed under conscious sedation with intravenous pethidine hydrochloride (35 mg; Opystan, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), supplemented with diazepam (5-10 mg, Takeda Pharmaceutical Co., Osaka, Japan). In order to suppress esophageal peristalsis, scopolamine butylbromide (20 mg; Buscopan, Boeringer Ingelhei, GmbH, Ingelheim, Germany) was also administered intravenously. Conventional and ultra-high magnification examination was performed simultaneously. Flushing with water containing a small amount of simethicone was carried out to eliminate gas and foamy mucus from the esophagus before the procedure.

Conventional white light endoscopy (WLE) showed typical long-segment Barrett's esophagus, without visible lesions (Figure 1A). NBI clearly visualized small squamous cell islands within normal Barrett's mucosa, which were also identified by WLE with difficulty (Figure 1B).

After double CM staining, ECS with gradual magnification followed. A total amount of 10 mL CM mixture was directly injected through the working channel with a 5 mL syringe to esophageal Barrett's mucosa. No catheter spray was necessary. The CM mixture is routinely prepared for ECS use, from 0.05% crystal violet and 0.1% methylene blue due solutions. After waiting 60 s to stain nuclei and cytoplasm, ECS followed.

RESULTS

Initially, detailed endocytoscopic observation on the back-

Table 1 Revised Vienna classification of gastrointestinal epithelial neoplasia

Category	Diagnosis
Group 1	Negative for neoplasia
Group 2	Indefinite for neoplasia
Group 3	Mucosal low grade neoplasia
	Low grade adenoma
	Low grade dysplasia
Group 4	Mucosal high grade neoplasia
Subgroup 4.1	High grade adenoma/dysplasia
Subgroup 4.2	Non-invasive carcinoma (carcinoma *in situ*)
Subgroup 4.3	Suspicious for invasive carcinoma
Subgroup 4.4	Intramucosal carcinoma
Group 5	Submucosal invasion by carcinoma

The Endocytoscopic Atypia (ECA) Classification[10] for superficial esophageal squamous cell lesions is as follow: ECA 1: Large, cytoplasm-rich cells with a rhomboid shape are found in a regular arrangement. Small nuclei are located at their center. This appearance corresponds to healthy squamous epithelium in the esophagus; ECA 2: The cell margin often becomes round. Different-sized small nuclei are observed. The image often shows inflammatory or reactive changes; ECA 3: The cell becomes smaller in size but the nuclei are still compact. This appearance is often observed in borderline lesions; ECA 4: The number of cells increases with an increased nucleus-cytoplasm ratio. This appearance strongly suggests a malignant lesion; ECA 5: Cells of various sizes are arranged irregularly with a high nucleus-cytoplasm ratio. This appearance is recognized endoscopically as a definitely malignant lesion. All images were categorized according to size and uniformity of nuclei, number of cells and regularity of cellular arrangement. Higher ECA category is associated with stronger atypia. ECA 1 to ECA 3 corresponds to Vienna categories 1 to 3; ECA 4 to ECA 5 corresponds to Vienna categories 4 to 5. The data was quoted from the references of 13, 14.

ground mucosa showed regular Barrett's esophagus, without endocytoscopic signs of dysplasia (Figure 1C), while with higher magnification the adenomatous Barrett's glandular orifices were better visualized (Figure 1D). Particularly, high quality endocytoscopic images revealed normal cellular structures, with cells similar in size and shape, without crowding or overlapping and an equal uptake of methylene blue, uniformly oriented in a glandular structure. Furthermore, nuclei were uniform, regular in shape, small in size with normal nucleus/cytoplasm ratio.

Subsequently, ECS focused on the largest squamous cell island surrounded by regular Barrett's epithelium, which was previous identified by NBI. A typical squamous papillary protrusion was clearly identified within regular glandular Barrett's mucosa (Figure 2A). Endocytoscopic findings revealed combined round-shaped cytoplasm-rich cells in an almost regular arrangement, while different sized small nuclei were observed, corresponding to ECA2 according to endocytoscopic atypia classification[2] (Figure 2A). These findings were suggestive of mild inflammatory changes of esophageal squamous epithelium (DVD).

After detailed observation, biopsies were taken from the same area in order to obtain a pathological diagnosis. The location of endocytoscopic images were matched to histological images and complete correspondence of endocytoscopic images with histopathological images was obtained (Figure 2) based on the records of endocytoscopic examination (DVD).

Histological examination showed squamous epithelium within non-dysplastic columnar Barrett's epithelium (Figure 2B). No dysplasia or atypia was found in histopathology of both squamous cell islands and adenomatous Barrett's epithelium, which was in accordance with endocytoscopic images.

DISCUSSION

Barrett's esophagus is the transformation of the normal squamous esophageal mucosa into columnar epithelium and is considered a premalignant condition with high risk of esophageal adenocarcinoma[18-21]. Traditionally, the diagnosis of Barrett's esophagus is based on histology of biopsy specimens and hematoxylin eosin stain, revealing glandular structures combined with goblet cells[22,23]. The presence of goblet cells is the sine qua non of Barrett's esophagus[24,25].

Long-term endoscopic surveillance with multiple and repeated sets of biopsies are the standard recommended practice in Barrett's esophagus in an attempt to detect dysplasia or carcinoma at an early and potentially curable stage[26-29]. The Seattle multiple biopsy protocol (4 quadrant jumbo biopsies every 1 cm with additional biopsies of mucosal abnormalities), is considered to be the optimal method for surveillance of Barrett's esophagus, although it has never been validated[27,30]. However, even the most intensive biopsy protocols are associated with significant sampling errors[31,32].

By convention, there are four broad categories used by pathologists to describe the dysplastic process in Barrett's: (1) no dysplasia; (2) indefinite for dysplasia; (3) low-grade dysplasia; and (4) high-grade dysplasia; which corresponds to groups 1 to 4 according to the revised Vienna[14] classification for gastrointestinal epithelial neoplasia. The most significant category, high-grade dysplasia, is characterized by carcinoma *in situ* with malignant cells that do not invade the lamina propria. Category (5) corresponds to submucosal invasion by carcinoma[14,18].

However, the ability to grade dysplasia remains a subjective endeavor, particularly outside specialized centers with expert gastrointestinal pathologists[33]. Even among focused gastrointestinal pathologists there is discordance, particularly with regard to the presence of low-grade dysplasia[34]. This lack of precision inherent in histopathological grading has stimulated efforts to identify alternative methods of surveillance in patients with Barrett's esophagus, including more objective molecular and biochemical indicators of an increased risk for progression[18].

ECS is a revolutionized endoscopic imaging technique aiming to replace the histological examination of biopsy specimens, making "optical biopsy" possible while facilitating real time decision-making[8].

ECS after double CM staining using modern integrated type endocytoscopes enables *in vivo* visualization of living cells and evaluation of tissue atypia by approximating the tip of the endoscope onto the mucosal surface[10].

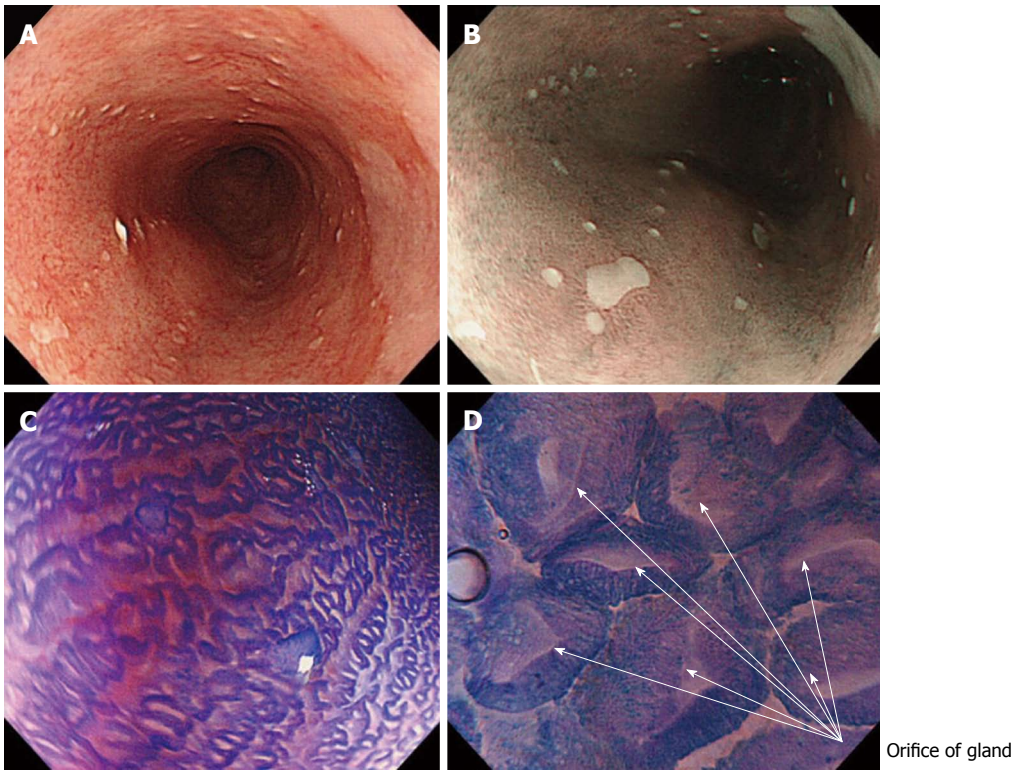


Figure 1 White light endoscopy, narrow-band imaging and endocytoscopy examination of long segment Barrett's esophagus. A: Long segment Barrett's esophagus under white light endoscopy (WLE); B: Narrow-band imaging with low magnification clearly visualized small squamous cell islands within regular columnar Barrett's epithelium, which are also identified by WLE with difficulty; C: Endocytoscopy (ECS) examination after crystal violet and methylene blue (CM) double staining; D: ECS examination under higher magnification (× 480) shows the glandular orifices of regular Barrett's epithelium.

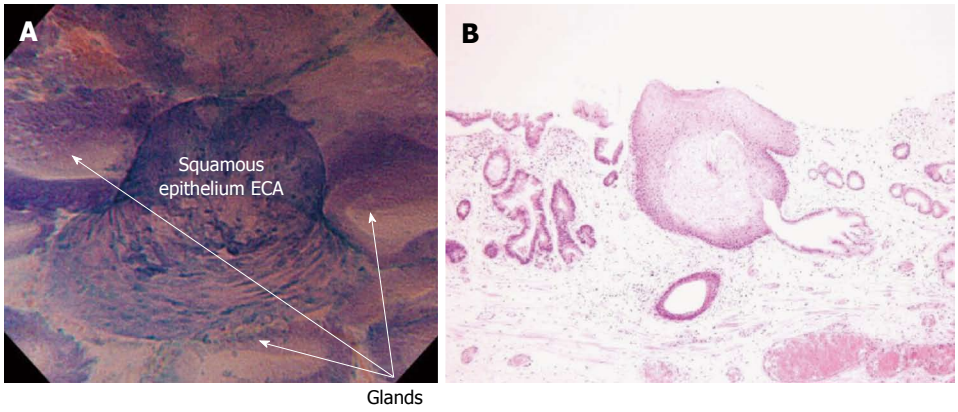


Figure 2 Endocytoscopy examination of histologically confirmed squamous cell islands within Barrett's esophagus. A: Endocytoscopy (ECS) examination shows squamous cell islands, within regular glandular structures of Barrett's esophagus. According to ECS examination, squamous papillary structure is classified as ECA2, (round-shaped cells with different-sized small nuclei, suggestive of inflammatory changes); B: Histological examination (hematoxylin and eosin stain magnification) of biopsies from the same area as in Figure (A) confirmed the presence of a squamous papillary structure surrounded by Barrett's glandular epithelium.

No serious complications of ECS have been reported yet[6].

At present, a standardized endocytoscopic atypia classification system has been described for esophageal squamous cell lesions[2] and colorectal[5] adenomatous lesions. ECS has been also applied for Barrett's esophagus[16,17,35,36], with controversial results, however, and without a standardized endocytoscopic classification system.

In contrast to previous endocytoscopic studies in Barrett's esophagus[16,17] where a soft catheter type endocytoscope was used, endocytoscopic evaluation of long-segment Barrett's esophagus in the present study was performed by a dual CCD integrated endocytoscope[2]. This scope has the advantage of gradual magnification at the center of the monitor, ensuring biopsies from the same area of ECS. This is important to compare endocytoscopic images to histological images. Standard endoscopy, supplemented by NBI and conventional magnification endoscopy was also performed by the same endoscope[2].

Another interesting finding of the present study is the

use of the double CM staining technique, which provided higher quality endocytoscopic images of both Barrett's metaplastic epithelium and esophageal squamous cell islands. Although double CM staining has been used in ECS of esophageal squamous cell lesions, to our knowledge, it has not been previously reported in endocytoscopic evaluation of Barrett's esophagus.

ECS may further allow target biopsy, as in the presented case, which is extremely important in surveillance of Barrett's esophagus where random biopsy protocols are currently in use. In the present case, ECS permitted *in vivo* high quality images of squamous cell islands within long-segment Barrett's epithelium comparable to histology. To our knowledge, this is the first report of *in vivo* visualization of typical esophageal squamous cell islands surrounded by glandular Barrett's epithelium. According to the positive results of the present study, although from only one case, endocytoscopic evaluation of Barrett's mucosa is promising. However, further studies and expertise are necessary.

COMMENTS

Background

Barrett's esophagus is the transformation of the normal squamous esophageal mucosa into columnar epithelium and is considered a premalignant condition with high risk of esophageal adenocarcinoma. Multiple biopsy protocols are currently the optimal practice in surveillance of Barrett's esophagus, with significant sampling errors, however. Moreover, there is discordance regarding the ability to grade dysplasia in Barrett's esophagus even among focused gastrointestinal pathologists. This lack of precision inherent in histopathological grading has stimulated efforts to identify alternative methods of surveillance in patients with Barrett's esophagus.

Research frontiers

Endocytoscopy (ECS) has emerged as a novel method of *in vivo* diagnosis of gastrointestinal mucosal lesions aimed at replacing the histological examination of biopsy specimens while facilitating real time decision-making.

Innovations and breakthroughs

ECS has been studied in surveillance of Barrett's esophagus, with controversial results. In contrast to previous studies in which a soft catheter type endocytoscope was used after single methylene blue dye for staining of Barrett's mucosa, in the present study, a novel integrated type endocytoscope after double crystal violet and methylene blue (CM) staining resulted in higher quality endocytoscopic images, corresponding to hematoxylin eosin histopathological images. To the knowledge, this is the first report of *in vivo* endocytoscopic visualization of typical esophageal squamous cell islands within regular glandular Barrett's epithelium.

Applications

Based on the encouraging results of the present study, ECS, according to the technique described in this article, would be reliably used for real time, *in vivo* diagnosis of Barrett's esophagus as an alternative to histological examination of biopsy specimens. ECS may allow target biopsy, as in the presented case, which is extremely important in surveillance of Barrett's esophagus where random biopsy protocols are currently in use. However, further studies and expertise are necessary, while a standardized endocytoscopic atypia classification system, similar to that described for esophageal squamous cell lesions and colorectal adenomatous lesions, is necessary and awaited.

Terminology

CCD: charged couple device; ECS is a novel endoscopic imaging of gastrointestinal mucosa, with ultra-high magnification (× 400-1100), permitting *in vivo* cellular imaging and observation of lumens and nuclei during routine endoscopic examination; The dual CCD integrated prototype (CIF-Y0001, EC1, Olympus, Tokyo, Japan) endocytoscope (× 480) carries both conventional magnification (× 80) and ultra-high magnification (× 480) abilities, which can be easily interchanged by pushing a button on the endocytoscope; The single CCD prototype (CIF-Y0002, EC2 Olympus) endocytoscope (× 380) has only one lens that can consecutively increase the magnification power from the conventional magnification power to × 380 using a hand lever; The revised Vienna classification of gastrointestinal epithelial neoplasia, which is based on the severity of cytological and architectural changes and on invasion status, has to some extent, resolved the differences between Western and Japanese pathologists in the diagnostic classification of gastrointestinal epithelial neoplastic lesions, especially in the use of the terminology of dysplasia, adenoma, early cancer and advanced cancer.

Peer review

It is very interesting brief report. Superb images and careful description of the technique are the strong points of the paper.

REFERENCES

1 **Inoue H**, Yokoyama A, Kudo SE. [Ultrahigh magnifying endoscopy: development of CM double staining for endocytoscopy and its safety]. *Nihon Rinsho* 2010; **68**: 1247-1252 [PMID: 20662202]

2 **Minami H**, Inoue H, Yokoyama A, Ikeda H, Satodate H, Hamatani S, Haji A, Kudo S. Recent advancement of observing living cells in the esophagus using CM double staining: endocytoscopic atypia classification. *Dis Esophagus* 2012; **25**: 235-241 [PMID: 21895852 DOI: 10.1111/j.1442-2050.2011.01241.x]

3 **Kumagai Y**, Kawada K, Yamazaki S, Iida M, Ochiai T, Momma K, Odajima H, Kawachi H, Nemoto T, Kawano T, Takubo K. Endocytoscopic observation of esophageal squamous cell carcinoma. *Dig Endosc* 2010; **22**: 10-16 [PMID: 20078658 DOI: 10.1111/j.1443-1661.2009.00931.x]

4 **Tomizawa Y**, Abdulla HM, Prasad GA, Wong Kee Song LM, Lutzke LS, Borkenhagen LS, Wang KK. Endocytoscopy in esophageal cancer. *Gastrointest Endosc Clin N Am* 2009; **19**: 273-281 [PMID: 19423024 DOI: 10.1016/j.giec.2009.02.006]

5 **Kudo SE**, Wakamura K, Ikehara N, Mori Y, Inoue H, Hamatani S. Diagnosis of colorectal lesions with a novel endocytoscopic classification - a pilot study. *Endoscopy* 2011; **43**: 869-875 [PMID: 21837586 DOI: 10.1055/s-0030-1256663]

6 **Kumagai Y**, Kawada K, Yamazaki S, Iida M, Odajima H, Ochiai T, Kawano T, Takubo K. Current status and limitations of the newly developed endocytoscope GIF-Y0002 with reference to its diagnostic performance for common esophageal lesions. *J Dig Dis* 2012; **13**: 393-400 [PMID: 22788924 DOI: 10.1111/j.1751-2980.2012.00612.x]

7 **Singh R**, Chen Yi Mei SL, Tam W, Raju D, Ruszkiewicz A. Real-time histology with the endocytoscope. *World J Gastroenterol* 2010; **16**: 5016-5019 [PMID: 20976836 DOI: 10.3748/wjg.v16.i40.5016]

8 **Neumann H**, Fuchs FS, Vieth M, Atreya R, Siebler J, Kiesslich R, Neurath MF. Review article: in vivo imaging by endocytoscopy. *Aliment Pharmacol Ther* 2011; **33**: 1183-1193 [PMID: 21457290 DOI: 10.1111/j.1365-2036.2011.04647.x]

9 **Galloro G**. High technology imaging in digestive endoscopy. *World J Gastrointest Endosc* 2012; **4**: 22-27 [PMID: 22347528 DOI: 10.4253/wjge.v4.i2.22]

10 **Inoue H**, Sasajima K, Kaga M, Sugaya S, Sato Y, Wada Y, Inui M, Satodate H, Kudo SE, Kimura S, Hamatani S, Shiokawa A. Endoscopic in vivo evaluation of tissue atypia in the esophagus using a newly designed integrated endocytoscope: a pilot trial. *Endoscopy* 2006; **38**: 891-895 [PMID: 16981105 DOI: 10.1055/s-2006-944667]

11 **Kodashima S**, Fujishiro M, Takubo K, Kammori M, Nomura S, Kakushima N, Muraki Y, Tateishi A, Kaminishi M, Omata M. Ex-vivo study of high-magnification chromoendoscopy in the gastrointestinal tract to determine the optimal staining conditions for endocytoscopy. *Endoscopy* 2006; **38**: 1115-1121 [PMID: 17111333 DOI: 10.1055/s-2006-944915]

12 **Dutt MK**. Basic dyes in the staining of DNA-phosphate

groups and DNA-aldehyde molecules in cell nuclei. *Microsc Acta* 1982; **85**: 361-368 [PMID: 6175883]
13 **Dixon MF**. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002; **51**: 130-131 [PMID: 12077106 DOI: 10.1136/gut.51.1.130]
14 **Stolte M**. The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages. *Virchows Arch* 2003; **442**: 99-106 [PMID: 12596058 DOI: 10.1007/s00428-002-0680-3]
15 **Kumagai Y**, Kawada K, Yamazaki S, Iida M, Momma K, Odajima H, Kawachi H, Nemoto T, Kawano T, Takubo K. Endocytoscopic observation for esophageal squamous cell carcinoma: can biopsy histology be omitted? *Dis Esophagus* 2009; **22**: 505-512 [PMID: 19302209 DOI: 10.1111/j.1442-2050.2009.00952.x]
16 **Eberl T**, Jechart G, Probst A, Golczyk M, Bittinger M, Scheubel R, Arnholdt H, Knuechel R, Messmann H. Can an endocytoscope system (ECS) predict histology in neoplastic lesions? *Endoscopy* 2007; **39**: 497-501 [PMID: 17554643 DOI: 10.1055/s-2007-966446]
17 **Pohl H**, Koch M, Khalifa A, Papanikolaou IS, Scheiner K, Wiedenmann B, Rösch T. Evaluation of endocytoscopy in the surveillance of patients with Barrett's esophagus. *Endoscopy* 2007; **39**: 492-496 [PMID: 17554642 DOI: 10.1055/s-2007-966340]
18 **Oh DS**, Demeester SR. Pathophysiology and treatment of Barrett's esophagus. *World J Gastroenterol* 2010; **16**: 3762-3772 [PMID: 20698038 DOI: 10.3748/wjg.v16.i30.3762]
19 **Hameeteman W**, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology* 1989; **96**: 1249-1256 [PMID: 2703113]
20 **Katona BW**, Falk GW. Barrett's esophagus surveillance: When, how often, does it work? *Gastrointest Endosc Clin N Am* 2011; **21**: 9-24 [PMID: 21112494 DOI: 10.1016/j.giec.2010.09.003]
21 **Fléjou JF**. Barrett's oesophagus: from metaplasia to dysplasia and cancer. *Gut* 2005; **54** Suppl 1: i6-12 [PMID: 15711008 DOI: 10.1136/gut.2004.041525]
22 **Wood NJ**. Barrett esophagus: Need for ongoing surveillance called into question for patients with non-dysplastic Barrett esophagus. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 657 [PMID: 22138905 DOI: 10.1038/nrgastro.2011.204]
23 **Bergman JJ**, Tytgat GN. New developments in the endoscopic surveillance of Barrett's oesophagus. *Gut* 2005; **54** Suppl 1: i38-i42 [PMID: 15711007 DOI: 10.1136/gut.2004.041590]
24 **Odze RD**. What the gastroenterologist needs to know about the histology of Barrett's esophagus. *Curr Opin Gastroenterol* 2011; **27**: 389-396 [PMID: 21543978 DOI: 10.1097/MOG.0b013e328346f551]
25 **Oberg S**, DeMeester TR, Peters JH, Hagen JA, Nigro JJ, DeMeester SR, Theisen J, Campos GM, Crookes PF. The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. *J Thorac Cardiovasc Surg* 1999; **117**: 572-580 [PMID: 10047662 DOI: 10.1016/S0022-5223(99)70337-5]
26 **Gupta N**, Mathur SC, Dumot JA, Singh V, Gaddam S, Wani SB, Bansal A, Rastogi A, Goldblum JR, Sharma P. Adequacy of esophageal squamous mucosa specimens obtained during endoscopy: are standard biopsies sufficient for postablation surveillance in Barrett's esophagus? *Gastrointest Endosc* 2012; **75**: 11-18 [PMID: 21907985 DOI: 10.1016/j.gie.2011.06.040]
27 **Abrams JA**, Kapel RC, Lindberg GM, Saboorian MH, Genta RM, Neugut AI, Lightdale CJ. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. *Clin Gastroenterol Hepatol* 2009; **7**: 736-742; quiz 710 [PMID: 19268726 DOI: 10.1016/j.cgh.2008.12.027]
28 **Seewald S**, Ang TL, Groth S, Zhong Y, Bertschinger P, Altorfer J, Thonke F, Soehendra N. Detection and endoscopic therapy of early esophageal adenocarcinoma. *Curr Opin Gastroenterol* 2008; **24**: 521-529 [PMID: 18622170 DOI: 10.1097/MOG.0b013e3282ff8b1f]
29 **Ramus JR**, Gatenby PA, Caygill CP, Winslet MC, Watson A. Surveillance of Barrett's columnar-lined oesophagus in the UK: endoscopic intervals and frequency of detection of dysplasia. *Eur J Gastroenterol Hepatol* 2009; **21**: 636-641 [PMID: 19177028 DOI: 10.1097/MEG.0b013e32832183bc]
30 **Peters FP**, Curvers WL, Rosmolen WD, de Vries CE, Ten Kate FJ, Krishnadath KK, Fockens P, Bergman JJ. Surveillance history of endoscopically treated patients with early Barrett's neoplasia: nonadherence to the Seattle biopsy protocol leads to sampling error. *Dis Esophagus* 2008; **21**: 475-479 [PMID: 18430186 DOI: 10.1111/j.1442-2050.2008.00813.x]
31 **Kariv R**, Plesec TP, Goldblum JR, Bronner M, Oldenburgh M, Rice TW, Falk GW. The Seattle protocol does not more reliably predict the detection of cancer at the time of esophagectomy than a less intensive surveillance protocol. *Clin Gastroenterol Hepatol* 2009; **7**: 653-668; quiz 606 [PMID: 19264576 DOI: 10.1016/j.cgh.2008.11.024]
32 **Mannath J**, Ragunath K. Era of Barrett's surveillance: does equipment matter? *World J Gastroenterol* 2010; **16**: 4640-4645 [PMID: 20872963 DOI: 10.3748/wjg.v16.i37.4640]
33 **Alikhan M**, Rex D, Khan A, Rahmani E, Cummings O, Ulbright TM. Variable pathologic interpretation of columnar lined esophagus by general pathologists in community practice. *Gastrointest Endosc* 1999; **50**: 23-26 [PMID: 10385717]
34 **Skacel M**, Petras RE, Gramlich TL, Sigel JE, Richter JE, Goldblum JR. The diagnosis of low-grade dysplasia in Barrett's esophagus and its implications for disease progression. *Am J Gastroenterol* 2000; **95**: 3383-3387 [PMID: 11151865 DOI: 10.1111/j.1572-0241.2000.03348.x]
35 **Thekkek N**, Anandasabapathy S, Richards-Kortum R. Optical molecular imaging for detection of Barrett's-associated neoplasia. *World J Gastroenterol* 2011; **17**: 53-62 [PMID: 21218084 DOI: 10.3748/wjg.v17.i1.53]
36 **Shukla R**, Abidi WM, Richards-Kortum R, Anandasabapathy S. Endoscopic imaging: How far are we from real-time histology? *World J Gastrointest Endosc* 2011; **3**: 183-194 [PMID: 22013499 DOI: 10.4253/wjge.v3.i10.183]

P- Reviewer Maluf-Filho F **S- Editor** Song XX
L- Editor Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.180

World J Gastrointest Endosc 2013 April 16; 5(4): 180-185
ISSN 1948-5190 (online)

CASE REPORT

Ischemic colitis induced by the newly reformulated multicomponent weight-loss supplement Hydroxycut®

Muhammed Sherid, Salih Samo, Samian Sulaiman, Joseph H Gaziano

Muhammed Sherid, Joseph H Gaziano, Department of Internal Medicine, Division of Gastroenterology, CGH Medical Center, Sterling, IL 61071, United States
Salih Samo, Samian Sulaiman, Department of Internal Medicine, Division of Gastroenterology, Saint Francis Hospital, Evanston, IL 61071, United States
Author contributions: Sherid M contributed to study design, literature review, data collection, data analysis, initial manuscript writing, manuscript review, approval of final version; Samo S, Sulaiman S and Gaziano JH contributed to study design, literature review, data collection, data analysis, manuscript review, approval of final version; Samo S is a first co-author.
Correspondence to: Muhammed Sherid, MD, Department of Internal Medicine, Division of Gastroenterology, CGH Medical Center, 100 East LeFevre Road, Sterling, IL 61071, United States. muhammedsherid@yahoo.com
Telephone: +1-224-4200229 Fax: +1-815-6252747
Received: October 3, 2012 Revised: November 30, 2012
Accepted: December 15, 2012
Published online: April 16, 2013

Abstract

Ischemic colitis accounts for 6%-18% of causes of acute lower gastrointestinal bleeding. It is more often multifactorial and more common in elderly. Drugs are considered important causative agents of this disease with different mechanisms. In this paper, we describe a 37-year-old otherwise healthy female presented with sudden onset diffuse abdominal pain and bloody stool. Radiologic, colonoscopic and histopathologic findings were all consistent with ischemic colitis. Her only suspected factor was hydroxycut which she had been taking for a period of 1 mo prior to her presentation. Her condition improved uneventfully after cessation of hydroxycut, bowel rest, intravenous hydration, and antibiotics. This is a first case of ischemic colitis with clear relationship with hydroxycut use (Naranjo score of 7). Our case demonstrates the importance of questioning patients regarding the usage of dietary supplements; especially since many patients consider them safe and do not disclose their use voluntarily to their physicians. Hydroxycut has to be considered as a potential trigger for otherwise unexplained ischemic colitis.

Key words: Hydroxycut; Weight-loss supplement; Herbal; Ischemic colitis; Gastrointestinal bleeding; Colonoscopy

Sherid M, Samo S, Sulaiman S, Gaziano JH. Ischemic colitis induced by the newly reformulated multicomponent weight-loss supplement Hydroxycut®. *World J Gastrointest Endosc* 2013; 5(4): 180-185 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/180.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.180

INTRODUCTION

Ischemic colitis results from a sudden decrease of splanchnic blood flow to the colon. It occurs more often in the splenic flexure and rectosigmoid junction, which are also known as watershed areas of the colon. These two areas have limited collateralization between superior mesenteric artery and inferior mesenteric artery, and inferior mesenteric artery and internal iliac artery which supply splenic flexure and rectosigmoid junction of the colon, respectively. Therefore, these two areas are more prone to ischemic colitis[1].

The mechanisms of developing ischemic colitis include hypoperfusion due to systemic hypotension secondary to sepsis, hemorrhage, cardiac failure or any other conditions that might cause hypotension. Vasoconstriction in the colonic vessels due to hypotension or certain substances such as cocaine and other sympathomimetic agents is another mechanism. The third mechanism is thromboembolism due to inherited or acquired hypercoagulable conditions such as antiphospholipid antibody syndrome. Also increased intracolic pressure is another mechanism for ischemic colitis by causing decrease of the

blood flow into the colon which can occur after screening colonoscopy. Final mechanism is vasculitis involving colonic vessels such as polyarteritis nodosa[1,2].

Advanced age, aortic surgery, diabetes mellitus, hypertension, and peripheral vascular disease have been also suggested to be predisposing factors for ischemic colitis[1]. Hydroxycut is an over-the-counter herbal product that has been used for purpose of the weight loss, body building and as an energy enhancer. It is a multicomponent dietary supplement which has been reformulated twice after warnings from the food and drug administration (FDA). It has been linked to serious medical conditions, mostly acute liver toxicity. We describe here a case of ischemic colitis developed in a healthy young female after a month of hydroxycut consumption for purpose of weight loss in the absence of any other risk factors for ischemic colitis.

CASE REPORT

A 37-year-old otherwise healthy female presented with severe crampy abdominal pain. Pain was diffuse but more pronounce in left lower quadrant of her abdomen. The pain was also associated with nausea and one episode of non-bloody, non-bilious emesis. She had two bloody bowel movements at home and later on she had another two with blood clots in the stool at the emergency room. She denied fever, chills, urinary symptoms, similar symptoms in the past, recent travel, sick contact, or recent use of antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs). She had no significant past medical history. She had hysterectomy 4 years ago for repeated abnormal Pap smears. She was not on any prescribed medications. She denied smoking or using illicit drugs, but was drinking alcohol occasionally. She had no family history of major medical problems including gastrointestinal diseases or blood disorders.

The patient was afebrile with temperature of 98.2 F°, blood pressure of 106/63 without orthostatic hypotension, heart rate of 65 bpm, weight of 181 pounds, and body mass index of 29.2 kg/m^2. Her physical exam was remarkable for diffuse generalized abdominal tenderness, especially in left upper and left lower quadrants without guarding or rebound tenderness. Rectal exam was remarkable for blood on digital exam. The rest of exam including cardiopulmonary, skin, and extremities were unremarkable. Laboratory studies were unremarkable including complete blood count (hemoglobin of 15.9 g/dL), basic metabolic panel, liver function tests, urinalysis, urine toxicology, stool studies (except for positive blood), lipase, amylase, cholesterol profile, hemoglobin A1c, and thyroid function tests. Computed tomography (CT) scan showed a moderately severe colonic wall thickening in the descending colon extending into rectosigmoid area (Figure 1A, B).

Colonoscopy revealed erythematous and edematous colonic mucosa with multiple superficial erosions and ulcerations from the distal descending colon up to the mid-transverse colon which was consistent with moderately severe ischemic colitis (Figure 2). Multiple biopsies were taken which were consistent also with ischemic colitis (Figure 1C, D). CT angiogram was performed and did not identify any stenosis, occlusion, or thrombosis in the intra-abdominal vessels.

On further questioning to determine the etiology of ischemic colitis in our patient, she reported taking hyrdoxycut in a recommended dose by the manufacturer for weight loss purposes for a period of one month prior to her presentation.

This temporal relationship between hydroxycut exposure and her symptoms, in the light of absence of other causes of ischemic colitis strongly raises the probability of hydroxycut as the potential trigger of ischemic colitis. This case scored a 7 on the Naranjo Nomogram for adverse drug reactions, indicating a probable association between hydroxycut exposure and the development of ischemic colitis (Probable: 5-8).

She was treated with intravenous fluids, bowel rest, intravenous antibiotics, and discontinuation of hydroxycut. Her hospitalization course was uneventful and she was discharged home 3 d later. She was counseled to stop hydroxycut consumption.

DISCUSSION

This case illustrates the importance of investigation for potential triggers for ischemic colitis when the classical risk factors are absent. The causes of ischemic colitis vary from systemic hypotension, aortoiliac surgery, atherosclerosis, thromboembolic events, vasculitis, to varieties of drugs[3].

Drugs have been implicated in the development of ischemic colitis by different mechanisms including decreasing blood flow *via* systemic hypotension such as angiotensin-converting enzyme inhibitors, causing vasospasm such as pseudoephedrine, promoting thromboembolism such as oral contraceptives, causing vasculitis such as gold salts, and increasing intracolic pressure such as alosetron[4]. The mechanism of some drugs reported to cause ischemic colitis has not yet determined. The Table 1 below shows a list of medications and their mechanisms for causing ischemic colitis[4].

Many case reports have linked ischemic colitis and some commonly used medications such as NSAIDs and triptans, chemotherapy such as bevacizumab and irinotecan, hepatitis C therapy with pegylated interferon and ribavirin, following screening colonoscopy, scuba diving, flying, snake bite, acute carbonic monoxide poisoning, electrical muscle stimulation of the abdominal wall, following long distance running, herbal remedies such as ma huang (ephedra), and weight loss medications such as phentermine[4].

A significant proportion of Americans and people all over the world are using herbal supplements for different purposes based on geographic, race, and cultural backgrounds. In a survey in 2007, 17.7% of adults in the United States and 3.9% of children were using some kind

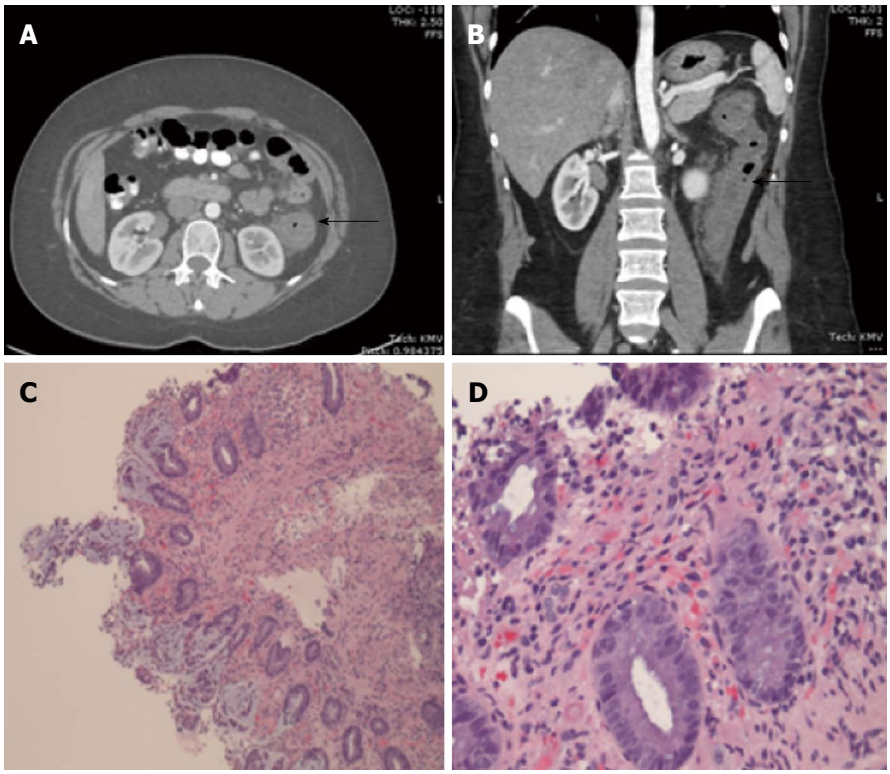


Figure 1 Computed tomography scan and histopathology. A, B: Computed tomography scan shows thickening of the colonic wall involving the descending colon (arrows); C, D: Histopathology shows: the overlying surface mucosa is eroded, the lamina propria is partially hyalinized with fibropurulent exudate and acute inflammation, consistent with ischemic colitis.

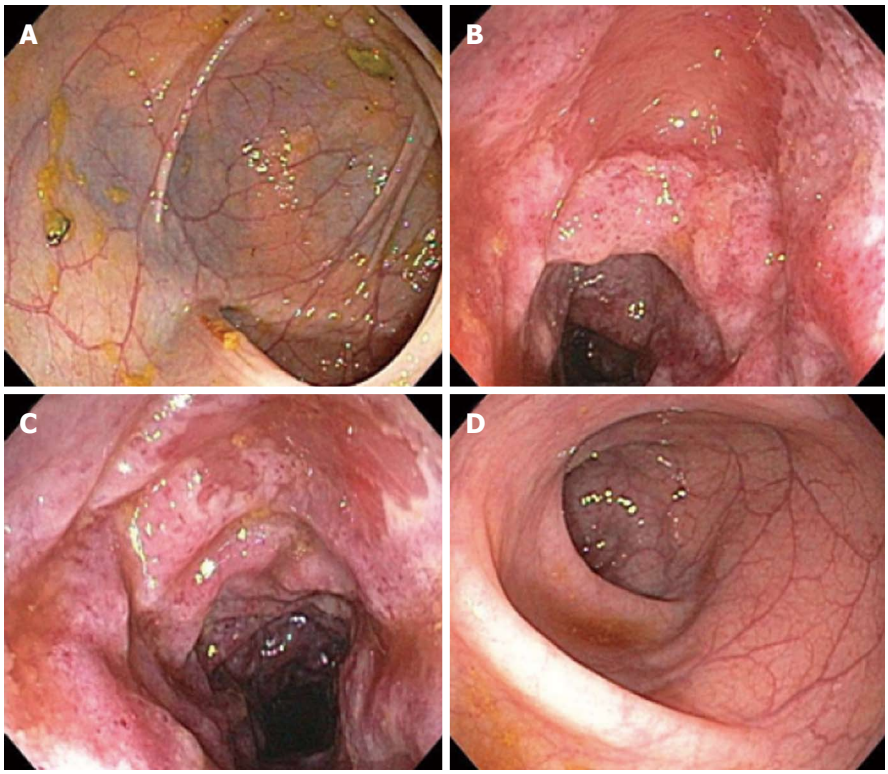


Figure 2 Colonoscopy shows. A: Normal mucosa of the right colon (hepatic flexure); B, C: Erythematous, edematous, erosive, and ulcerated mucosa of the splenic flexure of the colon, consistent with ischemic colitis; D: Normal mucosa of the sigmoid colon.

Table 1 Medications associated with ischemic colitis

Agent	Mechanism
Amphetamines	Vasoconstriction
Alosetron	
Catecholamines (epinephrine, norepinephrine)	
Cocaine	
Cyclosporine	
Digitalis	
Dopamine	
Ergot derivatives	
Nonsteriodal anti-inflammatory drugs	
Pseudoephedrine	
Triptans (Naratriptan, Rizatriptan, Sumatriptan)	
Vasopressin and vasopressin analogues	
Glycerin enema	Local vasospasm effect
Phosphosoda solution	
Angiotensin-converting enzyme inhibitors	Systemic hypotension
Antipsychotic (chlorpromazine)	
Beta blockers	
Barbiturates	
Diuretics	
Interleukin-2	
Tricyclic antidepressants	
Amphetamines	Vasculitis
Gold compounds	
Estrogens	Thrombotic lesion induction
Progestational agents	
Alosetron	Increased intracolic pressure
Danazol	
Glycerin enema	
Carboplatin	Undetermined
Flutamide	
Glutaraldehyde	
Hyperosmotic saline laxatives	
Interferon-α	
Mycophenolate mofetil	
Paclitaxel	
Simvastatin	
Tegaserod	

With permission to reuse from Elsevier[4].

of "non-vitamin, non-mineral, natural products" within the last 12 mo[5]. Factors associated with herbal supplements use are middle age, female gender, uninsured persons, and higher education[6]. Fifty eight percent of users do not disclose their use to their physicians[6].

Among the most popular herbal supplements used in the United States are weight-loss products as obesity is becoming epidemic in the United States affecting more than one-third of population[7]. These products are considered dietary supplements and are not regulated by the FDA[8]. Dietary supplement manufacturers only need low-level of evidence for their efficacy and safety to get market approval, with most studies of small sample size for a short duration[9]. In a systematic review of 19 human studies in 2009, the average number of participants was 64.4 (range: 24-153), and the average study duration was 15 wk (range: 2-36 wk)[9,10]. Under Dietary Supplement Health and Education Act, once a product is marketed, it is the FDA's responsibility to prove it unsafe before withdrawing or restricting its use, as opposed to conventional medications, for which pharmaceutical companies have to prove the safety of drug before marketing.

Hydroxycut is one of the most sold products among all weight-loss supplements. It is claimed to be a weight-loss aid, fat burner, and energy enhancer. Hydroxycut was introduced first containing ephedra as one of its components; however, after banning ephedra containing products by FDA in February 2004 for severe cardiovascular and neurologic toxicity, hydroxycut was withdrawn from the market and reformulated to exclude ephedra[4,11]. In May 2009, FDA warned consumers to stop taking any hydroxycut products due to 23 reported cases of severe serious health events related to Hydroxycut, especially liver toxicity resulting in one death[12].

The safety of hydroxycut (as well as its efficacy) is unstudied extensively and it is based on post-marketing case reports. Since 2004, after ephedra was withdrawn from hydroxycut, it has been reported 30 cases of serious medical conditions associated with hydroxycut ingestion including hepatotoxicity, in form of hepatocellular injury, immune-mediated hepatitis, or cholestasis patterns (n = 26), reversible cerebral vasoconstriction syndrome (n = 1), hypertensive retinopathy (n = 1), rhabdomyolysis (n = 1), atrial fibrillation (n = 1)[13-24].

Prior to May 2009, its primary ingredients included *Gymnema sylvestre*, *Garcinia cambogia*, Rhodiola rosea extract, Withania somnifera extract, *Citrus Aurantium*, chromium, caffeine, and green tea extract (as *Camellia sinensis*), however; it has been reformulated again since then to have a variety of different herbal mixtures including Lady's mantle extract (as *Alchenilla vulgaris*), Wild olive extract (as *Alea europaea*), Komijn extract (as *Cuminum cyminum*), Wild mint extract (as *Mentha longifolia*), Acerola concentrate (as *Malpighia glabra*), Goji extract (as *Lycium barbarum*), blueberry (as *vaccinium corymbosum*), Pomegranate (as *Punica grantum*), Bilberyy extract (as *Vaccinium myritillas*), Brazilian acai concentrate (as *Euterpe oleracea*), Green coffee extract (as *Cunephora robusta*), Cayenne pepper (as *Capsicum annuum*), Yohimbe extract (as *Pausinystalia yohimbe*), caffeine, many amino acids, vitamins and minerals[25].

It has not determined clearly which substance(s) is responsible for reported toxicities. It has been suggested hydroxycitric acid, *Garcinia cambogia*, chromium, epigallocatechi-2-gallate (EGCG), green tea extract (as *Camellia sinensis*), and contaminated chemicals or bacteria as the cause of hepatotoxicity; however studies' results are conflicting[13,16,20,26,27]. EGCG in Hydroxycut has been suggested as the suspected causative component for developing atrial fibrillation by blocking the atrial-specific *KCNA5* potassium channel[24].

The proposed mechanism for hydroxycut-induced ischemic colitis is the local vasoconstriction of vessels supplying the colon due to one or more substances. High dose of caffeine in hydroxycut has been suggested as a sympathomimetic agent causing vasoconstriction in the brain which might cause similar effects in other organs such as colon; however, it is unproven[21,22,28]. Chromium

Table 2 Naranjo adverse drug reaction nomogram in our patient

	Yes	No	Our patient
1: Are there previous conclusive reports on this reaction?	1	0	0
2: Did the adverse event appear after the suspected drug was administered?	2	-1	2
3: Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	1
4: Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5: Are there alternative causes (other than the drug) that could have, on their own, caused the reaction?	-1	2	2
6: Did the reaction appear when a placebo was given?	-1	1	1
7: Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	1	0	0
8: Was the reaction more severe when the dose was increased or less severe when dose was decreased?	1	0	0
9: Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10: Was the adverse event confirmed by any objective evidence?	1	0	1

Definite: Score ≥ 9; Probable: 5-8; Possible: 1-4; Doubtful: ≤ 0.

in prior formulas is another suggested substance to cause vasoconstriction by activating sympathetic nervous system[23]. Other components are also possible causes by causing direct or indirect vasoconstriction in susceptible subjects; especially hydroxycut has multiple ingredients with limited known information regarding their precise mechanisms of action. Hydroxycut may work in serotonergic or adrenergic systems as many conventional weight-loss medications, however, it is difficult to identify the exact ingredient or mechanism by which hydroxycut works or causes its side effects.

While causation is impossible to confirm, the temporal relationship between initiation of this product and development of ischemic colitis, in the light of absence of other etiologies, raises the suspicion of hydroxycut as a potential culprit in this case. When applying Naranjo nomogram in our patient, a score of 7 was granted indicating a probable likelihood (Table 2).

Naranjo nomogram for adverse drug reaction consists of 10 questions to assess the cause-effect relationship between any potential offending drug and any event. The likelihood of a drug-event relationship is defined as definitive if score is 9 or greater, probable if the score is 5-8, possible if the score is 1-4, and doubtful if the score is 0 or less[29]. It is considered a useful tool for evaluating the causality of any potential drug-induced event.

In conclusion, this is the first case report of ischemic colitis associated with ephedra-free weight-loss supplement hydroxycut. Our case demonstrates the importance of questioning patients regarding the usage of these supplements; especially since many patients consider them safe and do not disclose their use voluntarily to their physicians. Hydroxycut has to be considered as the potential cause for otherwise unexplained ischemic colitis.

REFERENCES

1 **Theodoropoulou A**, Koutroubakis IE. Ischemic colitis: clinical practice in diagnosis and treatment. *World J Gastroenterol* 2008; **14**: 7302-7308 [PMID: 19109863 DOI: 10.3748/wjg.14.7302]

2 **Strate LL**. Lower GI bleeding: epidemiology and diagnosis. *Gastroenterol Clin North Am* 2005; **34**: 643-664 [PMID: 16303575 DOI: 10.1016/j.gtc.2005.08.007]

3 **Stamatakos M**, Douzinas E, Stefanaki C, Petropoulou C, Arampatzi H, Safioleas C, Giannopoulos G, Chatziconstantinou C, Xiromeritis C, Safioleas M. Ischemic colitis: surging waves of update. *Tohoku J Exp Med* 2009; **218**: 83-92 [PMID: 19478463 DOI: 10.1620/tjem.218.83]

4 **Sherid M**, Ehrenpreis ED. Types of colitis based on histology. *Dis Mon* 2011; **57**: 457-489 [PMID: 21944389 DOI: 10.1016/j.disamonth.2011.05.004]

5 **Barnes PM**, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report* 2008; (**12**): 1-23 [PMID: 19361005]

6 **Gardiner P**, Graham R, Legedza AT, Ahn AC, Eisenberg DM, Phillips RS. Factors associated with herbal therapy use by adults in the United States. *Altern Ther Health Med* 2007; **13**: 22-29 [PMID: 17405675 DOI: 10.1186/1472-6882-7-39]

7 **Ogden CL**, Margaret D. Carroll MD. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1960–1962 Through 2007–2008. Available from: URL: http://www.cdc.gov/nchs/data/hestat/obesity_adult_07_08/obesity_adult_07_08.htm

8 Dietary Supplement Health and Education Act of 1994. Public Law 103-417. 103rd Congress. Available from: URL: http://ods.od.nih.gov/About/DSHEA_Wording.aspx

9 **Lobb A**. Science of weight loss supplements: compromised by conflicts of interest? *World J Gastroenterol* 2010; **16**: 4880-4882 [PMID: 20939120 DOI: 10.3748/wjg.v16.i38.4880]

10 **Hasani-Ranjbar S**, Nayebi N, Larijani B, Abdollahi M. A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. *World J Gastroenterol* 2009; **15**: 3073-3085 [PMID: 19575486 DOI: 10.3748/wjg.15.3073]

11 FDA Issues Regulation Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids and Reiterates Its Advice That Consumers Stop Using These Products. Available from: URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108242.htm

12 FDA Warns Consumers to Stop Using Hydroxycut Products. Dietary Supplements Linked to One Death; Pose Risk of Liver Injury. Available from: URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149575.htm

13 **Chen GC**, Ramanathan VS, Law D, Funchain P, Chen GC, French S, Shlopov B, Eysselein V, Chung D, Reicher S, Pham BV. Acute liver injury induced by weight-loss herbal supplements. *World J Hepatol* 2010; **2**: 410-415 [PMID: 21173910 DOI: 10.4254/wjh.v2.i11.410]

14 **Sharma T**, Wong L, Tsai N, Wong RD. Hydroxycut(®) (herbal weight loss supplement) induced hepatotoxicity: a case report and review of literature. *Hawaii Med J* 2010; **69**: 188-190 [PMID: 20845283]

15 **Rashid NN**, Grant J. Hydroxycut hepatotoxicity. *Med J Aust* 2010; **192**: 173-174 [PMID: 20121691]

16 **Shim M**, Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. *Dig Dis Sci* 2009; **54**: 406-408 [PMID: 18661239 DOI: 10.1007/s10620-008-0353-4]

17 **Fong TL**, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ, Hayashi P, Lee WM, Seeff LB. Hepatotoxicity due to hydroxycut: a case series. *Am J Gastroenterol* 2010; **105**: 1561-1566 [PMID: 20104221 DOI: 10.1038/ajg.2010.5]

18 **Jones FJ**, Andrews AH. Acute liver injury associated with the herbal supplement hydroxycut in a soldier deployed to Iraq. *Am J Gastroenterol* 2007; **102**: 2357-2358 [PMID: 17897352 DOI: 10.1111/j.1572-0241.2007.01353_10.x]

19 **Stevens T**, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. *Ann Intern Med* 2005; **142**: 477-478 [PMID: 15767636]

20 **Dara L**, Hewett J, Lim JK. Hydroxycut hepatotoxicity: a case series and review of liver toxicity from herbal weight loss supplements. *World J Gastroenterol* 2008; **14**: 6999-7004 [PMID: 19058338 DOI: 10.3748/wjg.14.6999]

21 **Cvetanovich GL**, Ramakrishnan P, Klein JP, Rao VR, Ropper AH. Reversible cerebral vasoconstriction syndrome in a patient taking citalopram and Hydroxycut: a case report. *J Med Case Rep* 2011; **5**: 548 [PMID: 22074635 DOI: 10.1186/1752-1947-5-548]

22 **Willis SL**, Moawad FJ, Hartzell JD, Iglesias M, Jackson WL. Hypertensive retinopathy associated with use of the ephedra-free weight-loss herbal supplement Hydroxycut. *MedGenMed* 2006; **8**: 82 [PMID: 17406200]

23 **Dehoney S**, Wellein M. Rhabdomyolysis associated with the nutritional supplement Hydroxycut. *Am J Health Syst Pharm* 2009; **66**: 142-148 [PMID: 19139478 DOI: 10.2146/ajhp070640]

24 **Karth A**, Holoshitz N, Kavinsky CJ, Trohman R, McBride BF. A case report of atrial fibrillation potentially induced by hydroxycut: a multicomponent dietary weight loss supplement devoid of sympathomimetic amines. *J Pharm Pract* 2010; **23**: 245-249 [PMID: 21507821 DOI: 10.1177/0897190010362104]

25 Hydroxycut products. Available from: URL: http://www.hydroxycut.com

26 **De Smet PA**. Herbal remedies. *N Engl J Med* 2002; **347**: 2046-2056 [PMID: 12490687 DOI: 10.1056/NEJMra020398]

27 **Stohs SJ**, Preuss HG, Ohia SE, Kaats GR, Keen CL, Williams LD, Burdock GA. No evidence demonstrating hepatotoxicity associated with hydroxycitric acid. *World J Gastroenterol* 2009; **15**: 4087-4089 [PMID: 19705510 DOI: 10.3748/wjg.15.4087]

28 **Kockler DR**, McCarthy MW, Lawson CL. Seizure activity and unresponsiveness after hydroxycut ingestion. *Pharmacotherapy* 2001; **21**: 647-651 [PMID: 11349754 DOI: 10.1592/phco.21.6.647.34542]

29 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245 [PMID: 7249508 DOI: 10.1038/clpt.1981.154]

P- Reviewers Chung WC, Contini S **S- Editor** Huang XZ
L- Editor A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.186

World J Gastrointest Endosc 2013 April 16; 5(4): 186-188
ISSN 1948-5190 (online)

CASE REPORT

Endoscopic retrieval of a duodenal perforating teaspoon

Ivo Boškoski, Andrea Tringali, Rosario Landi, Pietro Familiari, Anna Chiara Iolanda Contini, Claudio Pintus, Guido Costamagna

Ivo Boškoski, Andrea Tringali, Rosario Landi, Pietro Familiari, Guido Costamagna, Digestive Endoscopy Unit, Catholic University of Rome, 00168 Roma, Italy
Anna Chiara Iolanda Contini, Claudio Pintus, Pediatrics Department, Catholic University of Rome, 00168 Roma, Italy
Author contributions: Boškoski I, Tringali A, Landi R, Familiari P, Contini ACI, Pintus C and Costamagna G contributed equally to the paper.
Correspondence to: Ivo Boškoski, MD, Digestive Endoscopy Unit, Catholic University of Rome, Largo A. Gemelli, 8, 00168 Roma, Italy. ivoboskoski@yahoo.com
Telephone: +39-6-30156580 Fax: +39-6-30156581
Received: July 26, 2012 Revised: December 22, 2012
Accepted: January 5, 2013
Published online: April 16, 2013

Abstract

Foreign objects ingestion occur commonly in pediatric patients. The majority of ingested foreign bodies pass spontaneously the gastrointestinal tract and surgery is rarely required for extraction. Endoscopic removal of foreign bodies larger than 10 cm has not yet been described. We present the case of a 16 years old bulimic girl that swallowed a 12 cm long teaspoon in order to provoke vomiting. The teaspoon perforated the duodenum. However, it was removed during gastroscopy and the site of perforation was closed endoscopically. This particular case shows the importance of endoscopy for retrieval of large foreign bodies, and the possibility to endoscopically close a perforated duodenal wall.

Key words: Foreign body ingestion; Upper endoscopy; Bowel perforation; Bulimia

Boškoski I, Tringali A, Landi R, Familiari P, Contini ACI, Pintus C, Costamagna G. Endoscopic retrieval of a duodenal perforating teaspoon. *World J Gastrointest Endosc* 2013; 5(4): 186-188 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/186.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.186

INTRODUCTION

Foreign objects ingestion occur commonly in pediatric patients, psychiatric patients, and those suffering from bulimia or anorexia. Mostly 90% of the foreign bodies pass spontaneously the gastrointestinal tract, 10%-20% require endoscopic removal, and less than 1% require surgery[1].

Ingestion of long, sharp and rigid foreign bodies is associated with an increased risk of impaction, perforation and bleeding. Foreign bodies may also impact or perforate the bowel wall. Symptoms are variable and mostly related to the site of impaction or perforation of the bowel wall. Foreign bodies can also be found incidentally on X-rays done for other reasons.

Anatomical sites where foreign bodies impact most commonly are pylorus, duodenal C-loop and ileo-cecal valve. Foreign bodies longer than 10 cm mostly impact in the duodenal C-loop because this part is fixed in the retroperitoneum[2]. Endoscopic removal of these objects should be attempted in a way to avoid perforation and if this fails, surgery should be considered.

CASE REPORT

A 16-year-old bulimic girl swallowed a teaspoon in a way to induce vomiting. She informed the parents only 24 h later, when she had abdominal pain. On plain abdominal X-ray the teaspoon was in the right upper abdominal quadrant without evidence of intra-abdominal air (Figure 1A). On urgent upper endoscopy, there was a large amount of food in the stomach and in the duodenal bulb despite prolonged fasting. The tip of the teaspoon handle was found impacted into the duodenal mucosa at the level of the superior duodenal genu with suspected duodenal perforation (Figure 1B). With delicate maneuvers

using a rat-tooth forceps the impacted teaspoon handle was removed from the duodenal wall, brought into the stomach and then extracted. The spoon was 12 cm long, 2 cm large at the cup and 0.5 cm at the handle, which was sharp (Figure 1C). Control endoscopy was performed immediately after extraction of the teaspoon, and this confirmed perforation of the duodenal wall. The mucosal flaps on the site of perforation were closed by placing 5 clips (EZ clips long, Olympus, Tokyo, Japan), and by injection of 3 mL of fibrin glue (Beriplast, Nycomed, Germany) over the clips in a way to consolidate the closure. Air injection during endoscopy induced the onset of subcutaneous emphysema, which was diagnosed on palpation. On urgent computed tomography (CT) scan there was diffuse bilateral retro-pneumoperitoneum extending to the right inguinal region, with a small amount of fluid into the retro-duodenal region near the right kidney (Figure 1D).

White blood cells count was 12.240 (normal value 4.100-9.800), without fever. On physical examination there was abdominal tenderness without signs of peritonitis. The patient started *iv* therapy with broad spectrum antibiotics and proton pump inhibitors. Clinical course was uneventful during the following days, and white blood cells count normalized without occurrence of fever. Four days later upper gastrointestinal enema with water soluble contrast confirmed the absence of leaks at the site of perforation. On control CT scan after 7 d diffuse retro-peritoneum was still present without evidence of fluid collections and upper endoscopy confirmed complete closure of the perforation. One week later the patient started oral nutrition and was discharged in good clinical conditions.

DISCUSSION

Swallowing of large objects (> 10 cm) may occur, but these usually do not pass spontaneously through the gastrointestinal tract, and often require urgent surgery due to perforation[2]. In the setting of intentional foreign body ingestion, the rate of endoscopic intervention may be much higher (63%-76%) and the need for surgical intervention ranges from 12% to 16%[3,4]. This however depends on the size of the foreign body (usually < 10 cm). Mortality rate in these patients is extremely low[5]. The technique of fibrin glue injection has already been described[6]. Our patient developed diffuse subcutaneous emphysema during endoscopy. The use of carbon dioxide instead of air should be preferred in these circumstances because of much more rapid reabsorption. Timing of endoscopy in these patients is very important, in order to reduce the risk of bacterial contamination in case of perforation[5].

This particular case shows the importance of endoscopy for retrieval of large foreign bodies, and the possibility to endoscopically close a perforated duodenal wall. The endoscopic approach was essential in this case and avoided surgery to this young patient.

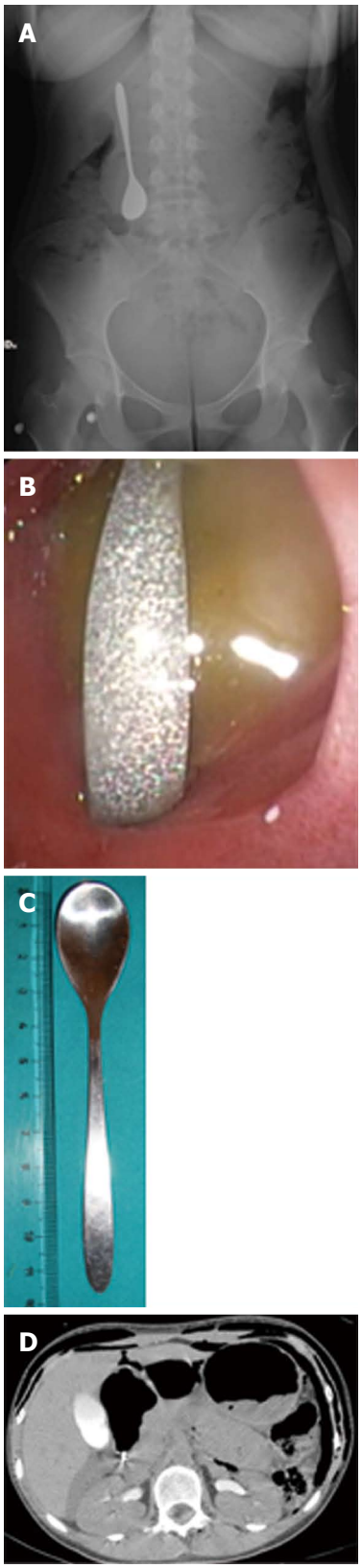


Figure 1 Endoscopic retrieval of a duodenal perforating teaspoon. A: Plain abdominal X-ray showing the teaspoon in the right upper abdominal quadrant. Note the absence of free intra-abdominal air; B: The tip of the teaspoon handle impacted into the duodenal mucosa at the level of the superior duodenal genu; C: The spoon after extraction: 12 cm long, 2 cm large at the cup and 0.5 cm at the handle; D: Urgent computed tomography scan showing diffuse bilateral retro-pneumoperitoneum extending to the right inguinal region, with a small amount of fluid into the retro-duodenal region near the right kidney.

REFERENCES

1 **Arana A**, Hauser B, Hachimi-Idrissi S, Vandenplas Y. Management of ingested foreign bodies in childhood and review of the literature. *Eur J Pediatr* 2001; **160**: 468-472 [PMID: 11548183 DOI: 10.1007/s004310100788]

2 **Karcz WK**, Kulemann B, Seifert GJ, Schrag HJ, Küsters S, Marjanovic G, Grüneberger JM, Braun A. Video. Laparoscopic extirpation of a fork from the duodenum. *Surg Endosc* 2011; **25**: 2363 [PMID: 21416187 DOI: 10.1007/s00464-010-1533-9]

3 **Palta R**, Sahota A, Bemarki A, Salama P, Simpson N, Laine L. Foreign-body ingestion: characteristics and outcomes in a lower socioeconomic population with predominantly intentional ingestion. *Gastrointest Endosc* 2009; **69**: 426-433 [PMID: 19019363 DOI: 10.1016/j.gie.2008.05.072]

4 **Simic MA**, Budakov BM. Fatal upper esophageal hemorrhage caused by a previously ingested chicken bone: case report. *Am J Forensic Med Pathol* 1998; **19**: 166-168 [PMID: 9662114 DOI: 10.1097/00000433-199806000-00013]

5 **Ikenberry SO**, Jue TL, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, Decker GA, Fanelli RD, Fisher LR, Fukami N, Harrison ME, Jain R, Khan KM, Krinsky ML, Maple JT, Sharaf R, Strohmeyer L, Dominitz JA. Management of ingested foreign bodies and food impactions. *Gastrointest Endosc* 2011; **73**: 1085-1091 [PMID: 21628009 DOI: 10.1016/j.gie.2010.11.010]

6 **Mutignani M**, Iacopini F, Dokas S, Larghi A, Familiari P, Tringali A, Costamagna G. Successful endoscopic closure of a lateral duodenal perforation at ERCP with fibrin glue. *Gastrointest Endosc* 2006; **63**: 725-727 [PMID: 16564890 DOI: 10.1016/j.gie.2005.11.028]

P- Reviewer Ciaccio EJ **S- Editor** Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.189

World J Gastrointest Endosc 2013 April 16; 5(4): 189-190
ISSN 1948-5190 (online)

CASE REPORT

Diagnosis of *Ascaris lumbricoides* infection using capsule endoscopy

Eduardo Tomohissa Yamashita, Wagner Takahashi, Daniel Yuiti Kuwashima, Tiago Ribeiro Langoni, Adriana Costa-Genzini

Eduardo Tomohissa Yamashita, Wagner Takahashi, Daniel Yuiti Kuwashima, Tiago Ribeiro Langoni, Adriana Costa-Genzini, Advanced Center of Diagnostic and Therapeutic Endoscopy, UNIMED Santa Helena Hospital, 01508-000 São Paulo, Brazil

Author contributions: All authors contributed to the preparation of this manuscript; Yamashita ET, Kuwashima DY and Langoni TR wrote the text and prepared the figures; Costa-Genzini A and Takahashi W made revisions and gave final approval of the version to be published.

Correspondence to: Eduardo Tomohissa Yamashita, MD, Advanced Center of Diagnostic and Therapeutic Endoscopy, UNIMED Santa Helena Hospital, Rua São Joaquim, 36 - 2º andar do Centro Médico, Liberdade, 01508-000 São Paulo, Brazil. edutomo@gmail.com
Telephone: +55-11-30917978 Fax: +55-11-38138587

Received: October 1, 2012 Revised: November 5, 2012
Accepted: January 5, 2013
Published online: April 16, 2013

Abstract

Ascaris lumbricoides (*A. lumbricoides*) is the most common intestinal roundworm parasite, infecting approximately one quarter of the world's population. Infection can lead to various complications because it can spread along the gastrointestinal tract. Although *A. lumbricoides* infection is a serious healthcare issue in developing countries, it now also has a worldwide distribution as a result of increased immigration and travel. Intestinal obstruction is the most common complication of *A. lumbricoides* infection, potentially leading to even more serious consequences such as small bowel perforation and peritonitis. Diagnosis is based primarily on stool samples and the patient's history. Early diagnosis, aided in part by knowledge of the local prevalence, can result in early treatment, thereby preventing surgical complications associated with intestinal obstruction. Further, delay in diagnosis may have fatal consequences. Capsule endoscopy can serve as a crucial, non-invasive diagnostic tool for *A. lumbricoides* infection, especially when other diagnostic methods have failed to detect the parasite. We report a case of *A. lumbricoides* infection that resulted in intestinal obstruction at the level of the ileum. Both stool sample examination and open surgery failed to indicate the presence of *A. lumbricoides*, and the cause of the obstruction was only revealed by capsule endoscopy. The patient was treated with anthelmintics.

Key words: Capsule endoscopy; *Ascaris lumbricoides*; Intestinal obstruction

Yamashita ET, Takahashi W, Kuwashima DY, Langoni TR, Costa-Genzini A. Diagnosis of *Ascaris lumbricoides* infection using capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(4): 189-190 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/189.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.189

INTRODUCTION

Ascaris lumbricoides (*A. lumbricoides*) has a worldwide distribution, but occurs most frequently in underdeveloped regions where sanitation is poor[1,2]. In most cases the infection remains asymptomatic until the number of worms in the intestines increases considerably. It can cause serious complications, the most common of which is intestinal obstruction, although pancreatitis, cholangitis, bleeding, and obstructive jaundice can also occur[3,4]. The diagnosis of *A. lumbricoides* infection is based mainly on patient history and stool samples, but complementary exams such as abdominal radiography and computed tomography can also aid in the diagnosis[5]. We report a case of *A. lumbricoides* infection that resulted in intestinal obstruction. Although the obstruction was apparent during open surgery and imaging, neither they, nor the stool

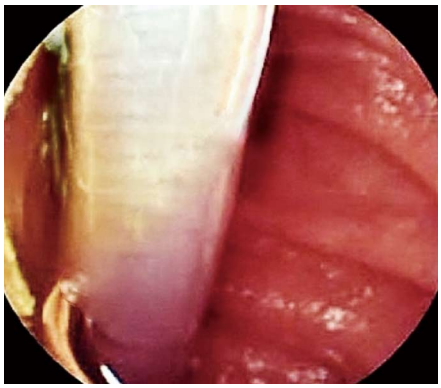


Figure 1 *Ascaris lumbricoides* roundworm physically blocking the small bowel.

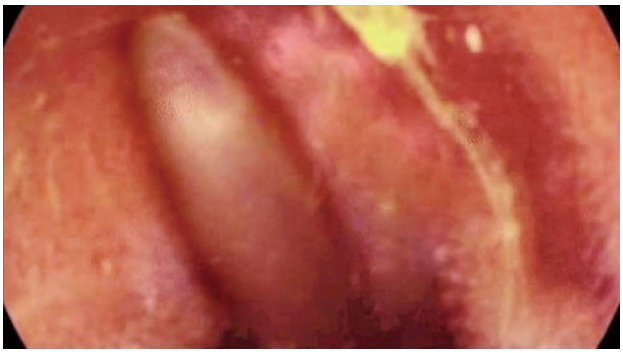


Figure 2 Infection of the ileum with live *Ascaris lumbricoides*.

samples analysis revealed the presence of *A. lumbricoides*. The presence of this parasite was however determined by video capsule endoscopy.

CASE REPORT

A 64-year-old Brazilian woman presented with abdominal discomfort and intermittent subocclusive episodes that had developed over the previous few weeks. The discomfort was relieved by evacuation. Physical examination indicated good health, and no abdominal tenderness was noted. The patient had undergone 2 previous exploratory laparoscopy procedures to examine the subocclusion, but the findings were normal. A stool sample was analyzed to detect the possible presence of a parasitic infection, but the findings were negative. However, contrast radiography and computed tomography revealed a partial obstruction with an undetermined tube-like structure at the level of the ileum, suggesting a parasitic infection. Capsule endoscopy (MiroCam capsule; Intromedic, Seoul, South Korea) was performed to determine the cause of the obstruction. A diagnosis of roundworm infection with partial obstruction of the ileum with live *A. lumbricoides* was confirmed (Figures 1 and 2). The first roundworm was seen 1 h 34 min after capsule ingestion (Figure 1) and the last one was seen 2 h later (Figure 2). Treatment with albendazole and piperazine was initiated, and the patient made a full recovery.

DISCUSSION

A. lumbricoides is the most common intestinal helminth parasite, infecting approximately one quarter of the world's population[6]. It has long been endemic in developing countries, but it now has a worldwide distribution due to the increase in immigration and travel[7]. Capsule endoscopy is an important tool for evaluation of small bowel disorders, allowing for non-invasive diagnosis of many diseases. In this case, it was used successfully to reveal the cause of intestinal obstruction as being due to *A. lumbricoides* infection. This was after stool sample analysis and open surgery, which are currently considered to be the gold standard for *A. lumbricoides*.

REFERENCES

1 **Cooper PJ**, Chico ME, Sandoval C, Espinel I, Guevara A, Kennedy MW, Urban Jr JF, Griffin GE, Nutman TB. Human infection with Ascaris lumbricoides is associated with a polarized cytokine response. *J Infect Dis* 2000; **182**: 1207-1213 [PMID: 10979919 DOI: 10.1086/315830]

2 **Ziegelbauer K**, Speich B, Mäusezahl D, Bos R, Keiser J, Utzinger J. Effect of sanitation on soil-transmitted helminth infection: systematic review and meta-analysis. *PLoS Med* 2012; **9**: e1001162 [PMID: 22291577 DOI: 10.1371/journal.pmed.1001162]

3 **Akgun Y**. Intestinal obstruction caused by Ascaris lumbricoides. *Dis Colon Rectum* 1996; **39**: 1159-1163 [PMID: 8831534 DOI: 10.1007/BF02081419]

4 **de Silva NR**, Guyatt HL, Bundy DA. Morbidity and mortality due to Ascaris-induced intestinal obstruction. *Trans R Soc Trop Med Hyg* 1997; **91**: 31-36 [PMID: 9093623 DOI: 10.1016/S0035-9203(97)90384-9]

5 **Reeder MM**. The radiological and ultrasound evaluation of ascariasis of the gastrointestinal, biliary, and respiratory tracts. *Semin Roentgenol* 1998; **33**: 57-78 [PMID: 9516689 DOI: 10.1016/S0037-198X(98)80031-X]

6 **Zheng PP**, Wang BY, Wang F, Ao R, Wang Y. Esophageal space-occupying lesion caused by Ascaris lumbricoides. *World J Gastroenterol* 2012; **18**: 1552-1554 [PMID: 22509089 DOI: 10.3748/wjg.v18.i13.1552]

7 **Masucci L**, Graffeo R, Bani S, Bugli F, Boccia S, Nicolotti N, Fiori B, Fadda G, Spanu T. Intestinal parasites isolated in a large teaching hospital, Italy, 1 May 2006 to 31 December 2008. *Euro Surveill* 2011; **16**: 19891 [PMID: 21699767]

P- Reviewer Tokuhara D **S- Editor** Song XX
L- Editor A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.191

World J Gastrointest Endosc 2013 April 16; 5(4): 191-196
ISSN 1948-5190 (online)

CASE REPORT

Mucosal-incision assisted biopsy for suspected gastric gastrointestinal stromal tumors

Eikichi Ihara, Hiroshi Matsuzaka, Kuniomi Honda, Yoshitaka Hata, Yorinobu Sumida, Hirotada Akiho, Tadashi Misawa, Satoshi Toyoshima, Yoshiharu Chijiiwa, Kazuhiko Nakamura, Ryoichi Takayanagi

Eikichi Ihara, Kazuhiko Nakamura, Ryoichi Takayanagi, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka 812-8582, Japan
Hiroshi Matsuzaka, Yoshiharu Chijiiwa, Department of Gastroenterology, Hara-Sanshin General Hospital, Fukuoka 812-0033, Japan
Kuniomi Honda, Yoshitaka Hata, Yorinobu Sumida, Hirotada Akiho, Tadashi Misawa, Department of Gastroenterology, Kitakyushu Municipal Medical Center, Kokurakitaku, Kitakyushu 802-0077, Japan
Satoshi Toyoshima, Department of Pathology, Kitakyushu Municipal Medical Center, Kokurakitaku, Kitakyushu 802-0077, Japan
Author contributions: Ihara E, Matsuzaka H, Honda K, Hata Y, Sumida Y, Akiho H and Misawa T performed procedure of mucosal-incision assisted biopsy; Ihara E mainly wrote the manuscript; Toyoshima S contributed to pathological analysis of the biopsied samples; Misawa T, Chijiiwa Y, Nakamura K and Takayanagi R designed the study and edited the manuscript.
Correspondence to: Eikichi Ihara, MD, PhD, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. eikichi@intmed3.med.kyushu-u.ac.jp
Telephone: +81-92-6425286 Fax: +81-92-6425287
Received: November 2, 2012 Revised: January 16, 2013
Accepted: January 23, 2013
Published online: April 16, 2013

Abstract

To evaluate the diagnostic yield of the procedure, mucosal-incision assisted biopsy (MIAB), for the histological diagnosis of gastric gastrointestinal stromal tumor (GIST), we performed a retrospective review of the 27 patients with suspected gastric GIST who underwent MIAB in our hospitals. Tissue samples obtained by MIAB were sufficient to make a histological diagnosis (diagnostic MIAB) in 23 out of the 27 patients, where the lesions had intraluminal growth patterns. Alternatively, the samples were insufficient (non-diagnostic MIAB) in remaining 4 patients, three of whom had gastric submucosal tumor with extraluminal growth patterns. Although endoscopic ultrasound and fine needle aspiration is the gold standard for obtaining tissue specimens for histological and cytological analysis of suspected gastric GISTs, MIAB can be used as an alternative method for obtaining biopsy specimens of lesions with an intraluminal growth pattern.

Key words: Endoscopic ultrasound-guided fine-needle aspiration; Gastrointestinal stromal tumor; Mucosal-incision assisted biopsy; Submucosal tumor; Endoscopic submucosal dissection

Ihara E, Matsuzaka H, Honda K, Hata Y, Sumida Y, Akiho H, Misawa T, Toyoshima S, Chijiiwa Y, Nakamura K, Takayanagi R. Mucosal-incision assisted biopsy for suspected gastric gastrointestinal stromal tumors. *World J Gastrointest Endosc* 2013; 5(4): 191-196 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/191.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.191

INTRODUCTION

Gastric submucosal tumors (SMTs) are a wide range of diverse conditions including neoplastic lesions such as gastrointestinal stromal tumor (GIST), leiomyoma, leiomyosarcoma, schwannoma, granular cell tumor and non-neoplastic lesions such as inflammatory fibroid polyp, gastric varices, heterotopic pancreas and heterotopic gastric mucosa[1,2]. Endoscopic ultrasonography (EUS) is one of the most useful modalities for diagnosing gastric SMTs[3,4]. However, it is usually not possible to differentiate GIST from benign conditions such as leiomyoma or schwannoma by EUS. Tissue sampling is necessary for definitive diagnosis of GIST. Endoscopic ultrasound-

guided fine-needle aspiration (EUS-FNA) has been developed for tissue sampling of suspected GIST and is generally accepted to be a very useful for the diagnosis of this lesion[5]. When considering the diagnostic yield of EUS-FNA for suspected gastric GIST, it is important to evaluate whether the samples obtained are adequate for both cytological and histological analysis, as immunohistological analysis is indispensable for a definitive diagnosis. In general, the success rate of EUS-FNA for tissue sampling for cytology has been reported to be relatively high (83%), but the success rate for histology does not seem to be satisfactory (62%)[6]. Therefore, there has been an interest in exploring an alternative modality for tissue sampling in suspected GIST.

Endoscopic submucosal dissection (ESD) has been developed as an advanced endoscopic therapy for superficial gastric neoplasms[7] and ESD has rapidly become widely used. In this situation we have become interested in using ESD-associated techniques for tissue sampling of suspected GIST instead of using EUS-FNA. More recently, Lee *et al*[8] has shown the cases where the ESD-associated technique was useful for tissue sampling of suspected GISTs. It remains, however, to be determined whether the ESD-associated technique would be suitable for tissue sampling of any of suspected GISTs. Although an official term for this procedure has yet to be determined, we have named it mucosal-incision assisted biopsy (MIAB). We reviewed 27 cases with gastric SMTs in which MIAB was performed to obtain biopsy specimens. In the present study, we have shown that MIAB can be as an alternative diagnostic modality for tissue sampling of suspected GISTs when the lesions have an intraluminal growth pattern. MIAB may be contraindicated in suspected gastric GISTs with an extraluminal growth pattern.

CASE REPORT

We undertook a retrospective review of the 27 patients with gastric SMTs who underwent MIAB in our hospitals between May 2005 and August 2011 in order to distinguish GIST from benign causes of SMT. An extraluminal growth pattern was defined as growth in an extraluminal direction with little intraluminal growth. An intraluminal growth pattern was defined as growth in an intraluminal direction, regardless of any extraluminal growth. Informed consent was obtained from all patients before MIAB was undertaken. MIAB was performed as follows; In brief, a mucosal incision line was chosen which was usually not directly over the lesion, for easier closure with endoclips after the biopsy. Saline with 0.001% epinephrine was injected into the submucosa at the chosen incision line. A mucosal incision was made in the same way as the circumferential mucosal incision is made for ESD, using electrosurgical knives such as the flush knife or needle knife, followed by careful submucosal dissection until a portion of the SMT was exposed. When a single mucosal incision did not provide satisfactory exposure, an second incision was made perpendicular to the first incision. Several biopsy specimens were taken under direct vision using conventional biopsy forceps. The mucosal incisions were then closed with endoclips to prevent post-procedure complications including bleeding and/or perforation. The biopsy samples obtained by MIAB were fixed in formalin solution and stained with hematoxylin and eosin (HE). If applicable, specimens underwent immunohistochemical analysis. Applicable data were expressed as the mean ± SE.

Characteristics of patients who underwent MIAB

Individual patient characteristics are shown in Table 1 and a summary is shown in Table 2. Fourteen females and 13 males were included in the study, with a mean age of 58.9 ± 2.4 years. Gastric SMT lesions were 10-36 mm in diameter with a mean diameter of 21.2 ± 1.0 mm. In 23 of the 27 patients, tissue samples obtained by MIAB were sufficient to make a histological diagnosis (diagnostic MIAB). We diagnosed GIST in 16 patients, leiomyoma in 4 patients, aberrant pancreas in one patient, inflammatory granuloma in one patient, and glomus tumor in one patient. In 23 patients with diagnostic MIAB, all of the lesions had intraluminal growth patterns. Fourteen of sixteen patients underwent surgical resection based on a preoperative diagnosis of GIST; the other patients (Cases 5 and 15) did not accept surgical resection and is currently under close follow-up. The post-operative pathological findings in all fourteen cases of GIST were identical to those obtained with MIAB, including findings on HE staining and immunohistochemical analysis. On the other hand, four patients (Cases 17, 25-27) resulted in non-diagnostic MIAB. In three of them, the SMT lesions had extraluminal growth patterns. In one patient with non-diagnostic MIAB (Case 17), the samples obtained by MIAB suggested a spindle cell tumor on HE staining. We could not obtain the further pathological diagnosis. In this case, since the lesion was growing rapidly and suspected to be a GIST, a surgical resection was performed. As a result, the final pathological diagnosis after surgery was a GIST (Table 1). The mean procedure time was 32.0 ± 2.4 min and no procedure-related complications (including uncontrolled bleeding or perforation) were observed. We present two representative cases below.

Case 1

A 70-year-old man was referred to our hospital for evaluation of a suspected gastric SMT. EGD revealed a solid, round, protruding lesion covered with normal mucosa, measuring about 20 mm in diameter, at the middle of the lesser curvature of the body of the stomach (Figure 1A). EUS with a miniature probe showed a hypoechoic mass was observed, which originated from the 4th layer (muscularis propria) (Figure 1B), confirming that the lesion was an SMT. The lesion was thought to be a gastrointestinal mesenchymal tumor (GIMT) such as a GIST, leiomyoma or schwannoma. EUS findings showed an intraluminal growth pattern. MIAB was performed to obtain biopsy samples for histological diagnosis. Two mucosal incision

Table 1 Characteristics of the patients with submucosal tumor who underwent mucosal-incision assisted biopsy

Case	Age	Sex	Location of SMT	Size (mm)	Growth pattern	Diagnosis by MIAB	Post-operativediagnosis
1	70	M	Body, LC	21	Intraluminal	GIST	GIST
2	60	M	Body, LC	20	Intraluminal	GIST	GIST
3	55	F	Angulus, LC	36	Intraluminal	GIST	GIST
4	73	M	Body, LC	26	Intraluminal	GIST	GIST
5	72	F	Body, LC	20	Intraluminal	GIST	Not applicable
6	69	F	Fundus	19	Intraluminal	GIST	GIST
7	72	F	Body, LC	23	Intraluminal	GIST	GIST
8	53	M	Body, PW	23	Intraluminal	GIST	GIST
9	79	F	Body, GC	24	Intraluminal	GIST	GIST
10	66	F	Angulus, GC	22	Intraluminal	GIST	GIST
11	66	F	Body, PW	25	Intraluminal	GIST	GIST
12	39	M	Body, PW	15	Intraluminal	GIST	GIST
13	58	M	Body, GC	20	Intraluminal	GIST	GIST
14	24	M	Cardia, AW	30	Intraluminal	GIST	GIST
15	60	F	Body, PW	10	Intraluminal	GIST	Not applicable
16	57	M	Body, PW	20	Intraluminal	GIST	GIST
17	40	F	Body, PW	30	Intraluminal	IS	GIST
18	55	M	Cardia, LC	23	Intraluminal	Leiomyoma	Not applicable
19	36	F	Cardia, LC	19	Intraluminal	Leiomyoma	Not applicable
20	62	F	Cardia, LC	25	Intraluminal	Leiomyoma	Not applicable
21	57	F	Body, LC	15	Intraluminal	Leiomyoma	Not applicable
22	50	M	Antrum, AW	20	Intraluminal	Glomus tumor	Glomus tumor
23	63	M	Body, LC	20	Intraluminal	Aberrant pancreas	Not applicable
24	57	M	Body, GC	20	Intraluminal	Inflammatory change	Not applicable
25	66	M	Body, GC	15	Extraluminal	IS	Not applicable
26	71	F	Body, LC	15	Extraluminal	IS	Not applicable
27	61	F	Antrum, GC	17	Extraluminal	IS	Not applicable

IS: Insufficient samples for diagnosis; GIST: Gastrointestinal stromal tumor; MIAB: Mucosal-incision assisted biopsy; SMT: Submucosal tumor; PW: Posterior wall; LC: Lesser curvature; GC: Greater curvature; M: Male; F: Female.

Table 2 Summary of the cases which underwent mucosal-incision assisted biopsy

Age	58.9 ± 2.4 (27)
Sex	Female (13)/male (14)
Location of SMT	Fundus (1)
	Cardia (4)
	Body (18)
	Angulus (2)
	Antrum (2)
Size of the lesion (mm)	21.2 ± 1.0 (27)
Growth pattern	Intraluminal (24)
	Extraluminal (3)
Diagnosis by MIAB	GIST (16)
	Leiomyoma (4)
	Aberrant pancreas (1)
	Inflammatory changes (1)
	Glomus tumor (1)
	Not diagnosed (4)

GIST: Gastrointestinal stromal tumor; MIAB: Mucosal-incision assisted biopsy; SMT: Submucosal tumor.

lines were made perpendicular to each other to expose the surface of the SMT (Figure 1C) and tissue samples were successfully obtained (Figure 1D), followed by closure of the mucosal incisions with endoclips (Figure 1E). Pathological examination of the biopsy specimens showed a spindle cell mesenchymal tumor with abundant hyalinized fibrous stroma on HE staining. Immunohistochemical analysis was positive for c-Kit and CD34 and negative for desmin, which enabled us to make a diagnosis of GIST. The patient underwent surgical resection of the lesion. The final pathological diagnosis after surgery was GIST with a 21 mm diameter and mitotic index less than 5/50 HPFs, indicating a very low risk GIST according to Miettinen *et al*[9] (Figure 1F).

Case 25

A 66-year-old man was referred to our hospital for evaluation of a suspected gastric SMT at the greater curvature of the lower body. EGD did not initially reveal any lesion (Figure 2A), but an SMT-like lesion was detected later during the examination (Figure 2B). As we were unable to detect the lesion by EUS with a miniature prove, conventional EUS was undertaken, revealing a hypoechoic, oval mass originating from the 4th layer (Figure 2C) which was suggestive of a GIMT such as a GIST, leiomyoma or schwannoma. The lesion had an extraluminal growth pattern. MIAB was undertaken to obtain biopsy specimens for a histological diagnosis. In this case we were unable to expose the lesion clearly due to risk of perforation (Figure 2D and E). The lesion appeared to be covered with normal smooth muscle of the muscularis propria. Some tissue samples were obtained, followed by closure of the incision with endoclips (Figure 2F). Pathological examination of the biopsy specimens with HE staining showed fascicles of smooth muscle cells accompanied by small fragments of spindle-shaped cells. Immunohistochemical analysis showed that the spindle-shaped cells were probably positive for c-Kit and CD34. These findings

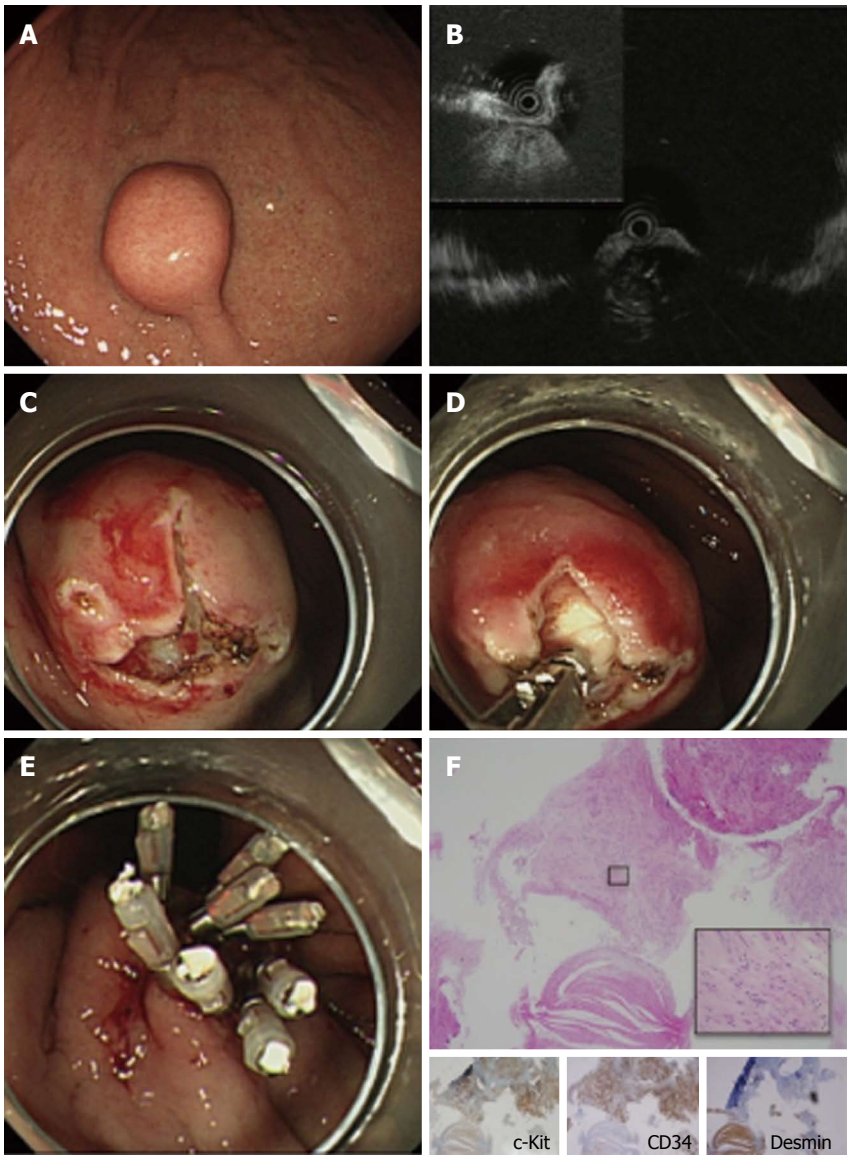


Figure 1 Case 1 of gastrointestinal stromal tumor which underwent mucosal incision assisted biopsy. A: Endoscopic image of the lesion. The lesion was covered by normal mucosa with a bridging fold; B: Endoscopic ultrasonography imaging of the lesion with a miniature probe. The lesion was located in the 4th layer (muscularis propria); C: Two mucosal incisions were made to expose a portion of the lesion; D: Tissue samples were obtained using biopsy forceps; E: Closure of the mucosal incisions with endoclips; F: Pathological examination of the biopsied specimen. Immunohistochemical analysis showed that the lesion was positive for c-Kit and CD34 and negative for desmin. The biopsy samples also contained normal smooth muscle tissue, which was negative for c-Kit and CD34 and positive for desmin.

were suggestive of GIST, but not conclusive. In this case, MIAB was considered a non-diagnostic procedure.

DISCUSSION

In the present study, we retrospectively reviewed 27 cases with suspected GIST, in which MIAB was undertaken to obtain tissue samples for histological diagnosis. A definitive histological diagnosis was obtained in 23 of the 27 patients (85.2 %) who had gastric SMTs with intraluminal growth pattern. MIAB resulted in insufficient tissue sampling in the other four patients. In three of them, the SMT lesions had extraluminal growth patterns. We have shown that MIAB can be as an alternative diagnostic modality for tissue sampling of suspected GISTs when the lesions have an intraluminal growth pattern. MIAB may be contraindicated in suspected gastric GISTs with an extraluminal growth pattern[10,11].

EUS-FNA has been developed for tissue sampling and analysis of suspected GIST and plays an important role in making a histological diagnosis of this lesion[5]. Even though EUS-FNA has become the gold standard for obtaining biopsy samples for cytological and histological analysis of suspected gastric GIST, the procedure does not seem satisfactory. Mekky *et al*[6] recently reported the diagnostic yield from EUS-FNA for a total of 141 patients with gastric SMTs. They reported adequate samples in 117 of 141 cases (83%). In 29 cases of the 117 cases, however, the samples were sufficient for suggestion of a diagnosis based on cytological examination, but were inadequate for immunohistochemical analysis. Adequate samples for histological diagnosis were there-

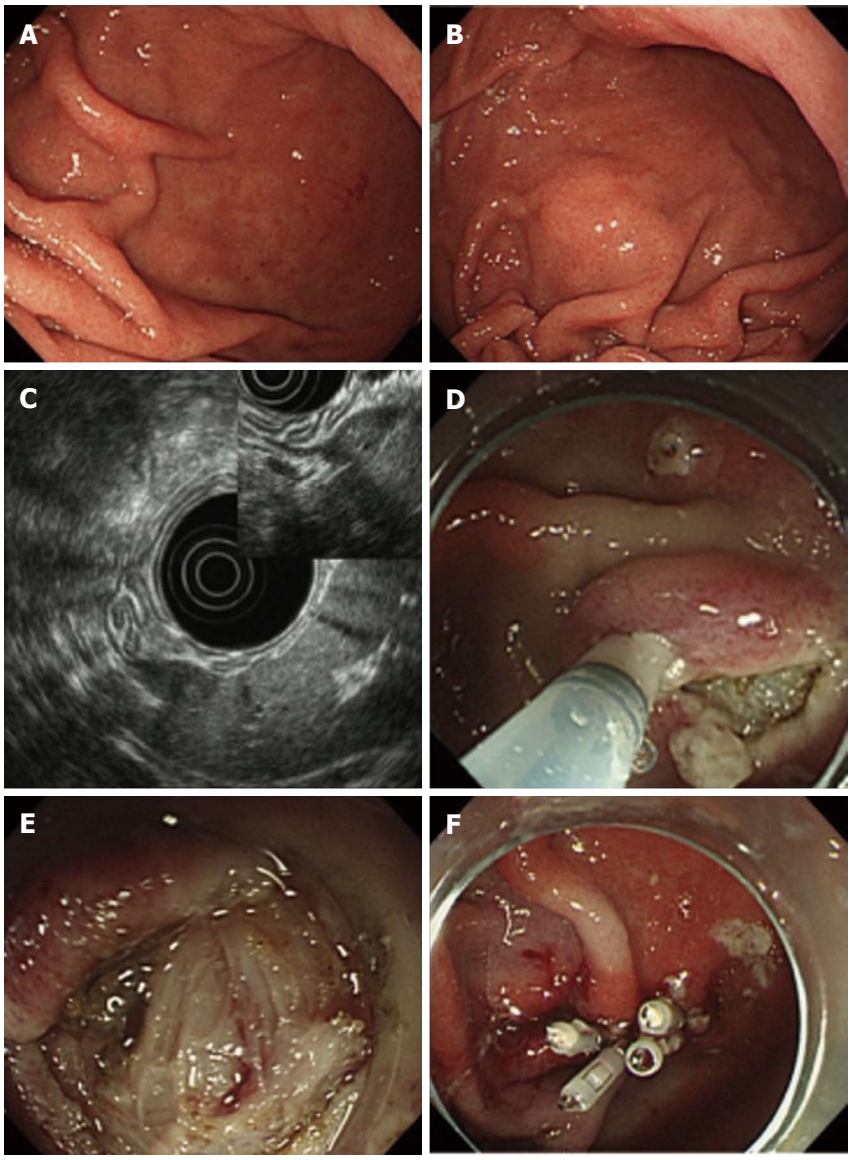


Figure 2 Case 25 of submucosal tumor with an extraluminal growth pattern in which mucosal incision assisted biopsy was non-diagnostic. A: No submucosal tumor (SMT)-like lesion was initially detected; B: Later during the procedure, the SMT-like lesion was detectable; C: Conventional endoscopic ultrasonography showed that the lesion was located in the 4th layer (muscularis propria) and had an extraluminal growth pattern; D, E: Due to the risk of perforation, the lesion could not be clearly exposed. The lesion appeared to be covered with the normal smooth muscle of the muscularis propria; F: Closure of the mucosal incision with endoclips. Pathological examination of the biopsy samples suggested gastrointestinal stromal tumor, but was not conclusive.

fore obtained in only 88 of 141 cases (62%). Since immunohistochemical analysis is indispensable for a definitive diagnosis of GIST, the diagnostic yield of EUS-FNA for suspected GIST was not satisfactory. Therefore, there has been an interest in developing an alternative modality for tissue sampling of suspected GIST. Reasonably, we have become interested in using ESD-associated techniques for tissue sampling of suspected GIST instead of using EUS-FNA as recently shown by Lee *et al*[8].

MIAB has the following advantages over EUS-FNA. First, MIAB would be less costly than EUS-FNA. Although both ESD and EUS-FNA require a high skill level, ESD only needs an electrosurgical generator and electrosurgical knives (such as the flush knife, insulation-tipped electrosurgical knife, or grasping-type scissors forceps[12], and does not need expensive equipment such as the linear echoendoscopy used for EUS-FNA. Second, on-site cytologists are not required for MIAB, whereas they need to be scheduled for successful EUS-FNA. Third, when the gastric SMT proves to be a GIST, tissue samples obtained by MIAB are large enough for pathologists to calculate or estimate the Ki-67 labeling index, which gives information about the relative risk of malignant behavior. Calculation of the Ki-67 labeling index is not possible with EUS-FNA biopsy samples. It is very advantageous to have an indication of the risk of malignant behavior of a GIST before surgical resection.

There are, however, some disadvantages and limitations to MIAB. First, MIAB does not seem to be appropriate for tissue sampling of gastric SMTs with an extraluminal growth pattern. In our study, MIAB was non-diagnostic in cases 25-27 in which the gastric SMTs

had an extraluminal growth pattern. In contrast, EUS-FNA is generally considered to be useful for obtaining tissue samples of gastric SMTs regardless of growth patterns. Other possible disadvantages are procedure-related complications including bleeding and perforation. MIAB may have a higher rate of procedure-related bleeding than EUS-FNA, but all bleeding was easily controlled by endoscopic hemostatic procedures in our cases. No perforation occurred in our cases, but extra care should be taken to prevent perforation in cases with an extraluminal growth pattern. It is not known whether procedure-related dissemination will be a possible late complication, but this has not been reported to date. It is important to close the mucosal incisions appropriately with endoclips after tissue sampling to prevent post-procedure complications.

In conclusion, although it is generally accepted that EUS-FNA is the gold standard for obtaining biopsies for histological and cytological analysis of suspected gastric GIST, MIAB may be chosen as an alternative diagnostic modality only when the lesion has an intraluminal growth pattern. Further studies will be required to further assess MIAB, including randomized controlled trials to compare MIAB with EUS-FNA.

REFERENCES

1 **Papanikolaou IS**, Triantafyllou K, Kourikou A, Rösch T. Endoscopic ultrasonography for gastric submucosal lesions. *World J Gastrointest Endosc* 2011; **3**: 86-94 [PMID: 21772939 DOI: 10.4253/wjge.v3.i5.862]

2 **Ponsaing LG**, Kiss K, Loft A, Jensen LI, Hansen MB. Diagnostic procedures for submucosal tumors in the gastrointestinal tract. *World J Gastroenterol* 2007; **13**: 3301-3310 [PMID: 17659668]

3 **Buscarini E**, Stasi MD, Rossi S, Silva M, Giangregorio F, Adriano Z, Buscarini L. Endosonographic diagnosis of submucosal upper gastrointestinal tract lesions and large fold gastropathies by catheter ultrasound probe. *Gastrointest Endosc* 1999; **49**: 184-191 [PMID: 9925696]

4 **Rösch T**, Kapfer B, Will U, Baronius W, Strobel M, Lorenz R, Ulm K. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. *Scand J Gastroenterol* 2002; **37**: 856-862 [PMID: 12190103]

5 **Ando N**, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, Hayakawa T. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. *Gastrointest Endosc* 2002; **55**: 37-43 [PMID: 11756912 DOI: 10.1067/mge.2002.120323]

6 **Mekky MA**, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA, Osman AM, Koshikawa T, Yatabe Y, Bhatia V. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. *Gastrointest Endosc* 2010; **71**: 913-919 [PMID: 20226456 DOI: 10.1016/j.gie.2009.11.044]

7 **Kakushima N**, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 2962-2967 [PMID: 18494043]

8 **Lee HL**, Kwon OW, Lee KN, Jun DW, Eun CS, Lee OY, Jeon YC, Han DS, Yoon BC, Choi HS, Hahm JS, Paik SS. Endoscopic histologic diagnosis of gastric GI submucosal tumors via the endoscopic submucosal dissection technique. *Gastrointest Endosc* 2011; **74**: 693-695 [PMID: 21762901 DOI: 10.1016/j.gie.2011.04.037]

9 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006; **23**: 70-83 [PMID: 17193820]

10 **Lee CK**, Chung IK, Lee SH, Lee SH, Lee TH, Park SH, Kim HS, Kim SJ, Cho HD. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). *Gastrointest Endosc* 2010; **71**: 188-194 [PMID: 19879567 DOI: 10.1016/j.gie.2009.07.029]

11 **de la Serna-Higuera C**, Pérez-Miranda M, Díez-Redondo P, Gil-Simón P, Herranz T, Pérez-Martín E, Ochoa C, Caro-Patón A. EUS-guided single-incision needle-knife biopsy: description and results of a new method for tissue sampling of subepithelial GI tumors (with video). *Gastrointest Endosc* 2011; **74**: 672-676 [PMID: 21872716 DOI: 10.1016/j.gie.2011.05.042]

12 **Akahoshi K**, Akahane H. A new breakthrough: ESD using a newly developed grasping type scissor forceps for early gastrointestinal tract neoplasms. *World J Gastrointest Endosc* 2010; **2**: 90-96 [PMID: 21160708 DOI: 10.4253/wjge.v2.i3.90]

P- Reviewers Armstrong D, Cho YS **S- Editor** Gou SX
L- Editor A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.197

World J Gastrointest Endosc 2013 April 16; 5(4): 197-200
ISSN 1948-5190 (online)

CASE REPORT

Endoscopic mucosal resection with circumferential mucosal incision of duodenal carcinoid tumors

Yuzo Otaki, Kiyoaki Homma, Yoshitakata Nawata, Kazuomi Imaizumi, Shigeru Arai

Yuzo Otaki, Kiyoaki Homma, Yoshitakata Nawata, Department of Therapeutic Endoscopy, Nihonkai General Hospital, Yamagata 998-0828, Japan
Kazuomi Imaizumi, Department of Gastroenterology, Nihonkai General Hospital, Yamagata 998-0828, Japan
Shigeru Arai, Department of Pathology, Nihonkai General Hospital, Sakata, Yamagata 998-0828, Japan
Author contributions: Otaki Y and Nawata Y designed the report; Homma K, Nawata Y and Imaizumi K were attending doctors for the patients; Homma K performed endoscopic operation; Arai S performed pathological examinations; Homma K and Imaizumi K were performed image diagnosis; Otaki Y organized the report and wrote paper.
Correspondence to: Yuzo Otaki, MD, Department of Therapeutic Endoscopy, Nihonkai General Hospital, 30 Akiho, Sakata, Yamagata 998-0828, Japan. 99016yo@jichi.ac.jp
Telephone: +81-234-262001 Fax: +81-234-265114
Received: December 21, 2012 Revised: January 7, 2013
Accepted: January 29, 2013
Published online: April 16, 2013

Abstract

Duodenal carcinoids are a rare form of neuroendocrine tumors, and tend to invade the submucosa during the early stage. Endoscopic treatment is generally recommended for duodenal carcinoids less than 10 mm in diameter. Although a few reports have described the use of endoscopic resection of duodenal carcinoids, there are no published studies on endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI). We performed EMR-CMI for 5 cases of duodenal carcinoids in the duodenal bulb. The mean tumor diameter was 4.6 ± 1.8 mm. Although all of the tumors were located in the submucosa, R0 resection was performed without complication in each case. EMR-CMI may thus be a safe and effective treatment for duodenal carcinoids less than 10 mm in diameter.

Key words: Case study; Digestive system endoscopic surgery; Duodenal neoplasms; Submucosa; Neuroendocrine tumor

Core tip: Endoscopic treatment for duodenal carcinoids is generally recommended less than 10 mm in diameter. Although a few reports have described endoscopic resection of duodenal carcinoids, there are no published studies on endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI). We performed EMR-CMI for 5 cases of duodenal carcinoids in the duodenal bulb. The mean tumor diameter was 4.6 mm. Although all of the tumors were located in the submucosa, R0 resection was performed without complication in each case. EMR-CMI may thus be a safe and effective treatment for duodenal carcinoids less than 10 mm in diameter.

Otaki Y, Homma K, Nawata Y, Imaizumi K, Arai S. Endoscopic mucosal resection with circumferential mucosal incision of duodenal carcinoid tumors. *World J Gastrointest Endosc* 2013; 5(4): 197-200 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/197.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.197

INTRODUCTION

Carcinoid tumors are a rare neuroendocrine malignancies that are most frequently found in the gastrointestinal (GI) tract[1]. Duodenal carcinoids account for 2%-5% of GI carcinoid tumors, and usually present as solitary small lesions confined to the duodenal submucosa[2,3]. Endoscopic treatment is generally recommended for duodenal carcinoids less than 10 mm as it is associated with a low frequency of lymph node invasion and distant metastases[3-5]. A few reports have described the use of endoscopic resection for the treatment of duodenal carcinoids. However, to our knowledge, no studies have been published to date on endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI) for

these tumors. In this study, we described our experience of EMR-CMI for the treatment of 5 cases of duodenal carcinoids.

CASE REPORT

Between December 2006 and September 2012, 5 patients (4 men and 1 woman) with a duodenal carcinoid tumor underwent EMR-CMI at Nihonkai General Hospital. All patients were asymptomatic, and the tumors were incidentally detected during a screening esophago-gastroduodenoscopy (EGD). All procedures were performed by a single endoscopist (Homma K), and all patients were examined by endoscopic ultrasonography (EUS) and abdominal computed tomography (CT) before EMR-CMI. The diagnosis of carcinoid tumor was confirmed by an endoscopic forceps biopsy. Indications for treatment by EMR-CMI were a tumor of diameter 10 mm or less that was confined to the submucosal layer with a clear separation between the tumor and the muscularis propria layer, as assessed by a 20-MHz EUS microprobe (UM2R, Olympus, Tokyo, Japan), and no lymph node invasion or distant metastases on abdominal CT.

After obtaining informed consent from the patient, EMR-CMI was performed under moderate sedation with a combination of pentazocine and flunitrazepam. A single-channel upper GI endoscope with a water-jet system (GIF-Q260J, Olympus) was used. The procedure began with a submucosal injection of hyaluronic acid solution (Mucoup, Johnson and Johnson, Japan) with a 0.1 mL mixture of 0.1% epinephrine and 0.4% indigocarmine dye in order to maintain prolonged elevation and good visibility. A circumferential mucosal incision was performed using a SB knife Jr (Sumitomo Bakelite, Tokyo, Japan) or Mantis Hook (Pentax, Tokyo, Japan), and an additional submucosal injection of hyaluronic acid solution was given beneath the lesion. The adequately raised lesion was then ensnared using a snare (B wave; Zeon Medical, Tokyo, Japan or K-snare; Pentax) in the same manner as the standard polypectomy technique. After EMR-CMI, the mucosal wound was closed with endoscopic clippings as much as possible in order to prevent postoperative bleeding and delayed perforation. To evaluate local recurrence at the resection site, periodic follow-up EGD was performed for all patients. The average age at the time of diagnosis was 64.2 ± 10.2 years (range 47-74 years). The tumors were located in the submucosa within the duodenal bulb in all cases, and the mean tumor size was 4.6 ± 1.8 mm (range 3-8 mm). *En bloc* resection was performed for all patients, and no complications were observed. The average resection time was 19.4 ± 3.6 min (Table 1) and the subsequent postoperative hospitalization period was 5 d in all patients. The median follow-up period was 13 ± 8.8 mo (range 2-29 mo).

In this study, we described one of the cases in greater detail in order to illustrate the typical endoscopic and histological findings associated with these tumors (Case 1). A 74-year-old woman presented with a carcinoid tumor located in the anterior wall of the duodenal bulb (Figure 1A). EUS revealed a hypoechoic mass measuring 3 mm in diameter, originating from the submucosal layer (Figure 1B). Abdominal CT revealed no lymph-node invasion or distant metastases. After local injection of hyaluronic acid solution with epinephrine and an indigocarmine dye to the submucosa around the lesion, a circumferential incision was performed using a SB knife Jr (Figure 2A). *En bloc* resection was then performed by using a standard polypectomy technique with K-snare (Figure 2B and C). The mucosal defect was closed with endoscopic clippings, and the entire procedure was completed in 26 min. A negative surgical margin was confirmed histologically (Figure 3).

DISCUSSION

Duodenal carcinoids are generally considered to be indolent tumors, but because of rarity, their natural history has not been adequately described to date[6]. The metastatic potential of duodenal carcinoids is closely dependent on the size of the tumor. In a series of 99 duodenal carcinoids, Burke *et al*[3] reported that the mean tumor diameter was 18 mm (range 2-50 mm) and that metastasis was presented in 21% of the cases. None of the patients with tumors less than 10 mm in diameter developed metastatic disease during a mean follow-up period of 65 mo. Zyromski *et al*[6] also reported that 24 patients with duodenal carcinoid tumors less than 20 mm remained disease free after local excision during a mean follow-up of 46 mo. In another author described 14% of 201 patients with duodenal carcinoids less than 10 mm in diameter developed metastases, whereas this increased to 47% for patients with tumor diameters between 21 and 50 mm[7].

In addition to the tumor size, involvement of the muscularis propria and the presence of mitotic figures have also been proposed as possible risk factors for metastases in duodenal carcinoids[3]. Therefore, the accurate assessment of invasion depth is important for a successful treatment outcome. EUS has been reported to be an appropriate method for assessing carcinoid tumors including duodenal lesions[8-10]. In a series of 36 GI carcinoid tumors including 7 duodenal lesions evaluated by EUS, Yoshikane *et al*[8] reported that the tumors were generally visualized as hypoechoic and homogenous lesions, and the accuracy of determining the depth of invasion was 75%. Furthermore, when limiting this assessment to the lesions detectable on EUS, the accuracy was as high as 90%. In the present study, all cases were detectable on EUS and the accuracy of determining the depth of invasion was 100%, despite the relatively small number of cases.

European guidelines recommended that duodenal carcinoids less than 10 mm in diameter that are confined to the submucosa as seen on EUS should be treated by endoscopy in the absence of apparent lymph node invasion and distant metastases[5]. However, the appropriate treatment for duodenal carcinoids larger than 10 mm is still controversial. Endoscopic treatment might be considered in patients with a high risk of perioperative complications because of old age or advanced comorbidity. If endos-

Table 1 Characteristics of five patients with a duodenal carcinoid tumor

No.	Age (yr)	Sex	Site	Size (mm)	Depth	Time (min)	*En bloc* resection	Complication
1	74	F	Bulb, anterior	3	Sm	20	Yes	No
2	67	M	Bulb, anterior	4	Sm	15	Yes	No
3	47	M	Bulb, anterior	5	Sm	21	Yes	No
4	74	M	Bulb, anterior	3	Sm	25	Yes	No
5	59	M	Bulb, anterior	8	Sm	16	Yes	No

F: Female; M: Male; Sm: Submucosa.

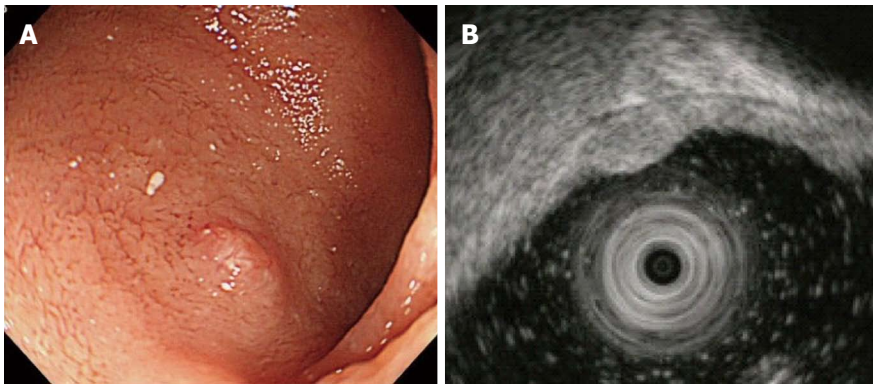


Figure 1 Endoscopic and endoscopic ultrasonography findings. A: Endoscopic image showing an elevated lesion in the anterior wall of duodenal bulb; B: Endoscopic ultrasonography image of the lesion, a 3 mm hypoechoic mass lesion that was located in the submucosal layer.

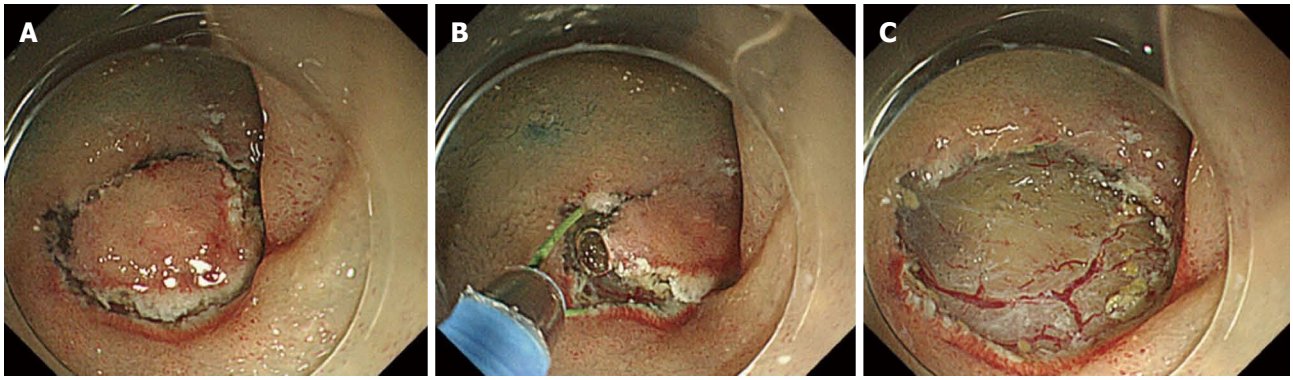


Figure 2 Endoscopic image showing the endoscopic mucosal resection with circumferential mucosal incision procedures. A-C: The entire lesion was removed *en bloc*.

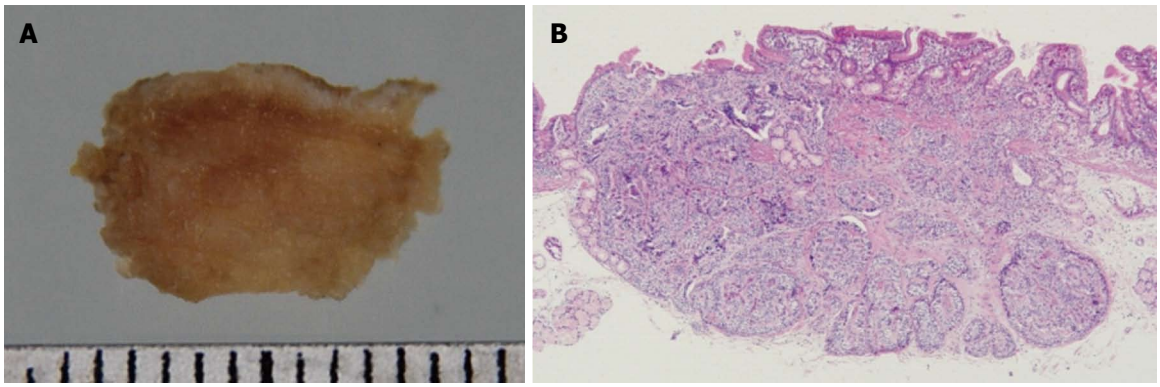


Figure 3 Histopathologic assessment of the resected specimen. A: Macroscopic view of the resected specimen; B: Well-differentiated neuroendocrine tumor was confined to the submucosa (hematoxylin and eosin, original magnification × 20).

copy is deemed unsuitable, laparoscopic techniques could be a suitable alternative[11].

Several endoscopic approaches have been reported for the treatment of carcinoid tumors. Endoscopic resection of carcinoid tumors with polypectomy or strip biopsy with grasping forceps is sometimes associated with margin involvement and crush injury of the resected specimens[12-14]. EMR with band ligation, which is clinically accepted for R0 resection method for carcinoid tumors in the rectum, has been scarcely reported in the duodenal lesions, and its safety profile for the treatment of duodenal carcinoids is unknown[15,16]. We believe that duodenal wall is thin, and band ligation of duodenal wall has a potential risk of muscular involvement. Endoscopic submucosal dissection, which is an emerging technique for the treatment of superficial GI lesion, has high perforation rates for the treatment of duodenal carcinoids (Suzuki *et al*[17]; 2/3 perforations, Matsumoto *et al*[18]; 2/5 perforations). Meanwhile, EMR-CMI was originally introduced as a preferred technique for large colonic lesions by Moss *et al*[19]. They reported that EMR-CMI resulted in deeper submucosal resections histologically compared to conventional EMR, which would be a preferred feature for the resection of duodenal carcinoids originating from the submucosa. In the present study, in which the tumors originated from the submucosa, R0 resection was successfully completed in all of the cases without any complications. We believe that adequate injection of hyaluronic acid solution into the submucosa and careful mucosal incision using a scissor-type knife was key to perform EMR-CMI safely. The average resection time, of nearly 20 min, was considered to be a safe even for older patients.

In conclusion, EMR-CMI may be a safe and effective approach for the treatment of duodenal carcinoids less than 10 mm in diameter in the absence of lymph node invasion or distant metastases. We hope that further clinical studies will help to verify these findings.

REFERENCES

1 **Thomas RM**, Sobin LH. Gastrointestinal cancer. *Cancer* 1995; **75**: 154-170 [PMID: 8000994 DOI: 10.1002/1097-0142(19950101)75]

2 **Klöppel G**, Heitz PU, Capella C, Solcia E. Pathology and nomenclature of human gastrointestinal neuroendocrine (carcinoid) tumors and related lesions. *World J Surg* 1996; **20**: 132-141 [PMID: 8661808]

3 **Burke AP**, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Carcinoid tumors of the duodenum. A clinicopathologic study of 99 cases. *Arch Pathol Lab Med* 1990; **114**: 700-704 [PMID: 1694655 DOI: 10.1097/00000478-198910000-00002]

4 **Mullen JT**, Wang H, Yao JC, Lee JH, Perrier ND, Pisters PW, Lee JE, Evans DB. Carcinoid tumors of the duodenum. *Surgery* 2005; **138**: 971-97; discussion 971-97; [PMID: 16360380 DOI: 10.1016/j.surg.2005.09.016]

5 **Delle Fave G**, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, Sasano H, Tomassetti P, Salazar R, Ruszniewski P. ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. *Neuroendocrinology* 2012; **95**: 74-87 [PMID: 22262004 DOI: 10.1159/000335595]

6 **Zyromski NJ**, Kendrick ML, Nagorney DM, Grant CS, Donohue JH, Farnell MB, Thompson GB, Farley DR, Sarr MG. Duodenal carcinoid tumors: how aggressive should we be? *J Gastrointest Surg* 2001; **5**: 588-593 [PMID: 12086896 DOI: 10.1016/S1091-255X(01)80100-1]

7 **Soga J**. Endocrinocarcinomas (carcinoids and their variants) of the duodenum. An evaluation of 927 cases. *J Exp Clin Cancer Res* 2003; **22**: 349-363 [PMID: 14582691 DOI: 10.3919/jjsa.64.2953]

8 **Yoshikane H**, Tsukamoto Y, Niwa Y, Goto H, Hase S, Mizutani K, Nakamura T. Carcinoid tumors of the gastrointestinal tract: evaluation with endoscopic ultrasonography. *Gastrointest Endosc* 1993; **39**: 375-383 [PMID: 8514069 DOI: 10.1016/S0016-5107(93)70109-1]

9 **Nishimori I**, Morita M, Sano S, Kino-Ohsaki J, Kohsaki T, Suenaga K, Yokoyama Y, Onishi S, Sugimoto T, Araki K. Endosonography-guided endoscopic resection of duodenal carcinoid tumor. *Endoscopy* 1997; **29**: 214-217 [PMID: 9201475 DOI: 10.1055/s-2007-1004167]

10 **Karagiannis S**, Eshagzaiy K, Duecker C, Feyerabend B, Mozdzanowski E, Faiss S. Endoscopic resection with the cap technique of a carcinoid tumor in the duodenal bulb. *Endoscopy* 2009; **41** Suppl 2: E288-E289 [PMID: 19899043 DOI: 10.1055/s-0029-1215123]

11 **Dalenbäck J**, Havel G. Local endoscopic removal of duodenal carcinoid tumors. *Endoscopy* 2004; **36**: 651-655 [PMID: 15243891 DOI: 10.1055/s-2004-814539]

12 **Shirouzu K**, Isomoto H, Kakegawa T, Morimatsu M. Treatment of rectal carcinoid tumors. *Am J Surg* 1990; **160**: 262-265 [PMID: 2393053 DOI: 10.1016/S0002-9610(06)80019-X]

13 **Matsui K**, Iwase T, Kitagawa M. Small, polypoid-appearing carcinoid tumors of the rectum: clinicopathologic study of 16 cases and effectiveness of endoscopic treatment. *Am J Gastroenterol* 1993; **88**: 1949-1953 [PMID: 8237948]

14 **Iishi H**, Tatsuta M, Yano H, Narahara H, Iseki K, Ishiguro S. More effective endoscopic resection with a two-channel colonoscope for carcinoid tumors of the rectum. *Dis Colon Rectum* 1996; **39**: 1438-1439 [PMID: 8969673 DOI: 10.1007/BF02054536]

15 **Gomez V**, Groce JR, Xaio SY, Bhutani MS, Raju GS. Band ligation resection of duodenal carcinoid (with video). *Gastrointest Endosc* 2007; **66**: 397; discussion 398 [PMID: 17643721 DOI: 10.1016/j.gie.2007.01.029]

16 **Mashimo Y**, Matsuda T, Uraoka T, Saito Y, Sano Y, Fu K, Kozu T, Ono A, Fujii T, Saito D. Endoscopic submucosal resection with a ligation device is an effective and safe treatment for carcinoid tumors in the lower rectum. *J Gastroenterol Hepatol* 2008; **23**: 218-221 [PMID: 18289355 DOI: 10.1111/j.1440-1746.2008.05313.x]

17 **Suzuki S**, Ishii N, Uemura M, Deshpande GA, Matsuda M, Iizuka Y, Fukuda K, Suzuki K, Fujita Y. Endoscopic submucosal dissection (ESD) for gastrointestinal carcinoid tumors. *Surg Endosc* 2012; **26**: 759-763 [PMID: 21993939 DOI: 10.1007/s00464-011-1948-y]

18 **Matsumoto S**, Miyatani H, Yoshida Y, Nokubi M. Duodenal carcinoid tumors: 5 cases treated by endoscopic submucosal dissection. *Gastrointest Endosc* 2011; **74**: 1152-1156 [PMID: 21944312 DOI: 10.1016/j.gie.2011.07.029]

19 **Moss A**, Bourke MJ, Tran K, Godfrey C, McKay G, Chandra AP, Sharma S. Lesion isolation by circumferential submucosal incision prior to endoscopic mucosal resection (CSI-EMR) substantially improves en bloc resection rates for 40-mm colonic lesions. *Endoscopy* 2010; **42**: 400-404 [PMID: 20213591 DOI: 10.1055/s-0029-1243990]

P- Reviewer Garcia-Cano J **S- Editor** Gou SX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.201

World J Gastrointest Endosc 2013 April 16; 5(4): 201-202
ISSN 1948-5190 (online)

Interference between pacemakers/implantable cardioverter defibrillators and video capsule endoscopy

Dirk Bandorski, Johannes Gehron, Reinhard Höltgen

Dirk Bandorski, Medical Clinic II, University Hospital Giessen und Marburg GmbH, 35392 Giessen, Germany
Johannes Gehron, Department of Cardiac Surgery, University Hospital Giessen und Marburg GmbH, 35392 Giessen, Germany
Reinhard Höltgen, Medical Clinic III, St.-Agnes Hospital Bocholt, 46397 Bocholt, Germany
Author contributions: All authors read and analysed the article, discussed the results and defined the comments for the Letter to the Editor; Bandorski D and Höltgen R wrote the text of the Letter.
Correspondence to: Dirk Bandorski, MD, FESC, Medical Clinic II, University Hospital Giessen und Marburg GmbH, Excellence Cluster Cardio-Pulmonary System (ECCPS), Klinikstrasse 36, 35392 Giessen,
Germany. dirk.bandorski@hkw.med.uni-giessen.de
Telephone: +49-641-98551251 Fax: +49-641-98551259
Received: July 15, 2012 Revised: November 21, 2012
Accepted: January 16, 2013
Published online: April 16, 2013

Abstract

Our Letter to the Editor, related to the article "Small bowel capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter defibrillators: Outcome analysis using telemetry" by Cuschieri *et al*, comments on some small errors, that slipped into the authors discussions. The given informations concerning the pacemaker- and implantable cardioverter defibrillators modes were inaccurate and differ between the text and the table. Moreover, as 8 of 20 patient's pacemakers were programmed to VOO or DOO ("interference mode") and one patient was not monitored by telemetry during capsule endoscopy, 9 of 20 patients (45%) lack the informations of possible interference between capsule endoscopy their implanted device. Another objection refers to the interpretation of an electrocardiogram (figure 1, trace B) presented: in contrast to the author's opinion the marked spike should be interpreted as an artefact and not as "undersensing of a fibrillatory wave". Finally, three comments to cited reviews were not complete respectively not quoted correctly.

Key words: Capsule endoscopy; Small bowel capsule endoscopy; Interference; Cardiac pacemaker; Implantable cardioverter defibrillator; Telemetry

Bandorski D, Gehron J, Höltgen R. Interference between pacemakers/implantable cardioverter defibrillators and video capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(4): 201-202 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/201.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.201

TO THE EDITOR

In our perception, small errors crept in the interesting article by Cuschieri *et al*[1] "Small bowel capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter defibrillators: Outcome analysis telemetry review". Therefore it should be subject to the following comments.

First of all, the informations concerning the pacemaker-/implantable cardioverter defibrillators (ICD)-modes, the devices were programmed into during the small bowel capsule endoscopy (SBCE), given in table 1 differ from the informations in the text: whereas the text referring to table 1 contents the information, that "three were set to DDD, six to DDDR, one to DOO, four to VOO, one to VVIR, and one to AAI→DDD (table 1)", the presented table 1 shows three set to DOO, no one was set from AAI to DDD and five were set to VOO [Pacemaker-Code (North American Society of Pacing and Electrophysiology-NASPE and British Pacing and Electrophysiology Group-BPEG: the first letter identifies the chamber paced, the second letter identifies the chamber sensed: V - ventricular, A - atrial, D - dual; the third letter identifies the response to sensing: I - inhibited, T - triggered, D - dual; the fourth letter identifies

the response rate (R)]. The error may partially result from the fact, that the authors did not clearly understand the different meaning of the "→" and the "↔" arrows. "AAI ↔ DDD" does not mean a change in programming, but describes a novel pacemaker function, allowing to change from the AAI- to the DDD-mode automatically, if necessary, and it describes the "managed ventricular pacing" function in Medtronic-pacemakers.

As a second remark, the study included 20 patients, in 8 of whom the pacemaker were programmed to VOO or DOO. In these modes ("interference mode"), pacemakers revert to noise-mode function stimulating the ventricle (VOO) or atrium and ventricle (DOO) without sensing the native rhythm. Additionally, one patient (DDD-Mode, table 2) was not monitored during capsule endoscopy (CE). Consecutively, in 9 of 20 patients (45%) the question of the study, in how far SBCE would influence pacemakers, could not be answered, as the pacemakers cannot be influenced at all. Considering to our study[2] without evidence of interference between CE and implantable cardioverter defibrillators (ICDs) it remains unclear, why the sensing function of the ICDs was turned off.

The third objection refers to the spike in figure 1, trace B, preceding the third (narrow) QRS-complex: QRS-complexes # 4, 5 and 6 are clearly stimulated, proving that ventricular stimulation works well in this patient. So the stimulus preceding QRS-complex 3 cannot be a ventricular one, because it should be able to capture the ventricle. There is no pacemaker-system available with mode switching to AAI or AOO. So if mode switch was the reason for this spike, it must stimulate the ventricle. Moreover: the orientation of this "spike" is exactly antipodal (positive in lead 1, negative in lead 2) compared with the orientation of the effective ventricular spikes (negative in lead 1, positive in lead 2), this is most unlikely in conventional holter/telemetry recordings, usually you find same polarities for atrial and ventricular spikes in surface electrodes. So this "spike" should be interpreted as an artefact.

In two patients, the authors assumed "inappropriate pacer spikes due to undersensing of very subtle atrial fibrillation", and they mentioned, that similar episodes were documented before and after CE. In this context, it would be interesting, if those patients suffered from paroxysmal, persistent or permanent atrial fibrillation. In the opinion of the authors "the mostly likely possibility is that the thresholds for atrial pacing were set too high". According to this presumption, further details to the programming of the pacemakers should have been presented.

Another concern against the study of Cuschieri *et al*[1] is that there is only a few number of patients left (11/20) for the (real) investigation of interference between CE and devices to be able to derive their conclusions from their data.

Finally, there are three comments to the cited references: (1) The radiated power of CE is mentioned with 50 nW. The reference cited in this connection is wrong. CE is not mentioned in this article[3]; and (2) In our study for interference between CE and ICD[4], we "electrically simulated the situation in a patient". The pacemakers and CE were placed in a saline solution (resistivity corresponding to that of low frequency range of muscle tissue), not water, in analogy to a study, in which the interference behaviour of mobile phones with respect to pacemakers was investigated[5]; and (3) The authors discuss that "it is conceivable that the site of entry for the noise signals is the unshielded part of the connector block which could occur, as the swallowed CE passes posterior to the heart while descending through the esophagus, consisting with studies on mobile phones", as a possibility for interference between CE and devices. Cited references for this hypothesis are the study of Dubner *et al*[6] and our study[4]. In none of the cited studies mobile phones were used.

REFERENCES

1 **Cuschieri JR**, Osman MN, Wong RC, Chak A, Isenberg GA. Small bowel capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter defibrillators: Outcome analysis using telemetry review. *World J Gastrointest Endosc* 2012; **4**: 87-93 [PMID: 22442746 DOI: 10.4253/wjge.v4.i3.87]

2 **Bandorski D**, Irnich W, Brück M, Kramer W, Jakobs R. Do endoscopy capsules interfere with implantable cardioverter-defibrillators? *Endoscopy* 2009; **41**: 457-461 [PMID: 19353490 DOI: 10.1055/s-0029-1214610)]

3 **Kolb C**, Schmieder S, Lehmann G, Zrenner B, Karch MR, Plewan A, Schmitt C. Do airport metal detectors interfere with implantable pacemakers or cardioverter-defibrillators? *J Am Coll Cardiol* 2003; **41**: 2054-2059 [PMID: 12798581 DOI: 10.1016/S0735-1097(03)00424-8)]

4 **Bandorski D**, Irnich W, Brück M, Beyer N, Kramer W, Jakobs R. Capsule endoscopy and cardiac pacemakers: investigation for possible interference. *Endoscopy* 2008; **40**: 36-39 [PMID: 18067067 DOI: 10.1055/s-2007-995353)]

5 **Irnich W**, Batz L, Müller R, Tobisch R. Electromagnetic interference of pacemakers by mobile phones. *Pacing Clin Electrophysiol* 1996; **19**: 1431-1446 [PMID: 8904533 DOI: 10.1111/j.1540-8159.1996.tb03155.x)]

6 **Dubner S**, Dubner Y, Gallino S, Spallone L, Zagalsky D, Rubio H, Zimmerman J, Goldin E. Electromagnetic interference with implantable cardiac pacemakers by video capsule. *Gastrointest Endosc* 2005; **61**: 250-254 [PMID: 15729234 DOI: 10.1016/S0016-5107(04)02834-2)]

P- Reviewer Koulaouzidis A **S- Editor** Wen LL **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2013 April 16; 5(4): I-V
ISSN 1948-5190 (online)

GENERAL INFORMATION

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

Aim and scope

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

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

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

Columns

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

Name of journal

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

Launch date

October 15, 2009

Frequency

Monthly

Editor-in-Chief

Nadeem Ahmad Afzal, MD, MBBS, MRCP, MRCPCH, Consultant Paediatric Gastroenterologist and Honorary Senior

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

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

Production center
Beijing Baishideng BioMed Scientific Co., Limited
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893

Representative office
USA Office
8226 Regency Drive,
Pleasanton, CA 94588-3144, United States

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

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

SPECIAL STATEMENT

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

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

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

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

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

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

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

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally ac-

cepted 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 copyedit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

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

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjge@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

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

Title page

Title: Title should be less than 12 words.

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

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

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

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

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

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

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381892 Fax: +86-10-85381893

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

Abstract

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

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

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

Core tip

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

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

Illustrations

Figures should be numbered as 1, 2, 3, *etc*., and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names

should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc*. It is our principle to publish high resolution-figures for the E-versions.

Tables

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

Notes in tables and illustrations

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

Acknowledgments

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

REFERENCES

Coding system

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

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

PMID and DOI

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

Style for journal references

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

Style for book references

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

Format

Journals

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

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

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

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

In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

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

Units

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

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5190/g_info_20100107135346.htm.

Abbreviations

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

Italics

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

Examples for paper writing

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

RESUBMISSION OF THE REVISED MANUSCRIPTS

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

Language evaluation

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

Copyright assignment form

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

Responses to reviewers

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

Proof of financial support

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

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.

Publication fee

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

百世登

Baishideng®

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