ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2017 October 16; 9(10): 499-539

Published by Baishideng Publishing Group Inc

WJGE World Journal of Gastrointestinal Endoscopy

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

Editorial Board

2014-2017

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 330 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 40 countries, including Australia (3), Austria (3), Brazil (6), Canada (3), China (62), Croatia (1), Czech Republic (1), Denmark (1), Ecuador (1), Egypt (3), France (1), Germany (8), Greece (10), Hungary (2), India (11), Indonesia (1), Iran (6), Iraq (1), Ireland (2), Israel (1), Italy (37), Japan (43), Lebanon (1), Lithuania (1), Malaysia (1), Mexico (4), Netherlands (1), Norway (2), Poland (4), Portugal (5), Romania (1), Singapore (3), Slovenia (2), South Korea (19), Spain (9), Thailand (2), Turkey (11), United Arab Emirates (1), United Kingdom (14), and United States (43).

Poland

Thomas Brzozowski, *Cracow*
Piotr Pierzchalski, *Krakow*
Stanislaw Sulkowski, *Bialystok*
Andrzej Szkaradkiewicz, *Poznań*

Portugal

Andreia Albuquerque, *Porto*
Pedro N Figueiredo, *Coimbra*
Ana Isabel Lopes, *Lisbon*
Rui A Silva, *Porto*
Filipa F Vale, *Lisbon*

Romania

Lucian Negreanu, *Bucharest*

Singapore

Surendra Mantoo, *Singapore*
Francis Seow-Choen, *Singapore*
Kok-Yang Tan, *Singapore*

Slovenia

Pavel Skok, *Maribor*
Bojan Tepes, *Rogaska Slatina*

South Korea

Seung Hyuk Baik, *Seoul*
Joo Young Cho, *Seoul*
Young-Seok Cho, *Uijeongbu*
Ho-Seong Han, *Seoul*
Hye S Han, *Seoul*
Seong Woo Jeon, *Daegu*
Won Joong Jeon, *Jeju*
Min Kyu Jung, *Daegu*
Gwang Ha Kim, *Busan*
Song Cheol Kim, *Seoul*
Tae Il Kim, *Seoul*
Young Ho Kim, *Daegu*
Hyung-Sik Lee, *Busan*
Kil Yeon Lee, *Seoul*
SangKil Lee, *Seoul*
Jong-Baeck Lim, *Seoul*
Do Youn Park, *Busan*
Dong Kyun Park, *Incheon*
Jaekyu Sung, *Daejeon*

Spain

Sergi Castellvi-Bel, *Barcelona*
Angel Cuadrado-Garcia, *Sanse*
Alfredo J Lucendo, *Tomelloso*
José F Noguera, *Valencia*
Enrique Quintero, *Tenerife*
Luis Rabago, *Madrid*
Eduardo Redondo-Cerezo, *Granada*
Juan J Vila, *Pamplona*

Thailand

Somchai Amornyotin, *Bangkok*
Pradermchai Kongkam, *Pathumwan*

Turkey

Ziya Anadol, *Ankara*
Cemil Bilir, *Rize*
Ertan Bulbuloglu, *Kahramanmaras*
Vedat Goral, *Izmir*
Alp Gurkan, *Istanbul*
Serkan Kahyaoglu, *Ankara*
Erdinc Kamer, *Izmir*
Cuneyt Kayaalp, *Malatya*
Erdal Kurtoglu, *Turkey*
Oner Mentes, *Ankara*
Orhan V Ozkan, *Sakarya*

United Arab Emirates

Maher A Abbas, *Abu Dhabi*

United Kingdom

Nadeem A Afzal, *Southampton*
Emad H Aly, *Aberdeen*
Gianpiero Gravante, *Leicester*
Karim Mukhtar, *Liverpool*
Samir Pathak, *East Yorkshire*
Jayesh Sagar, *Frimley*
Muhammad S Sajid, *Worthing, West Sussex*
Sanchoy Sarkar, *Liverpool*
Audun S Sigurdsson, *Telford*
Tony CK Tham, *Belfast*
Kym Thorne, *Swansea*
Her Hsin Tsai, *Hull*
Edward Tudor, *Taunton*
Weiguang Wang, *Wolverhampton*

United States

Emmanuel Atta Agaba, *Bronx*
Mohammad Alsolaiman, *Lehi*
Erman Aytac, *Cleveland*
Jodie A Barkin, *Miami*
Corey E Basch, *Wayne*
Charles Bellows, *Albuquerque*
Jianyuan Chai, *Long Beach*
Edward J Ciaccio, *New York*
Konstantinos Economopoulos, *Boston*
Viktor E Eysselein, *Torrance*
Michael R Hamblin, *Boston*
Shantel Hebert-Magee, *Orlando*
Cheryl L Holt, *College Park*
Timothy D Kane, *Washington*
Matthew Kroh, *Cleveland*
I Michael Leitman, *New York*
Wanguo Liu, *New Orleans*
Charles Maltz, *New York*
Robert CG Martin, *Louisville*
Hiroshi Mashimo, *West Roxbury*
Abraham Mathew, *Hershey*
Amosy E M'Koma, *Nashville*
Klaus Monkemuller, *Birmingham*
James M Mullin, *Wynnewood*
Farr Reza Nezhat, *New York*
Gelu Osian, *Baltimore*
Eric M Pauli, *Hershey*
Srinivas R Puli, *Peoria*
Isaac Raijman, *Houston*
Robert J Richards, *Stony Brook*
William S Richardson, *New Orleans*
Bryan K Richmond, *Charleston*
Praveen K Roy, *Marshfield*
Rodrigo Ruano, *Houston*
Danny Sherwinter, *Brooklyn*
Bronislaw L Slomiany, *Newark*
Aijaz Sofi, *Toledo*
Stanislaw P Stawicki, *Columbus*
Nicholas Stylopoulos, *Boston*
XiangLin Tan, *New Brunswick*
Wahid Wassef, *Worcester*
Nathaniel S Winstead, *Houma*

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 9 Number 10 October 16, 2017

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

CASE REPORT

Contents

World Journal of Gastrointestinal Endoscopy
Volume 9 Number 10 October 16, 2017

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
October 16, 2017

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

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2017 October 16; 9(10): 499-505

DOI: 10.4253/wjge.v9.i10.499

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic ultrasound: Current roles and future directions

Scott R Friedberg, Jesse Lachter

Scott R Friedberg, Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, United States

Jesse Lachter, Rambam Healthcare Campus, Technion Israel Institute of Technology, Haifa 3109601, Israel

Author contributions: Friedberg SR wrote the paper; Lachter J edited the paper.

Conflict-of-interest statement: There were no conflicts of interest in writing this review.

Manuscript source: Unsolicited manuscript

Correspondence to: Scott R Friedberg, MD, Department of Internal Medicine, University of Pittsburgh Medical Center, 200 Lothrop St., Pittsburgh, PA 15213,
United States. friedbergsr@upmc.edu
Telephone: +1-305-6324895

Received: April 1, 2017
Peer-review started: April 10, 2017
First decision: May 11, 2017
Revised: May 20, 2017
Accepted: June 12, 2017
Article in press: June 13, 2017
Published online: October 16, 2017

Abstract

Endoscopic ultrasound (EUS), developed in the 1980s, was initially predominantly used for guidance of fine needle aspiration; the last 25 years, however, have witnessed a major expansion of EUS to various applications, both diagnostic and therapeutic. EUS has become much more than a tool to differentiate different tissue densities; tissue can now be characterized in great detail using modalities such as elastography; the extent of tissue vascularity can now be learned with increasing precision. Using these various techniques, targets for biopsy can be precisely pinpointed. Upon reaching the target, tissue can then be examined microscopically in real-time, ensuring optimal targeting and diagnosis. This article provides a comprehensive review of the various current roles of EUS, including drainage of lesions, visualization and characterization of lesions, injection, surgery, and vascular intervention. With EUS technology continuing to develop exponentially, the article emphasizes the future directions of each modality.

Key words: Endoscopic ultrasound; Future; Trends; Roles

Core tip: In recent years, endoscopic ultrasound (EUS) has evolved and is now used in various applications, both diagnostic and therapeutic. Classically used to differentiate different tissue densities, EUS is now used to characterize and localize tissue with much more precision. Upon reaching the target, tissue can then be examined microscopically in real-time, ensuring optimal targeting and diagnosis. This article provides a comprehensive review of the various current roles of EUS, including drainage of lesions, visualization and characterization of lesions, injection, surgery, and vascular intervention. With EUS technology continuing to develop exponentially, the article emphasizes the future directions of each modality.

Friedberg SR, Lachter J. Endoscopic ultrasound: Current roles and future directions. *World J Gastrointest Endosc* 2017; 9(10): 499-505 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i10/499.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i10.499

INTRODUCTION

Flexible endoscopy was first developed in 1911 and

ultrasound later arrived in 1956. In the 1980s, these modalities were merged to form the endoscopic ultrasound (EUS). EUS allowed the visualization of structures near the gastrointestinal tract. It did not have much of a role in gastroenterology, however, until the advent of the fine needle aspiration (FNA) in 1991. FNA was a major step for EUS; it was the first time structures outside the lumen could be interacted with and explored. It was the first time the vast length of the gastrointestinal tract could truly be exploited as a potential inlet to the rest of the body.

For the last 25 years, EUS has increasingly been used in the field of gastroenterology. This trend is likely to continue as novel technology is developed and the demand for minimally invasive techniques continues to grow. Procedures that utilize EUS-FNA have specifically spearheaded this growth, but EUS itself has also evolved to be useful for many other procedures, both diagnostic and therapeutic.

Certain EUS advances have caught on faster than others, and in this review several of such modalities will be discussed. The focus will be on the current status of each modality and the direction to which each is heading. Each EUS modality will be categorized in terms of its main function, that is, drainage, visualization, injection, surgery, and vascular interventions.

CHARACTERIZATION OF LESIONS

EUS-guided biopsy is the modality of choice to characterize and stage lesions in the GI tract, with the most commonly targeted organs being the pancreas, submucosal lesions, and lymph nodes[1].

Because of its success thus far, much of the EUS research has been focused on improving characterization of lesions. This has led to advancements which have improved the ability to characterize lesions both from afar (ultrasound) and up close (*via* biopsy). Ultrasound imaging is no longer limited to the conventional B mode imaging, and now includes newer, more advanced modalities such as contrast-enhanced ultrasound and elastography. Forward-viewing EUS (FV-EUS) has improved the ability to access lesions, and modern microscopy advancements now enable real-time optical biopsy.

Elastography

EUS elastography is a major recent advancement in EUS characterization of lesions. The underlying principle of elastography is that compression of a target tissue by a probe produces a smaller strain in hard (usually malignant) tissue than in soft (usually benign) tissue; therefore, elastography can indicate which areas are likely to be malignant *vs* benign.

Because elastography can be used in real-time, elastography serves as an important marker that can direct EUS-FNA. The sensitivity in identifying metastatic lymph nodes is at least 85%[2]. Another advantage of elastography is that it is relatively inexpensive and does not require extensive training, though it is operator-dependent and is therefore inherently subjective. In addition, elastography can be used in the diagnosis of other conditions, such as prostate cancer, and rectal cancer[3]. Elastography can potentially also be used for adrenal tumors and biliary duct cancers because of their proximity to the gastrointestinal tract, but this research is still in its very early stages[2].

Shear wave elastography is a special type of elastography that requires no manual compression of tissue as applied in conventional elastography, and is therefore less operator-dependent. Measurements of shear wave velocity yield additional information on the tissue's elasticity and therefore can help in diagnosis. Thus far shear wave elastography has been used mostly to characterize breast lesions, liver fibrosis, and thyroid lesions[2]. It has also been used in transrectal ultrasonography for prostate cancer[4]. It is anticipated that shear wave elastography will soon be used with EUS procedures.

Despite the promise that elastography has shown thus far, it is currently only used if EUS-FNA results are negative or inconclusive[3]. In the future, elastography may be able to be merged with other imaging techniques, such as fusion imaging, contrast-enhanced EUS, or 3D elastography to increase accuracy even further[2]. Another notable advancement in elastography is the automated histogram, which allows more quantitative, less subjective elastography, thereby increasing accuracy and reducing operator bias[2].

Tissue harmonic echo

Tissue harmonic echo (THE) imaging is a new technology that provides yet another modality of imaging pancreatic cystic lesions. THE mode imaging provides better characterization of lesions than conventional B mode images. The principle behind THE is that the sonogram is produced by higher harmonic frequencies as ultrasonic beams propagate through tissues. It has thus far only been used in abdominal ultrasound, but there is potential for EUS as well. More studies need to be done to determine whether THE significantly improves EUS diagnostics[5].

Contrast enhanced EUS

Contrast enhanced EUS (CE-EUS) is yet another advanced ultrasound modality. Its advantage is that it allows vascularity to be depicted, thereby improving accuracy, sensitivity, and specificity for diagnosing pancreatic masses and lymphadenopathy[3]. CE-EUS can also be used during EUS-FNA to help avoid vessels. Contrast enhanced color and power Color-Doppler sonography (CD-EUS) enable detection of intratumor vasculature, by producing pseudo Doppler signals from microbubbles. Contrast enhanced harmonic EUS (CH-EUS) was more recently developed to overcome the limitations of CD-EUS. CH-EUS can depict the microbubbles themselves rather than the entire flow

through the vessels thus allowing visualization of both microvessels and parenchymal perfusion[6].

CE-EUS is an emerging technique with promise, but it has been scrutinized for being qualitative in nature, and therefore research is underway to develop more quantitative techniques[3].

Needle-based confocal laser endomicroscopy

Needle-based confocal laser endomicroscopy (n-CLE) is a technique allowing *in-vivo* "optical" histology using fluorescent contrast. N-CLE therefore can show which areas are most suspicious for malignancy and require biopsy. Preliminary results of n-CLE studies have been very promising, and in the future n-CLE may stand as the second option for diagnosing pancreatic cysts when EUS-FNA is inconclusive[7]. In the near future, n-CLE may become routinely used after EUS-FNA of solid pancreatic masses returns inconclusive[7,8]. Despite how accurate n-CLE proves to be, it will likely catch on slowly due to high cost and the difficulty of predicting pathology based on surface characteristics[9]. N-CLE can theoretically one day deem classical tissue acquisition obsolete, although tissue acquisition will continue to provide diagnostic benefits, such as the ability to perform molecular testing, flow cytometry, and PCR[8]. Ideally, pancreatic cystic neoplasms will eventually be diagnosed in a personalized fashion, implementing the techniques of cytology, nCLE, and molecular markers differently for each patient[9]. With this arsenal, one may be able to accurately predict which lesions will progress quickly, and therefore require urgent treatment such as endoscopic ablation or surgery. At the same time, improved diagnostic techniques may also reveal those lesions that progress slowly and therefore can be followed less closely.

In summary, recent years have brought on many advances in the ability to characterize lesions, most notably pancreatic lesions. This boom has been spearheaded by the improvement of ultrasound technology, the most important currently being CH-EUS and elastography. For now, to obtain the most accurate characterization, a combination of the two are used in clinical practice[3]. In the future, ideally all techniques will be in the armamentarium, so that each patient can receive personalized treatment.

DRAINAGE

Pancreatic fluid collection

Pancreatic fluid collection (PFC) is a common complication of pancreatitis. The decision whether or not to drain depends on multiple factors, namely, clinical presentation, duration, size, and location. If drainage is indicated, it must be decided whether to intervene surgically, endoscopically, or radiologically (percutaneously). Currently, surgery is performed when a wall has not yet formed around the collection. Alternatively, if a wall has already formed, endoscopic drainage is considered[10]. Walled-off collections include both pseudocysts (fluid) and walled off necrosis (WON; solid). Studies have shown endoscopic drainage to have higher rates of treatment success than percutaneous drainage, as well as lower rates of re-interventions[11]. ERCP is considered if the collection communicates with the pancreatic duct.

Endoscopic drainage is aided by EUS guidance specifically when there is either no intraluminal bulge, portal hypertension, nearby collateral vessels, necrosis, or calcification in the wall[12,13]. EUS drainage is performed *via* either a transgastric or transduodenal approach, and therefore requires the collection to be near ($\leqslant$ 1 cm) the GI lumen[14]. EUS provides precise localization of the collection as well as precise measurement of the thickness of the wall and distance from the GI lumen.

EUS-guided drainage can be enhanced in many instances with the use of a self-expanding metallic stent (SEMS). This stent provides a wider diameter for drainage, thus leading to a quicker resolution of symptoms[15]. SEMS is most useful in WON, as it allows for repeated access for necrosectomy[16]. SEMS has greatly improved EUS-guided drainage, though additional research is needed on SEMS, as it is still a relatively new tool.

Alongside the current recommendations and considerations listed above, the decision how to drain ultimately depends not only on the actual collection but also the institution, local expertise, and the patient preference.

Pancreatic duct

EUS guidance may be helpful in decompression of the pancreatic duct during an obstruction. Currently, EUS is only used when ERCP-guided cannulation fails or when the papilla is inaccessible (*e.g.*, gastric or duodenal obstruction or surgically altered anatomy)[16]. The pancreatic duct can be drained either by the rendezvous procedure or translumenally, through the stomach or duodenum[16].

Biliary

Similar to pancreatic duct drainage, biliary drainage may be done endoscopically with EUS guidance when ERCP cannulation has failed, the papilla is inaccessible, or anatomy is surgically altered. Classically, the alternatives to ERCP have been percutaneous or surgical methods, but EUS provides a safer alternative[17], and internal drainage is considerably preferable from a patient perspective.

Like pancreatic duct drainage, EUS-guided biliary drainage can be done in three different ways[18]: Transpapillary rendezvous, or translumenally *via* either choledochoduodenostomy or hepaticogastrostomy. The data is still limited at this point, but many believe that the results are promising for EUS-guided biliary drainage, with the overall success rate around 90%[19] with a minimal complication rate. EUS-guided biliary drainage results have been so promising that experts increasingly argue that EUS should become the first-

line treatment, ahead of percutaneous drainage[16]. It is argued that EUS-guided drainage is superior because it both reduces adverse event rates and the need for re-interventions, thereby reducing costs of therapy[20].

As in PFC drainage, SEMS is also being used more often for biliary drainage. Forward viewing-EUS, a new tool discussed below, combined with a SEMS, has been shown to be the best method when performing EUS guided choledochoduodenostomy for malignant distal biliary obstruction[21]. Preliminary results suggest that, in the future, gastroenterologists may assume the responsibility of biliary drainage from surgeons, whether it be for ERCP or EUS.

Gallbladder

The gallbladder needs to be drained in cholecystitis if the patient is unfit for surgery or has an unresectable pancreatic cancer, or if the cholecystitis is refractory to antibiotics. Classically, drainage has been performed percutaneously, although studies have shown that EUS-guided endoscopic drainage is equally as successful as percutaneous drainage[22]. Drainage by EUS can be performed either with a plastic stent, metal stent, or naso-gallbladder/nasobiliary drain.

Abscesses

EUS has developed into a favorable alternative to traditional percutaneous drainage of abscesses[16]. Accessible abscesses include those in the mediastinum, lesser sac, perihepatic and subphrenic spaces, and pelvic and perirectal regions.

INJECTION

Nerve block

Nerve blocks are administered to reduce transmission through a nerve, thereby reducing chronic pain and the resulting need for opioids and analgesics. Nerve blocks are often conducted using neurolysis, in which cytolytic agents, commonly alcohol or phenol, are injected to damage the nerves. The nerves most commonly targeted are in the celiac plexus for pancreatic cancers and, less commonly, chronic pancreatitis. Neurolysis can be performed percutaneously or endoscopically by EUS. The percutaneous approach has been the more widely used approach, though studies have shown that endoscopic approach may provide more lasting results[16,23], as the injection is delivered under greater control.

Tattooing

EUS-guided fine-needle tattooing (EUS-FNT) is a technique in which carbon particle labels are injected into pancreatic lesions *via* EUS guidance. These labels then serve as markers during laparoscopic distal pancreatectomy, which ultimately reduces operating time, cost, and amount of healthy pancreas that is inadvertently resected[24].

Targeted destruction of lesions

Alcohol ablation: Alcohol can be injected using EUS guidance in order to ablate pancreatic lesions, neuroendocrine tumors, or metastases from the abdomen. Alcohol ablation has proven very effective, especially for certain pancreatic lesions, particularly when combined with taxols or other agents. Currently, alcohol ablation of neuroendocrine tumors is only indicated if the patient is unfit for surgery. It is uncertain how effective alcohol ablation has been for neuroendocrine tumors because there is not yet sufficient data for predicting prognoses.

Radiotherapy: Fiducials, which are small 3-5 mm radiopaque metal markers, may be placed in tumors or lymph nodes using EUS guidance and a 19-gauge FNA needle[17]. These fiducials act as points of reference for targeted external beam radiation therapy[25]. Alternatively, EUS can guide injection of seeds through 19-gauge needles for brachytherapy (internal radiotherapy, various plasmids).

Chemotherapy: Chemotherapeutic agents, commonly paclitaxel, have been injected using precise EUS guidance. Chemotherapy injection can be combined with other therapeutic methods such as alcohol ablation. EUS-guided chemotherapy has been used for pancreatic cysts and tumors and esophageal cancers, but much more research is needed to understand the long-term results[18].

Photodynamic therapy: Photosensitizing drugs can also be injected using EUS guidance. Exposure to the specific wavelength of light leads to cytotoxic effects, vascular effects, and inflammatory reactions, thereby leading to necrosis of the targeted site.

SURGERY

Natural orifice transluminal endoscopic surgery

Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique that uses the body's natural orifices as inlets to reach various organs *via* EUS guidance. Pioneered by Dr. Anthony Kalloo, NOTES procedures have a number of potential benefits. Without external incisions, there are no scars or risks of skin infection, and thus the NOTES approach offers a potentially quicker recovery and therefore shorter hospital stay. Furthermore, less anesthesia may be required. NOTES procedures are currently being developed to: Create anastomoses - Gastroduodenal anastomosis by NOTES has succeeded as a minimally invasive approach for certain gastrointestinal bypass procedures. These bypass procedures include treatment of obstructions, such as duodenal stenosis or gastric outlet obstruction. NOTES can also be used for gastrojejunal bypass, as a malabsorptive-type bariatric procedure. Studies are needed, however, to compare these NOTES procedures

directly with conventional surgical approaches[26].

Remove and biopsy organs-NOTES also has the potential to become a minimally invasive alternative to routine laparoscopic procedures. NOTES can be used for liver biopsy, cholecystectomy, appendectomy, thyroidectomy, and procedures involving mediastinal and spinal tissues. The transgastric approach has been the most studied inlet to date. So far, however, the majority of human NOTES procedures have been transvaginal cholecystectomy and appendectomy. More human research is needed on the transgastric and transrectal approaches.

NOTES has many advantages and therefore much potential, although it has undoubtedly been slow to catch on. Devices designed specifically to facilitate NOTES are needed. Despite NOTES being an endoscopic procedure and therefore inherently within a gastroenterologist's "jurisdiction", its ultimate procedural goal is often that of a surgeon. Techniques such as NOTES obscure the distinct borders of each specialist, and the medical community must come together and decide who is best trained to perform each procedure. To do so, it must first be decided how to base the decision; should the decision be based on the approach or the ultimate goal of the procedure? If based on the approach, it must then be asked if NOTES should be considered a surgical approach? How do we even define surgery today? Should a NOTES cholecystectomy be considered surgery even though EUS-FNA is not? If a consensus is reached among the medical community, NOTES may, like the arrival of laparoscopy in 1901, lead to a momentous step forward in medicine.

VASCULAR

Angiography

Angiography is another novel application of EUS. EUS can guide access into small vessels, such as the celiac branches and hepatic vein. Although thus far only conducted in animals, EUS can also be used to measure portal vein pressure and therefore guide portal hypertension therapy[25].

Bleeding control

EUS can also be applied to control gastrointestinal bleeding, such as treatment of varices, insertion of porto-systemic shunts, pseudoaneurysm control, embolization, and coil application. Studies have shown notable success, concluding that EUS should be considered when managing patients who have failed with conventional therapy[27]. Studies are still in their early stages, however, and much research on EUS and vascular interventions is on the horizon[18].

NOVEL TOOLS

Forward viewing EUS

Forward viewing EUS (FV-EUS), a relatively novel tool, is believed by some experts to be an upgrade to the conventional curved linear array EUS (CL-EUS)[21]. FV-EUS gives the endoscopist better and more stable access into cysts. It also is easier to maneuver because of its short, hard tip, thereby allowing for more dexterity during interventional procedures. This allows the endoscopist to reach more difficult locations within the GI tract; this is especially true in the lower GI tract, as FV-EUS has been shown to allow for easier cecal intubation[21]. FV-EUS also enables a shorter training time, which may lead to a more widespread usage than the conventional curved linear array EUS. In addition to its technical advantages over CL-EUS, some studies have also shown that FV-EUS can detect additional gastrointestinal lesions[28].

Disadvantages do exist though; the EUS view is reduced from 180 to 90 degrees; this however, reportedly, does not pose difficulty for experienced endosonographers. It is also more difficult with FV-EUS to intubate the cervical esophagus. It may also be more difficult to aspirate pancreatic pseudocysts because of the lack of fixation of the guide-wire without an elevator. Also regarding NOTES procedures, it is unclear if FV-EUS or CL-EUS is superior; a multicenter randomized trial, comparing the two endoscopes, found the same success rates, mean procedure times, and ease of access and complication rates[29]. FV-EUS and CL-EUS shared the same diagnostic yield of upper GI subepithelial lesions, though FV-EUS led to a shorter procedure time and a larger tissue sample area[30]. Clearly, more studies are needed on FV-EUS to determine when it provides significant advantage over the CL-EUS.

3D reconstruction

Three-dimensional imaging has been found useful in gynecologic ultrasound, and may also find a place in gastrointestinal EUS if proven advantageous.

CONCLUSION

EUS has come a long way in the last 25 years. Ultrasound has become much more than a tool to differentiate different tissue densities; tissue can now be characterized in great detail; the extent of vascularity within a tissue and how malignant the tissue appears can now be learned with increasing precision, all in real-time and without radiation. Using these techniques, targets for biopsy can be precisely pinpointed. Upon reaching the target, tissue can then be examined microscopically in real-time, to ensure optimal targeting and diagnosis.

EUS and its associated advancements have begun to take advantage of the fact that the gastrointestinal tract runs medially throughout the majority of the body and is very accessible; the gastrointestinal tract is now beginning to be used as an inlet to the rest of the body. After having brought ultrasound technology inside the gastrointestinal tract in the 1980s, EUS is

now being used as a guide outside the lumen. Many of these recent technologic advancements are in early stages and have not yet been studied extensively. The years ahead are therefore expected to be bright for EUS, as more research concludes and as these various technologies begin being implemented into clinical practice.

ACKNOWLEDGMENTS

The authors acknowledge the financial received by the Gastroenterology Institute at the Rambam Health Care Campus for the publishing of this literature review.

REFERENCES

1 **Wiersema MJ**, Hawes RH, Tao LC, Wiersema LM, Kopecky KK, Rex DK, Kumar S, Lehman GA. Endoscopic ultrasonography as an adjunct to fine needle aspiration cytology of the upper and lower gastrointestinal tract. *Gastrointest Endosc* 1992; **38**: 35-39 [PMID: 1612376 DOI: 10.1016/S0016-5107(92)70327-7]

2 **Cui XW**, Chang JM, Kan QC, Chiorean L, Ignee A, Dietrich CF. Endoscopic ultrasound elastography: Current status and future perspectives. *World J Gastroenterol* 2015; **21**: 13212-13224 [PMID: 26715804 DOI: 10.3748/wjg.v21.i47.13212]

3 **Meng FS**, Zhang ZH, Ji F. New endoscopic ultrasound techniques for digestive tract diseases: A comprehensive review. *World J Gastroenterol* 2015; **21**: 4809-4816 [PMID: 25944994 DOI: 10.3748/wjg.v21.i16.4809]

4 **Ahmad S**, Cao R, Varghese T, Bidaut L, Nabi G. Transrectal quantitative shear wave elastography in the detection and characterisation of prostate cancer. *Surg Endosc* 2013; **27**: 3280-3287 [PMID: 23525883 DOI: 10.1007/s00464-013-2906-7]

5 **Matsumoto K**, Katanuma A, Maguchi H, Takahashi K, Osanai M, Yane K, Kin T, Takaki R, Matsumori T, Gon K, Tomonari A, Nojima M. Performance of novel tissue harmonic echo imaging using endoscopic ultrasound for pancreatic diseases. *Endosc Int Open* 2016; **4**: E42-E50 [PMID: 26793784 DOI: 10.1055/s-0034-1393367]

6 **Kitano M**, Sakamoto H, Kudo M. Contrast-enhanced endoscopic ultrasound. *Dig Endosc* 2014; **26** Suppl 1: 79-85 [PMID: 24118242 DOI: 10.1111/den.12179]

7 **Giovannini M**. Needle-based confocal laser endomicroscopy. *Endosc Ultrasound* 2015; **4**: 284-288 [PMID: 26643694 DOI: 10.4103/2303-9027.170405]

8 **Deprez PH**. Future directions in EUS-guided tissue acquisition. *Gastrointest Endosc Clin N Am* 2014; **24**: 143-149 [PMID: 24215765 DOI: 10.1016/j.giec.2013.08.004]

9 **Bhutani MS**. Role of endoscopic ultrasound for pancreatic cystic lesions: Past, present, and future! *Endosc Ultrasound* 2015; **4**: 273-275 [PMID: 26643692 DOI: 10.4103/2303-9027.170400]

10 **Fisher JM**, Gardner TB. Endoscopic therapy of necrotizing pancreatitis and pseudocysts. *Gastrointest Endosc Clin N Am* 2013; **23**: 787-802 [PMID: 24079790 DOI: 10.1016/j.giec.2013.06.013]

11 **Keane MG**, Sze SF, Cieplik N, Murray S, Johnson GJ, Webster GJ, Thorburn D, Pereira SP. Endoscopic versus percutaneous drainage of symptomatic pancreatic fluid collections: a 14-year experience from a tertiary hepatobiliary centre. *Surg Endosc* 2016; **30**: 3730-3740 [PMID: 26675934 DOI: 10.1007/s00464-015-4668-x]

12 **Panamonta N**, Ngamruengphong S, Kijsirichareanchai K, Nugent K, Rakvit A. Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. *Eur J Gastroenterol Hepatol* 2012; **24**: 1355-1362 [PMID: 23114741 DOI: 10.1097/MEG.0b013e32835871eb]

13 **Rana SS**, Sharma V, Sharma R, Gupta R, Bhasin DK. Endoscopic ultrasound-guided transmural drainage of calcified pseudocyst in a patient with chronic calcific pancreatitis. *Ann Gastroenterol* 2015; **28**: 290 [PMID: 25831256]

14 **Habashi S**, Draganov PV. Pancreatic pseudocyst. *World J Gastroenterol* 2009; **15**: 38-47 [PMID: 19115466 DOI: 10.3748/wjg.15.38]

15 **Yamamoto N**, Isayama H, Kawakami H, Sasahira N, Hamada T, Ito Y, Takahara N, Uchino R, Miyabayashi K, Mizuno S, Kogure H, Sasaki T, Nakai Y, Kuwatani M, Hirano K, Tada M, Koike K. Preliminary report on a new, fully covered, metal stent designed for the treatment of pancreatic fluid collections. *Gastrointest Endosc* 2013; **77**: 809-814 [PMID: 23453183 DOI: 10.1016/j.gie.2013.01.009]

16 **Sharma V**, Rana SS, Bhasin DK. Endoscopic ultrasound guided interventional procedures. *World J Gastrointest Endosc* 2015; **7**: 628-642 [PMID: 26078831 DOI: 10.4253/wjge.v7.i6.628]

17 **Widmer JL**, Michel K. Endoscopic Ultrasound-Guided Treatment beyond Drainage: Hemostasis, Anastomosis, and Others. *Clin Endosc* 2014; **47**: 432-439 [PMID: 25325004 DOI: 10.5946/ce.2014.47.5.432]

18 **Mekky MA**, Abbas WA. Endoscopic ultrasound in gastroenterology: from diagnosis to therapeutic implications. *World J Gastroenterol* 2014; **20**: 7801-7807 [PMID: 24976718 DOI: 10.3748/wjg.v20.i24.7801]

19 **Iqbal S**, Friedel DM, Grendell JH, Stavropoulos SN. Outcomes of endoscopic-ultrasound-guided cholangiopancreatography: a literature review. *Gastroenterol Res Pract* 2013; **2013**: 869214 [PMID: 23573080 DOI: 10.1155/2013/869214]

20 **Khashab MA**, Valeshabad AK, Afghani E, Singh VK, Kumbhari V, Messallam A, Saxena P, El Zein M, Lennon AM, Canto MI, Kalloo AN. A comparative evaluation of EUS-guided biliary drainage and percutaneous drainage in patients with distal malignant biliary obstruction and failed ERCP. *Dig Dis Sci* 2015; **60**: 557-565 [PMID: 25081224 DOI: 10.1007/s10620-014-3300-6]

21 **Fuccio L**, Attili F, Larghi A. Forward-viewing linear echoendoscope: a new option in the endoscopic ultrasound armamentarium (with video). *J Hepatobiliary Pancreat Sci* 2015; **22**: 27-34 [PMID: 25345848 DOI: 10.1002/jhbp.181]

22 **Jang JW**, Lee SS, Song TJ, Hyun YS, Park DY, Seo DW, Lee SK, Kim MH, Yun SC. Endoscopic ultrasound-guided transmural and percutaneous transhepatic gallbladder drainage are comparable for acute cholecystitis. *Gastroenterology* 2012; **142**: 805-811 [PMID: 22245666 DOI: 10.1053/j.gastro.2011.12.051]

23 **Gress F**, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. *Am J Gastroenterol* 1999; **94**: 900-905 [PMID: 10201454 DOI: 10.1111/j.1572-0241.1999.01042.x]

24 **Lennon AM**, Newman N, Makary MA, Edil BH, Shin EJ, Khashab MA, Hruban RH, Wolfgang CL, Schulick RD, Giday S, Canto MI. EUS-guided tattooing before laparoscopic distal pancreatic resection (with video). *Gastrointest Endosc* 2010; **72**: 1089-1094 [PMID: 21034909 DOI: 10.1016/j.gie.2010.07.023]

25 **Saltzman JR**. EUS-guided angiography: a future indication for EUS? *Gastrointest Endosc* 2007; **66**: 592-595 [PMID: 17725952 DOI: 10.1016/j.gie.2007.03.1057]

26 **Barthet M**, Binmoeller KF, Vanbiervliet G, Gonzalez JM, Baron TH, Berdah S. Natural orifice transluminal endoscopic surgery gastroenterostomy with a biflanged lumen-apposing stent: first clinical experience (with videos). *Gastrointest Endosc* 2015; **81**: 215-218 [PMID: 25527056 DOI: 10.1016/j.gie.2014.09.039]

27 **Fujii-Lau LL**, Law R, Wong Kee Song LM, Gostout CJ, Kamath PS, Levy MJ. Endoscopic ultrasound (EUS)-guided coil injection therapy of esophagogastric and ectopic varices. *Surg Endosc* 2016; **30**: 1396-1404 [PMID: 26139494 DOI: 10.1007/s00464-015-4342-3]

28 **Thomas A**, Vamadevan AS, Slattery E, Sejpal DV, Trindade AJ. Performing forward-viewing endoscopy at time of pancreaticobiliary EUS and ERCP may detect additional upper gastrointestinal lesions. *Endosc Int Open* 2016; **4**: E193-E197 [PMID: 26878048 DOI: 10.1055/s-0041-109084]

29 **Voermans RP**, Ponchon T, Schumacher B, Fumex F, Bergman JJ, Larghi A, Neuhaus H, Costamagna G, Fockens P. Forward-viewing versus oblique-viewing echoendoscopes in transluminal drainage of pancreatic fluid collections: a multicenter, randomized, controlled trial. *Gastrointest Endosc* 2011; **74**: 1285-1293 [PMID: 21981813 DOI: 10.1016/j.gie.2011.07.059]

30 **Matsuzaki I**, Miyahara R, Hirooka Y, Funasaka K, Ohno E, Nakamura M, Kawashima H, Nukaga A, Shimoyama Y, Goto H. Forward-viewing versus oblique-viewing echoendoscopes in the diagnosis of upper GI subepithelial lesions with EUS-guided FNA: a prospective, randomized, crossover study. *Gastrointest Endosc* 2015; **82**: 287-295 [PMID: 25816723 DOI: 10.1016/j.gie.2014.12.051]

P- Reviewer: Cavalcoli F, Cui J, Matsumoto K, M'Koma AE
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2017 October 16; 9(10): 506-513

DOI: 10.4253/wjge.v9.i10.506

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic ultrasound elastography for solid pancreatic lesions

Tanyaporn Chantarojanasiri, Pradermchai Kongkam

Tanyaporn Chantarojanasiri, Department of Medicine, Police General Hospital, Patumwan, Bangkok 10400, Thailand

Pradermchai Kongkam, Gastrointestinal Endoscopy Excellent Center, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok 10330, Thailand

Author contributions: Both authors contributed to this paper.

Conflict-of-interest statement: The authors revealed no conflict of interest in relation to this review.

Manuscript source: Invited manuscript

Correspondence to: Pradermchai Kongkam, MD, Gastrointestinal Endoscopy Excellent Center, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, 1873, Rama 4 Road, Patumwan, Bangkok 10330, Thailand. pradermchai.k@chula.ac.th
Telephone: +66-2-2564356
Fax: +66-2-6524219

Received: January 30, 2017
Peer-review started: February 12, 2017
First decision: March 27, 2017
Revised: August 28, 2017
Accepted: September 4, 2017
Article in press: September 5, 2017
Published online: October 16, 2017

Abstract

Elastography is one of technologies assisting diagnosis of solid pancreatic lesions (SPL). This technology has been previously used for measuring the stiffness of various organs based on a principle of "harder the lesions, higher chance for malignancy". Two elastography techniques; strain and shear wave elastography, are available. For endoscopic ultrasound (EUS), only the former is existing. To interpret results of EUS elastography for SPL, 3 methods are used: (1) pattern recognition; (2) strain ratio; and (3) strain histogram. Based on results of existing studies, these 3 techniques provide high sensitivity but low to moderate specificity and accuracy rate. This review will summarize all available information in order to update current situation of using elastography for an evaluation of SPLs to readers.

Key words: Elastography; Endoscopic ultrasound; Solid pancreatic lesions; Pancreatic cancer; Chronic pancreatitis

Core tip: Elastography is a technology that can measure tissue stiffness. Endoscopic ultrasound (EUS) elastography has been increasingly used for an evaluation of solid pancreatic lesions (SPL). Several interpretation methods of EUS elastography for this purpose have been described in many previous studies. This review focuses on how to read and interpret findings of EUS elastography obtained from SPL. Readers should be competent for applying EUS elastography for diagnosing SPL after finishing reading the review.

Chantarojanasiri T, Kongkam P. Endoscopic ultrasound elastography for solid pancreatic lesions. *World J Gastrointest Endosc* 2017; 9(10): 506-513 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i10/506.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i10.506

INTRODUCTION

The diagnosis of solid pancreatic lesions (SPL) is a

challenging clinical problem. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the most commonly used diagnostic method. It has high specificity but moderate sensitivity. Due to the aggressiveness and poor outcomes of pancreatic cancer, several methods such as elastography or contrast enhancement have then been developed to assist in the diagnosis of SPL. Certainly, these software technologies cannot replace EUS-FNA because they are not pathological diagnostic tools, but they can help clinicians in many clinical scenarios such as in lesions with remarkably low EUS-FNA diagnostic yield including mass-forming chronic pancreatitis. Several previous studies have shown various efficacy values for these adjunctive technologies in their results. Elastography is one of these current assisting technologies diagnosing SPL. This technology measures the stiffness of the target lesion. In this review, the results of EUS elastography in the evaluation of SPL will be summarized.

This review summarizes characteristic findings of each SPL by EUS elastography. We searched the PubMed database for English-language journals with human studies published between 1988 and 2016. The following keywords were used in combination with EUS: Elastography, pancreas, and solid lesions. References to those identified articles were also examined for potentially relevant studies.

HISTORY OF ELASTOGRAPHY

Since 1988, the concepts of tissue deformability and elasticity of solid tumor has been described[1]. In 1991, tissue elasticity measurements were made by evaluation of the elastic modulus after applying a pressure (Figure 1); hence, the term "elastography" was first reported[2]. This led to the development of real-time imaging and the combination of elastography imaging with B mode imaging using a combined autocorrelation method in 2001[3]. Since then, elastography has been applied to the diagnosis of solid tumors of various organs such as breast, thyroids, lymph nodes and liver. In 2006, elastography for SPL was firstly reported[4]. The interpretation of elastography findings from SPL have been developed and applied to clinical management.

TYPES OF ELASTOGRAPHY

Elastography is classified into two categories based on different mechanical properties: Strain and shear wave elastography. The former evaluates tissue stiffness by measuring tissue distortion after applying pressure and the latter assess tissue stiffness by measuring tissue distortion after applying the acoustic radial force impulse[5]. However, only strain elastography is available for EUS.

STRAIN ELASTOGRAPHY MEASUREMENT METHODS

Strain elastography evaluates tissue stiffness *via* the displacement caused by manual compression or cardiovascular pulsation[6]. Larger strain or tissue displacement values represent softer tissue (Figure 2). The degree of strain-the relative indicator-can be displayed *via* three methods[6].

Pattern recognition

This method is to display as colors, with the green color as the mean stiffness, blue color represents harder tissue and red color represents softer tissue. This is the only method considered qualitative method whereas following methods are quantitative ones.

Strain ratio

This method is to display as gray scale image and compare strain ratio (SR) of area of interest with reference area.

Strain histogram

Pattern recognition: Color pattern analysis of elastography was first described in transcutaneous ultrasound elastography of the breast[7]. The EUS elastography pattern in pancreatic lesion was first described by Giovannini (Figure 3)[4] with 100% sensitivity but only 67% specificity in differential diagnosis of benign and malignant SPL. The same author later classified the previous 5-scale elastic score into 3 scores: A, B and C, representing benign, indeterminate, and malignant lesions, respectively[8]. This classification has 92.3% sensitivity and 80% specificity in differential diagnosis between benign and malignant SPL. Reports of different pattern analyses results in different clinical efficacy have been published. Another report by Janssen *et al*[9] classified color patterns into 3 types: Type 1 with homogeneous pattern, type 2 with 2 or 3 colors, and type 3 with a honeycomb pattern. In this report, however, the use of elastography in differential diagnosis between benign and malignant lesions was disappointing. Another study done by Iglesias-Garcia[10], classified the elastography into 4 patterns with 100% sensitivity and 85.5% specificity in the diagnosis of malignant SPL. The comparison of each report as well as sensitivity and specificity is shown in Table 1.

SR: SR compares the strain between the target area and other reference areas to provide more objective qualitative data[11]. In breast lesions, the strain of the lesion is compared to the strain of the surrounding fat tissue. Many studies use SR to differentially diagnose pancreatic carcinoma and chronic pancreatitis[11-14]. In some studies, the strain of the area surrounding the pancreas was used as the baseline compared with the strain of the lesion[11,15]. The peripancreatic surrounding the soft tissue was used as the baseline in other studies[12,13]. Moreover, according to the phantom study, the depth of the reference area has a significant impact on the evaluation of the SR[16]. The area of selection and cut-off point in each study are demonstrated in Table 2. Studies have correlated SR and chronic pancreatitis.

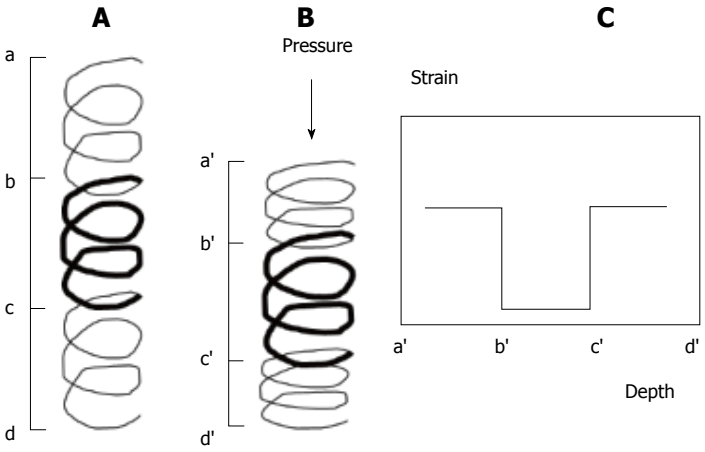


Figure 1 The principle of strain elastography is illustrated by coil spring appearance. A: After applying pressure, more deformation is demonstrated in tissue with higher elasticity; B: The strain on each tissue depends on the tissue stiffness; C: Higher strain is seen in softer tissue after compression (Adapted from Ophir[2]).

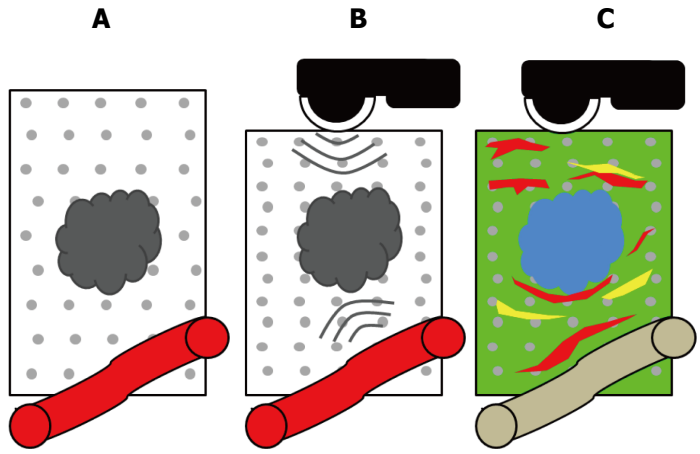


Figure 2 The principle of endoscopic ultrasound elastography for solid pancreatic lesions. A: Pancreatic carcinoma has more stiffness than normal pancreas; B: The strain elastography measured the degree of displacement after applying manual pressure or vascular pulsation; C: The degree of displacement is represented as colors: Green is the average stiffness, blue is stiffer tissue, and red is softer tissue.

Table 1 Results of 4 large studies using pattern recognition of elastography for diagnosis of solid pancreatic lesions

Author	Giovannini *et al*[4], 2006		Giovannini *et al*[8], 2009		Janssen *et al*[9], 2007			Iglesias-Garcia *et al*[10], 2009	
	Elastic score /pattern	Interpretation	Score	Inter-pretation	Type	Color	Interpretation	Pattern	Interpretation
Score and interpretation	Distortion for entire low echo area	Normal pancreas	A (elastic score 1 and 2)	Benign	Homogeneous	A = blue	B = normal pancreas	Homogeneous green	Normal pancreas
	No distortion on low echo area even for a part	Fibrosis, chronic pancreatitis						Heterogenous green	Inflammatory pancreas
	Distortion at the edge of low echo area, even for a part	Small adeno-carcinoma	B (elastic score 3)	Indeter-minate	2 or 3 colors	B = green/ yellow		Homogeneous blue	Ductal pancreatic adenocarcinoma
	No distortion for entire low echo area	Endocrine tumor	C (elastic score 4 and 5)	Malignant	Heterogeneous	C = red	A/B = chronic pancreatitis and neoplasia	Heterogeneous blue	Neuroendocrine tumor
	No distortion on low echo area and surrounding	Advanced adeno-carcinoma							
Sensitivity	100		92.3		65.9 (chronic pancreatitis), 93.8 (neoplasia)			100	
Specificity	67		80		56.9 (chronic pancreatitis), 65.4 (neoplasia)			85.5	
Accuracy	NA		89.2		60.2 (chronic pancreatitis), 73.5 (neoplasia)			94	

NA: Not available.

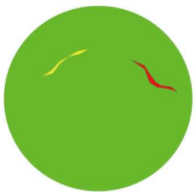
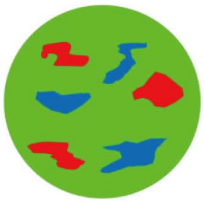
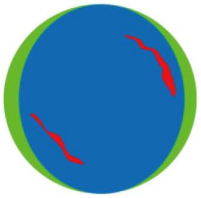
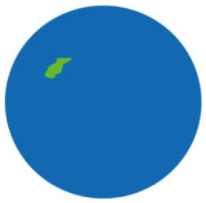
Elastic score	Elastography	Pattern	Condition
1		Distortion for entire low echo area	Normal pancreas
2		No distortion on low echo area even for a part	Fibrosis, chronic pancreatitis
3		Distortion at the edge of low echo area, even for a part	Small adenocarcinoma
4		No distortion for entire low echo area	Endocrine tumor
5		No distortion on low echo area and surrounding	Advanced adenocarcinoma

Figure 3 Classification of elastography findings proposed by Giovannini[4].

Iglesias-Garcia reported a cut-off of 2.25 for the diagnosis of chronic pancreatitis with a sensitivity of 91.2% and a specificity of 91% using the surrounding soft tissue as a reference[17]. Another study reported the correlation of SR and the presence of pancreatic exocrine insufficiency (PEI) with 87.0% probability of PEI in those with SR higher than 4.5 compared with 16.3% probability of PEI in those with SR lower than 4.5[18]. In this study, the normal surrounding gut wall was used as the reference. Iglesias-Garcias reported the mean elastic value to be 0.47%, 0.23%, 0.02% and 0.01% for normal pancreas, chronic pancreatitis, pancreatic cancer, and endocrine tumor, respectively[14]. Another report from South Korea demonstrated a mean elastic value of 0.53% for the normal pancreas and 0.02% for pancreatic cancer[19].

Many studies are based on the SR method, but there is no standardization for the reference area yet[5]. Moreover, the distance of the reference area from the ultrasound probe significantly impacted the SR measurements[16]. These two factors significantly impacted the reliability of the SR methods as a diagnostic test for SPL.

Strain histogram

The strain histogram is another type of the quantitative image analysis. To analyze the strain histogram, the color image of the elastography is converted into the gray scale (value) of 256 tones. It ranged from 0 to 255 with 0 representing the blue area (hard) and 255 representing the red area (soft) (Figure 4). The distribution of the gray scale is then calculated into various parameters as shown (Table 3). In some reports, the histograms were performed separately from the individual red/green/blue color[20]. The correlations of the parameters with the degree of pancreatic fibrosis have been published[21]. With increasing fibrosis, the mean and standard deviation decrease, while skewness and kurtosis increase. On the other hand, the histogram could be analyzed using the neural network analysis. The correlation between a cut-off mean level > 175 in pancreatic carcinoma

Table 2 Results of studies using strain ratio of elastography for an evaluation of solid pancreatic lesions

Ref.	Diseases of comparison (*n*)	Reference area	Cut off point	Sensitivity	Specificity
Iglesia-Garcia *et al*[14]	PC (49) *vs* CP (27)	Soft tissue	6.04	100	96.3
	PC (49) *vs* PNET (6)		26.63	100	87.8
Itokawa *et al*[11]	PC (72), PNET (9), CP (20), normal pancreas (8)	Normal pancreas	23.66 in MFP *vs* 39.08 in PC		
Dawwas *et al*[12]	Malignant (87): (PC, PNET, metastatic cancer) And benign (17) (pancreatitis)	Soft tissue	4.65	100	16.7
Kongkam *et al*[13]	PC (23), PNET (5), Meatastasis (1), CP (2), AIP (3), other (4)	Soft tissue	3.17	86.2	66.7
			6.04	75.9	77.8

PC: Pancreatic cancer; PNET: Pancreatic neuroendocrine tumor; CP: Chronic pancreatitis; AIP: Autoimmune pancreatitis.

Table 3 The histogram parameters[5,21,45]

Images	Parameters	Information	Interpretation
Gray scale images	Mean	Mean of the gray levels	Higher mean value indicates softer tissue
	Standard deviation	Standard deviation of the gray levels	Higher value indicating heterogeneous hardness
	ASM	Measure of the homogeneity on the gray scale image	
	Contrast	Measure of local gray level variation on the gray scale image	
	Correlation	Measure of gray level linear dependence on the gray scale image	
	Entropy	Measure of the randomness of gray level distribution	
	IDM	Measure of the homogeneity on the gray scale image	
	Skewness	Measure of the asymmetry of the gray level distribution	Higher value indicating higher or lower hardness
	Kurtosis	Measure of the "peakedness" of the gray level distribution	Higher value indicating concentration of a specific hardness
Black and white image	% area	Percentage of the white area (= hard area)	
	Mean of Complexity	Complex ratio of the shape of the white area (= hard area) and is calculated as periphery^2/area of the white area	

had a sensitivity of 91.4%-93.4% and a specificity of 66%-87.9%[22,23]. Another report analyzed the histogram by comparing the histogram of the tumor over the adjacent part of the pancreas[24]. The strain histogram's ratio with cut-off value of 1.15 indicated pancreatic malignancy with 98% sensitivity, 58% specificity, and 69% accuracy.

CLINICAL IMPLICATIONS

Pancreatic adenocarcinoma vs mass-forming chronic pancreatitis

Pancreatic adenocarcinoma is the most common type of pancreatic tumor, and it is characterized by many desmoplastic reactions[25]. Increased amounts of extracellular matrix including type Ⅰ and type Ⅴ collagen and fibronectin are found similar to those found in alcoholic chronic pancreatitis and tumor-induced chronic pancreatitis[26]. The differential diagnosis between pancreatic adenocarcinoma and mass-forming pancreatitis-especially on the background of chronic pancreatitis-remains a challenging problem. It is well known that the incidence of pancreatic adenocarcinoma is higher in patients with chronic pancreatitis[27]. Moreover, some features of chronic pancreatitis, such as calcification, may hinder the detection of pancreatic cancer[28]. Moreover, EUS-FNA of the pancreatic cancer (standard method for tissue acquisition from SPL) results in only 50%-73.9% sensitivity but with 73.7%-100% specificity in the presence of chronic pancreatitis[29-31]. In elastography, pancreatic adenocarcinoma usually manifests as a hard tumor with a predominate blue color pattern (Table 1 and Figure 5). It has a higher SR than mass-forming chronic pancreatitis. Another single report compared pancreatic adenocarcinoma and autoimmune pancreatitis. This demonstrated that in autoimmune pancreatitis the stiffness area not only forms the mass area but also the surrounding pancreatic tissue[32].

Pancreatic neuroendocrine tumor

Pancreatic neuroendocrine tumors (PNETs) are a rare type of solid pancreatic tumor that are characterized histologically by tumor cells arranged in solid nest, trabecular, or gland like formation surrounded by thin vascular stroma[33]. The elastography pattern of PNET was described as homogeneous blue and heterogeneous blue by Giovannini[4] and Iglesias-Garcia[10], respectively. In one prospective study that included 6 patients with PNET, the SR of PNET is 56.73-higher than the 17.41 SR seen in pancreatic adenocarcinoma[17].

Solid pseudopapillary neoplasm

Elastography studies in solid pseudopapillary neoplasm (SPN) are rare. Only one study with 1 SPN case was found. It had a SR near 15[17].

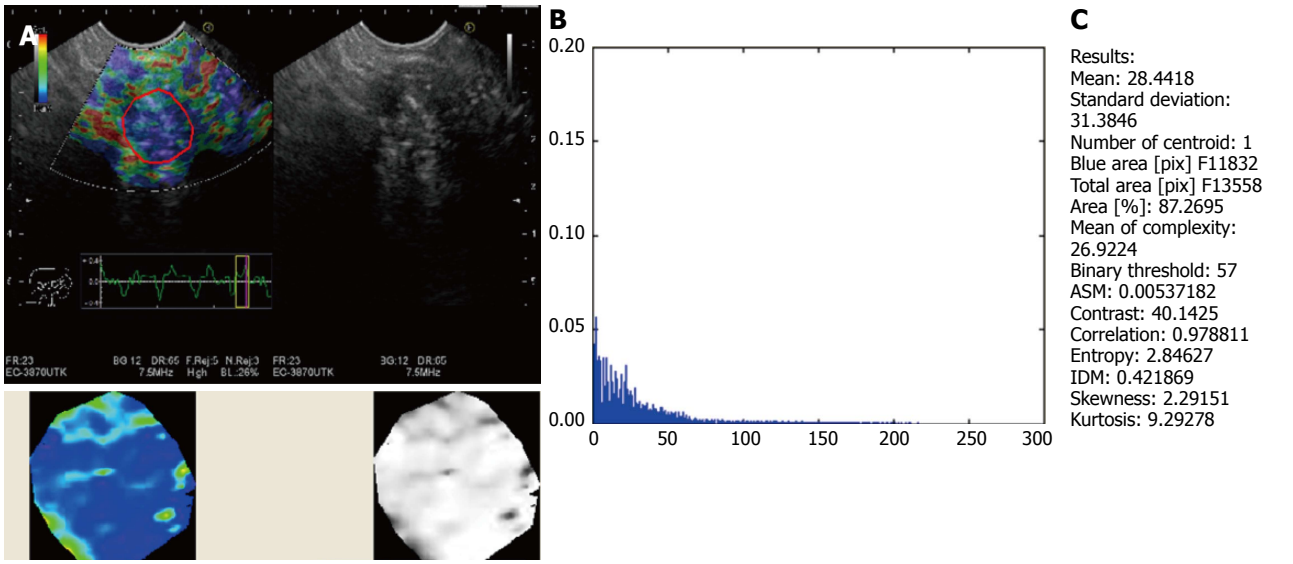


Figure 4 Histogram analysis using MATLABver 1.6.7. A and B: The color image of the elastography is converted into the gray scale (value) of 256 tones ranging from 0 to 255:0 represents the blue area (hard) and 255 represents the red area (soft); C: The distribution of the gray scale is presented as a histogram from which the parameters are calculated.

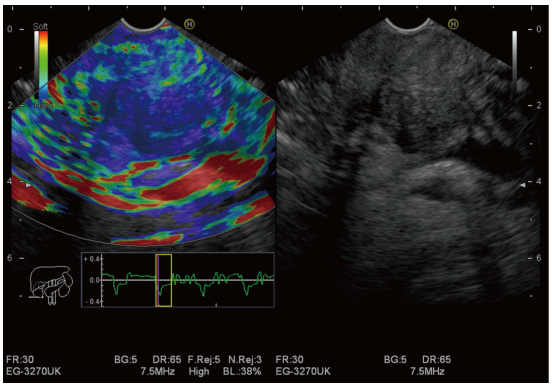


Figure 5 Endoscopic ultrasound elastography of pancreatic adenocarcinoma. The color pattern showed predominant blue color pattern without distortion of surrounding area.

OTHER UNCOMMON TUMORS

For pancreatic acinar cell carcinoma, there are limited reports of EUS elastography. Only one report of elastography in pancreatic acinar cell carcinoma has been published[34]. In this report, there was no specific pattern of elastography, and the pattern varied according to the acinar cell tumor pathologic phenotype. The data for more uncommon types of pancreatic cancers such as anaplastic cell carcinoma and adenosquamous cell carcinoma have not yet been reported.

Chronic pancreatitis

Elastography has been used in both the diagnosis of chronic pancreatitis and as a predictor of post-operative pancreatic fistula. Despite the usefulness of EUS in the diagnosis of pancreatic lesions, there are only limited data in EUS elastography studies in chronic pancreatitis. Many studies of elastography in chronic pancreatitis using transabdominal ultrasound with shear wave elastography for the detection of pancreatic fibrosis both in chronic pancreatitis and tumor-related fibrosis have been reported[35-38]. Apart from the transabdominal ultrasonography, intraoperative ultrasound elastography has been published. This demonstrated correlation between "soft pancreas" and the development of a post-operative pancreatic fistula[39,40].

In EUS studies, one prospective study demonstrated a higher SR in chronic pancreatitis with 91.2% sensitivity, 91.0% specificity, and 91.1% accuracy with a cut-off point of 2.25[17]. In this study, the SR also varied across groups according to Rosemond criteria for the diagnosis of chronic pancreatitis with a higher SR up to 8.12 in cases that fulfilled all criteria of chronic pancreatitis. Moreover, in patients with chronic pancreatitis, elastography with higher SR was seen in those with evidence of pancreatic enzyme insufficiency (SR 4.89 *vs* 2.99)[18]. This finding was consistent with another study demonstrating higher stiffness in more advanced pancreatic fibrosis using EUS elastography with histogram analysis[21]. A retrospective study of EUS elastography using histograms for analysis also demonstrate the correlation of mean value with the stage of chronic pancreatitis *via* the Rosemont criteria. This used cutoffs of 90.1 ± 19.3, 73.2 ± 10.6, 63.7 ± 14.2, and 56.1 ± 13.6, in normal pancreas, indeterminate for chronic pancreatitis, suggestive of chronic pancreatitis, and consistent with chronic pancreatitis, respectively[41].

Aging can cause several changes similar to early chronic pancreatitis[42]. A study using EUS also demonstrated abnormalities similar to chronic pancreatitis in elderly subjects without clinical chronic pancreatitis-particularly after the age of 60[43]. Elastography studies in aging populations also showed increased pancreatic stiffness with age demonstrated by both EUS[44]. and transabdominal ultrasonography[45]. These changes

become significant after age 40 to 60[44,45]. In one study, the mean histogram below 50 was more suggestive of chronic pancreatitis than usual aging changes[44].

COULD EUS ELASTOGRAPHY REPLACED TISSUE DIAGNOSIS?

While many studies have demonstrated excellent efficacy of elastography in the diagnosis of SPL, the value of elastography in cases with negative EUS FNA remains inconsistently demonstrated in all studies. Moreover, the method of image analysis is not yet standardized. Most reports demonstrated high sensitivity but low specificity, and the interpretation was performed by a center with many experienced elastographers. Hence, elastography cannot replace EUS-FNA for diagnosis[46].

CONCLUSION

In summary, EUS elastography is an improvement in the differential diagnosis between benign and malignant SPL in many studies. The main role of elastography in SPL is as an adjunct with other modalities in making diagnoses. Especially in chronic pancreatitis, EUS still has a promising role in both the diagnosis of early chronic pancreatitis and the prediction of complication. However, the overlapping of early chronic pancreatitis and aging changes makes the decision more difficult.

REFERENCES

1 **Ueno E**, Tohno E, Soeda S, Asaoka Y, Itoh K, Bamber JC, Blaszçzyk M, Davey J, Mckinna JA. Dynamic tests in real-time breast echography. *Ultrasound Med Biol* 1988; **14** Suppl 1: 53-57 [PMID: 3055603]

2 **Ophir J**, Céspedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 1991; **13**: 111-134 [PMID: 1858217]

3 **Shiina T**, Nitta N, Ueno E, Bamber JC. Real time tissue elasticity imaging using the combined autocorrelation method. *J Med Ultrason* (2001) 2002; **29**: 119-128 [PMID: 27277886 DOI: 10.1007/BF02481234]

4 **Giovannini M**, Hookey LC, Bories E, Pesenti C, Monges G, Delpero JR. Endoscopic ultrasound elastography: the first step towards virtual biopsy? Preliminary results in 49 patients. *Endoscopy* 2006; **38**: 344-348 [PMID: 16680632 DOI: 10.1055/s-2006-925158]

5 **Hirooka Y**, Kuwahara T, Irisawa A, Itokawa F, Uchida H, Sasahira N, Kawada N, Itoh Y, Shiina T. JSUM ultrasound elastography practice guidelines: pancreas. *J Med Ultrason* (2001) 2015; **42**: 151-174 [PMID: 26576568 DOI: 10.1007/s10396-014-0571-7]

6 **Shiina T**. JSUM ultrasound elastography practice guidelines: basics and terminology. *J Med Ultrason* (2001) 2013; **40**: 309-323 [PMID: 27277449 DOI: 10.1007/s10396-013-0490-z]

7 **Itoh A**, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, Yamakawa M, Matsumura T. Breast disease: clinical application of US elastography for diagnosis. *Radiology* 2006; **239**: 341-350 [PMID: 16484352 DOI: 10.1148/radiol.2391041676]

8 **Giovannini M**, Thomas B, Erwan B, Christian P, Fabrice C, Benjamin E, Geneviève M, Paolo A, Pierre D, Robert Y, Walter S, Hanz S, Carl S, Christoph D, Pierre E, Jean-Luc VL, Jacques D, Peter V, Andrian S. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. *World J Gastroenterol* 2009; **15**: 1587-1593 [PMID: 19340900 DOI: 10.3748/wjg.v15.i13.1587]

9 **Janssen J**, Schlörer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. *Gastrointest Endosc* 2007; **65**: 971-978 [PMID: 17531630 DOI: 10.1016/j.gie.2006.12.057]

10 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. *Gastrointest Endosc* 2009; **70**: 1101-1108 [PMID: 19647248 DOI: 10.1016/j.gie.2009.05.011]

11 **Itokawa F**, Itoi T, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Umeda J, Tanaka R, Yokoyama N, Moriyasu F, Kasuya K, Nagao T, Kamisawa T, Tsuchida A. EUS elastography combined with the strain ratio of tissue elasticity for diagnosis of solid pancreatic masses. *J Gastroenterol* 2011; **46**: 843-853 [PMID: 21505859 DOI: 10.1007/s00535-011-0399-5]

12 **Dawwas MF**, Taha H, Leeds JS, Nayar MK, Oppong KW. Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: a prospective, single-center study. *Gastrointest Endosc* 2012; **76**: 953-961 [PMID: 22854060 DOI: 10.1016/j.gie.2012.05.034]

13 **Kongkam P**, Lakananurak N, Navicharern P, Chantarojanasiri T, Aye K, Ridtitid W, Kritisin K, Angsuwatcharakon P, Aniwan S, Pittayanon R, Sampatanukul P, Treeprasertsuk S, Kullavanijaya P, Rerknimitr R. Combination of EUS-FNA and elastography (strain ratio) to exclude malignant solid pancreatic lesions: A prospective single-blinded study. *J Gastroenterol Hepatol* 2015; **30**: 1683-1689 [PMID: 26238152 DOI: 10.1111/jgh.13067]

14 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010; **139**: 1172-1180 [PMID: 20600020 DOI: 10.1053/j.gastro.2010.06.059]

15 **Kawada N**, Tanaka S, Uehara H, Takakura R, Katayama K, Fukuda J, Matsuno N, Takenaka A, Ishikawa O. Feasibility of second-generation transabdominal ultrasound-elastography to evaluate solid pancreatic tumors: preliminary report of 36 cases. *Pancreas* 2012; **41**: 978-980 [PMID: 22781915 DOI: 10.1097/MPA.0b013e3182499b84]

16 **Havre RF**, Waage JR, Gilja OH, Odegaard S, Nesje LB. Real-Time Elastography: Strain Ratio Measurements Are Influenced by the Position of the Reference Area. *Ultraschall Med* 2011; Epub ahead of print [PMID: 21667433 DOI: 10.1055/s-0031-1273247]

17 **Iglesias-Garcia J**, Domínguez-Muñoz JE, Castiñeira-Alvariño M, Luaces-Regueira M, Lariño-Noia J. Quantitative elastography associated with endoscopic ultrasound for the diagnosis of chronic pancreatitis. *Endoscopy* 2013; **45**: 781-788 [PMID: 24019131 DOI: 10.1055/s-0033-1344614]

18 **Dominguez-Muñoz JE**, Iglesias-Garcia J, Castiñeira Alvariño M, Luaces Regueira M, Lariño-Noia J. EUS elastography to predict pancreatic exocrine insufficiency in patients with chronic pancreatitis. *Gastrointest Endosc* 2015; **81**: 136-142 [PMID: 25088920 DOI: 10.1016/j.gie.2014.06.040]

19 **Lee TH**, Cho YD, Cha SW, Cho JY, Jang JY, Jeong SW, Choi HJ, Moon JH. Endoscopic ultrasound elastography for the pancreas in Korea: a preliminary single center study. *Clin Endosc* 2013; **46**: 172-177 [PMID: 23614128 DOI: 10.5946/ce.2013.46.2.172]

20 **Schrader H**, Wiese M, Ellrichmann M, Belyaev O, Uhl W, Tannapfel A, Schmidt W, Meier J. Diagnostic value of quantitative EUS elastography for malignant pancreatic tumors: relationship with pancreatic fibrosis. *Ultraschall Med* 2012; **33**: E196-E201 [PMID: 21630184 DOI: 10.1055/s-0031-1273256]

21 **Itoh Y**, Itoh A, Kawashima H, Ohno E, Nakamura Y, Hiramatsu T, Sugimoto H, Sumi H, Hayashi D, Kuwahara T, Morishima T, Funasaka K, Nakamura M, Miyahara R, Ohmiya N, Katano Y, Ishigami M, Goto H, Hirooka Y. Quantitative analysis of diagnosing pancreatic fibrosis using EUS-elastography (comparison with surgical specimens). *J Gastroenterol* 2014; **49**: 1183-1192 [PMID: 24026103 DOI: 10.1007/s00535-013-0880-4]

22 **Săftoiu A**, Vilmann P, Gorunescu F, Gheonea DI, Gorunescu M, Ciurea T, Popescu GL, Iordache A, Hassan H, Iordache S. Neural network analysis of dynamic sequences of EUS elastography used for

the differential diagnosis of chronic pancreatitis and pancreatic cancer. *Gastrointest Endosc* 2008; **68**: 1086-1094 [PMID: 18656186 DOI: 10.1016/j.gie.2008.04.031]

23 **Săftoiu A**, Vilmann P, Gorunescu F, Janssen J, Hocke M, Larsen M, Iglesias-Garcia J, Arcidiacono P, Will U, Giovannini M, Dietrich C, Havre R, Gheorghe C, McKay C, Gheonea DI, Ciurea T; European EUS Elastography Multicentric Study Group. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. *Endoscopy* 2011; **43**: 596-603 [PMID: 21437851 DOI: 10.1055/s-0030-1256314]

24 **Opačić D**, Rustemović N, Kalauz M, Markoš P, Ostojić Z, Majerović M, Ledinsky I, Višnjić A, Krznarić J, Opačić M. Endoscopic ultrasound elastography strain histograms in the evaluation of patients with pancreatic masses. *World J Gastroenterol* 2015; **21**: 4014-4019 [PMID: 25852289 DOI: 10.3748/wjg.v21.i13.4014]

25 **Pandol S**, Edderkaoui M, Gukovsky I, Lugea A, Gukovskaya A. Desmoplasia of pancreatic ductal adenocarcinoma. *Clin Gastroenterol Hepatol* 2009; **7**: S44-S47 [PMID: 19896098 DOI: 10.1016/j.cgh.2009.07.039]

26 **Imamura T**, Iguchi H, Manabe T, Ohshio G, Yoshimura T, Wang ZH, Suwa H, Ishigami S, Imamura M. Quantitative analysis of collagen and collagen subtypes I, III, and V in human pancreatic cancer, tumor-associated chronic pancreatitis, and alcoholic chronic pancreatitis. *Pancreas* 1995; **11**: 357-364 [PMID: 8532652]

27 **Raimondi S**, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 2010; **24**: 349-358 [PMID: 20510834 DOI: 10.1016/j.bpg.2010.02.007]

28 **Bang JY**, Varadarajulu S. Neoplasia in chronic pancreatitis: how to maximize the yield of endoscopic ultrasound-guided fine needle aspiration. *Clin Endosc* 2014; **47**: 420-424 [PMID: 25325001 DOI: 10.5946/ce.2014.47.5.420]

29 **Varadarajulu S**, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc* 2005; **62**: 728-736; quiz 751, 753 [PMID: 16246688 DOI: 10.1016/j.gie.2005.06.051]

30 **Iordache S**, Săftoiu A, Cazacu S, Gheonea DI, Dumitrescu D, Popescu C, Ciurea T. Endoscopic ultrasound approach of pancreatic cancer in chronic pancreatitis patients in a tertiary referral centre. *J Gastrointestin Liver Dis* 2008; **17**: 279-284 [PMID: 18836620]

31 **Fritscher-Ravens A**, Brand L, Knöfel WT, Bobrowski C, Topalidis T, Thonke F, de Werth A, Soehendra N. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. *Am J Gastroenterol* 2002; **97**: 2768-2775 [PMID: 12425546 DOI: 10.1111/j.1572-0241.2002.07020.x]

32 **Dietrich CF**, Hirche TO, Ott M, Ignee A. Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2009; **41**: 718-720 [PMID: 19618344 DOI: 10.1055/s-0029-1214866]

33 **Kasajima A**, Yazdani S, Sasano H. Pathology diagnosis of pancreatic neuroendocrine tumors. *J Hepatobiliary Pancreat Sci* 2015; **22**: 586-593 [PMID: 25641911 DOI: 10.1002/jhbp.208]

34 **Chantarojanasiri T**, Hirooka Y, Kawashima H, Ohno E, Yamamura T, Funasaka K, Nakamura M, Miyahara R, Ishigami M, Watanabe O, Nakaguro M, Shimoyama Y, Nakamura S, Goto H. Endoscopic ultrasound in the diagnosis of acinar cell carcinoma of the pancreas: contrast-enhanced endoscopic ultrasound, endoscopic ultrasound elastography, and pathological correlation. *Endosc Int Open* 2016; **4**: E1223-E1226 [PMID: 27853750 DOI: 10.1055/s-0042-110096]

35 **Yashima Y**, Sasahira N, Isayama H, Kogure H, Ikeda H, Hirano K, Mizuno S, Yagioka H, Kawakubo K, Sasaki T, Nakai Y, Tada M, Yoshida H, Omata M, Koike K. Acoustic radiation force impulse elastography for noninvasive assessment of chronic pancreatitis. *J Gastroenterol* 2012; **47**: 427-432 [PMID: 22065162 DOI: 10.1007/s00535-011-0491-x]

36 **Kuwahara T**, Hirooka Y, Kawashima H, Ohno E, Sugimoto H, Hayashi D, Morishima T, Kawai M, Suhara H, Takeyama T, Yamamura T, Funasaka K, Nakamura M, Miyahara R, Watanabe O, Ishigami M, Shimoyama Y, Nakamura S, Hashimoto S, Goto H. Quantitative evaluation of pancreatic tumor fibrosis using shear wave elastography. *Pancreatology* 2016; **16**: 1063-1068 [PMID: 27692969 DOI: 10.1016/j.pan.2016.09.012]

37 **Llamoza-Torres CJ**, Fuentes-Pardo M, Álvarez-Higueras FJ, Alberca-de-Las-Parras F, Carballo-Álvarez F. Usefulness of percutaneous elastography by acoustic radiation force impulse for the non-invasive diagnosis of chronic pancreatitis. *Rev Esp Enferm Dig* 2016; **108**: 450-456 [PMID: 27459032 DOI: 10.17235/reed.2016.4103/2015]

38 **Goertz RS**, Schuderer J, Strobel D, Pfeifer L, Neurath MF, Wildner D. Acoustic radiation force impulse shear wave elastography (ARFI) of acute and chronic pancreatitis and pancreatic tumor. *Eur J Radiol* 2016; **85**: 2211-2216 [PMID: 27842669 DOI: 10.1016/j.ejrad.2016.10.019]

39 **Hatano M**, Watanabe J, Kushihata F, Tohyama T, Kuroda T, Koizumi M, Kumagi T, Hisano Y, Sugita A, Takada Y. Quantification of pancreatic stiffness on intraoperative ultrasound elastography and evaluation of its relationship with postoperative pancreatic fistula. *Int Surg* 2015; **100**: 497-502 [PMID: 25785334 DOI: 10.9738/INTSURG-D-14-00040.1]

40 **Harada N**, Ishizawa T, Inoue Y, Aoki T, Sakamoto Y, Hasegawa K, Sugawara Y, Tanaka M, Fukayama M, Kokudo N. Acoustic radiation force impulse imaging of the pancreas for estimation of pathologic fibrosis and risk of postoperative pancreatic fistula. *J Am Coll Surg* 2014; **219**: 887-894.e5 [PMID: 25262282 DOI: 10.1016/j.jamcollsurg.2014.07.940]

41 **Kuwahara T**, Hirooka Y, Kawashima H, Ohno E, Ishikawa T, Kawai M, Suhara H, Takeyama T, Hashizume K, Koya T, Tanaka H, Sakai D, Yamamura T, Furukawa K, Funasaka K, Nakamura M, Miyahara R, Watanabe O, Ishigami M, Hashimoto S, Goto H. Quantitative diagnosis of chronic pancreatitis using EUS elastography. *J Gastroenterol* 2017; **52**: 868-874 [PMID: 27995327 DOI: 10.1007/s00535-016-1296-8]

42 **Chantarojanasiri T**, Hirooka Y, Ratanachu-Ek T, Kawashima H, Ohno E, Goto H. Evolution of pancreas in aging: degenerative variation or early changes of disease? *J Med Ultrason* (2001) 2015; **42**: 177-183 [PMID: 26576570 DOI: 10.1007/s10396-014-0576-2]

43 **Rajan E**, Clain JE, Levy MJ, Norton ID, Wang KK, Wiersema MJ, Vazquez-Sequeiros E, Nelson BJ, Jondal ML, Kendall RK, Harmsen WS, Zinsmeister AR. Age-related changes in the pancreas identified by EUS: a prospective evaluation. *Gastrointest Endosc* 2005; **61**: 401-406 [PMID: 15758911]

44 **Janssen J**, Papavassiliou I. Effect of aging and diffuse chronic pancreatitis on pancreas elasticity evaluated using semiquantitative EUS elastography. *Ultraschall Med* 2014; **35**: 253-258 [PMID: 24327468 DOI: 10.1055/s-0033-1355767]

45 **Chantarojanasiri T**, Hirooka Y, Kawashima H, Ohno E, Sugimoto H, Hayashi D, Kuwahara T, Yamamura T, Funasaka K, Nakamura M, Miyahara R, Ishigami M, Watanabe O, Hashimoto S, Goto H. Age-related changes in pancreatic elasticity: When should we be concerned about their effect on strain elastography? *Ultrasonics* 2016; **69**: 90-96 [PMID: 27070288 DOI: 10.1016/j.ultras.2016.03.018]

46 **Deprez PH**. EUS elastography: is it replacing or supplementing tissue acquisition? *Gastrointest Endosc* 2013; **77**: 590-592 [PMID: 23498142 DOI: 10.1016/j.gie.2012.11.040]

P- Reviewer: Gilabert JL, Hu H, Zhu YL **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2017 October 16; 9(10): 514-520

DOI: 10.4253/wjge.v9.i10.514

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Oral esomeprazole *vs* injectable omeprazole for the prevention of hemorrhage after endoscopic submucosal dissection

Takashi Uchiyama, Takuma Higurashi, Hitoshi Kuriyama, Yoshinobu Kondo, Yasuo Hata, Atsushi Nakajima

Takashi Uchiyama, Takuma Higurashi, Atsushi Nakajima, Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, Yokohama city, Kanagawa Prefecture 236-0042, Japan

Takashi Uchiyama, Hitoshi Kuriyama, Yasuo Hata, Department of Gastroenterology, Chigasaki Municipal Hospital, Chigasaki city, Kanagawa Prefecture 235-0042, Japan

Yoshinobu Kondo, Department of Endocrinology and Metabolism, Chigasaki Municipal Hospital, Chigasaki city, Kanagawa Prefecture 235-0042, Japan

Author contributions: Uchiyama T collected and analyzed the data, and drafted the manuscript; Higurashi T provided analytical oversight; Nakajima A supervised the study; Kuriyama H and Hata Y revised the manuscript for important intellectual content; Kondo Y offered the technical support; authors have read and approved the final version to be published.

Institutional review board statement: Ethics committee approval was received for this study from the ethics committee of Chigasaki Municipal Hospital.

Informed consent statement: All the treatment procedures were performed after obtaining informed consent in writing from the patients.

Conflict-of-interest statement: No conflict of interest was declared by the authors.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Takashi Uchiyama, MD, PhD, Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawaku, Yokohama city, Kanagawa 236-0004, Japan. tuchiyama-ykh@umin.ac.jp
Telephone: +81-45-7872640
Fax: +81-45-7843546

Received: March 22, 2017
Peer-review started: March 23, 2017
First decision: April 17, 2017
Revised: May 19, 2017
Accepted: July 14, 2017
Article in press: July 17, 2017
Published online: October 16, 2017

Abstract

AIM

To evaluate the effectiveness of oral esomeprazole (EPZ) *vs* injectable omeprazole (OPZ) therapy to prevent hemorrhage after endoscopic submucosal dissection (ESD).

METHODS

A case-control study was conducted using a quasi-randomized analysis with propensity score matching. A total of 258 patients were enrolled in this study. Patients were treated with either oral EPZ or injectable OPZ. The endpoint was the incidence of hemorrhage after ESD.

RESULTS

Data of 71 subjects treated with oral EPZ and 172 subjects treated with injectable OPZ were analyzed. Analysis of 65 matched samples revealed no difference in the incidence of hemorrhage after ESD between the oral EPZ and injectable OPZ groups (OR = 0.89, 95%CI:

0.35-2.27, $P \geqslant 0.99$).

CONCLUSION

We conclude that oral EPZ therapy is a useful alternative to injectable PPI therapy for the prevention of hemorrhage after ESD.

Key words: Endoscopic submucosal dissection; Proton pump inhibitors; Hemorrhage

Core tip: Proton pump inhibitors (PPIs) have been reported to be effective for suppressing hemorrhage after endoscopic submucosal dissection (ESD); however, it remains unclear whether oral PPI therapy or injectable PPI therapy is preferable. The results of the present study indicate that oral effectiveness of oral esomeprazole therapy is a useful alternative to injectable PPI therapy for the prevention of hemorrhage after ESD.

Uchiyama T, Higurashi T, Kuriyama H, Kondo Y, Hata Y, Nakajima A. Oral esomeprazole *vs* injectable omeprazole for the prevention of hemorrhage after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2017; 9(10): 514-520 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i10/514.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i10.514

INTRODUCTION

Endoscopic submucosal dissection (ESD) allows *en-bloc* resection of even large and ulcerated gastric tumors[1,2]. It enables accurate histopathological diagnosis and reduces the risk of local recurrence[3], and is a standard treatment for selected gastric tumors. However, ESD is technically difficult and is associated with a higher risk of adverse events than conventional endoscopic mucosal resection (EMR)[3-5]. Among the adverse events, hemorrhage is a frequently encountered and serious problem[6]. Hemorrhage after ESD can occur at a later stage than other complications of ESD, such as perforation, sometimes occurring even after hospital discharge. Furthermore, hemorrhage after gastric ESD can be serious, as it can be massive and complicated by life-threatening hemorrhagic shock[7]. Thus, the importance of preventing hemorrhage after ESD cannot be overemphasized. While some previous studies have reported the risk factors for hemorrhage after ESD[6-14], no consensus has been arrived at yet in respect of the risk factors. Proton pump inhibitors (PPIs) have been reported to be effective for controlling hemorrhage after ESD[15]. However, to the best of our knowledge, there have been no studies yet to compare the efficacy of oral PPI therapy *vs* injectable PPI therapy for the control of hemorrhage after ESD. It remains unclear whether oral PPI therapy or injectable PPI therapy is preferable for the prevention of hemorrhage after ESD.

Esomeprazole (EPZ) is the S-isomer of omeprazole (OPZ) and has more favorable pharmacokinetic and pharmacodynamic profiles than OPZ[16]. However, injectable EPZ is not available at present in our hospital. In the current study, therefore, we compared the efficacy of oral EPZ therapy with that of injectable OPZ (in place of EPZ) therapy for the prevention of hemorrhage after ESD by propensity score-matched analysis.

MATERIALS AND METHODS

Patients and methods

We conducted a retrospective study with propensity score-matched analysis. We registered patients who had undergone ESD for gastric tumors at our hospital between March 2008 and March 2014 (n = 258). The research protocol was approved by the Hospital Ethics Committee. Written informed consent was obtained from each of the participants of the study.

Treatment

Figure 1 shows the treatment protocol used. The patients received either oral EPZ (20 mg daily) for 8 wk after ESD (oral EPZ group) or injectable OPZ (20 mg twice daily) for the first 5 d, followed by oral OPZ (20 mg daily) from day 6 to the end of 8 wk after the ESD (injectable OPZ group). Additionally, all the patients underwent an endoscopic examination on day 2 and a third endoscopy on day 6 after the ESD. All patients were given sucralfate from day 2 to the end of 8 wk after the ESD. Antiplatelet/anticoagulant drugs were discontinued before the ESD.

ESD procedure

ESD was performed using a videoendoscope (GIF-Q260J), Electric scalpel for endoscopic surgery (IT-Knife2) (Olympus Corporation, Tokyo, Japan) and an electrosurgical unit (ICC 200) (ERBE Elektromedizin GmbH, Tubingen, Germany). After tumor resection, all the visible vessels in the created ulcer were coagulated using a coagulation device (Coagrasper) (Olympus Corporation).

Hemorrhage

Hemorrhage after ESD was defined as the presence of clinical evidence of hemorrhage, such as the occurrence of melena or hematemesis confirmed by the hospital staff, or confirmation of the presence of blood or bleeding spots in the post-ESD ulcer at the second or third endoscopy. Preventive hemostasis for visible vessels not showing evidence of hemorrhage during the second or third endoscopy was not included as evidence of hemorrhage after ESD. We also defined clinically significant hemorrhage after ESD as hemorrhage necessitating emergency endoscopy or blood transfusion.

Statistical analysis

Data are presented as mean ± SD or number, and the diagnostic outcomes were examined using the χ^2 test.

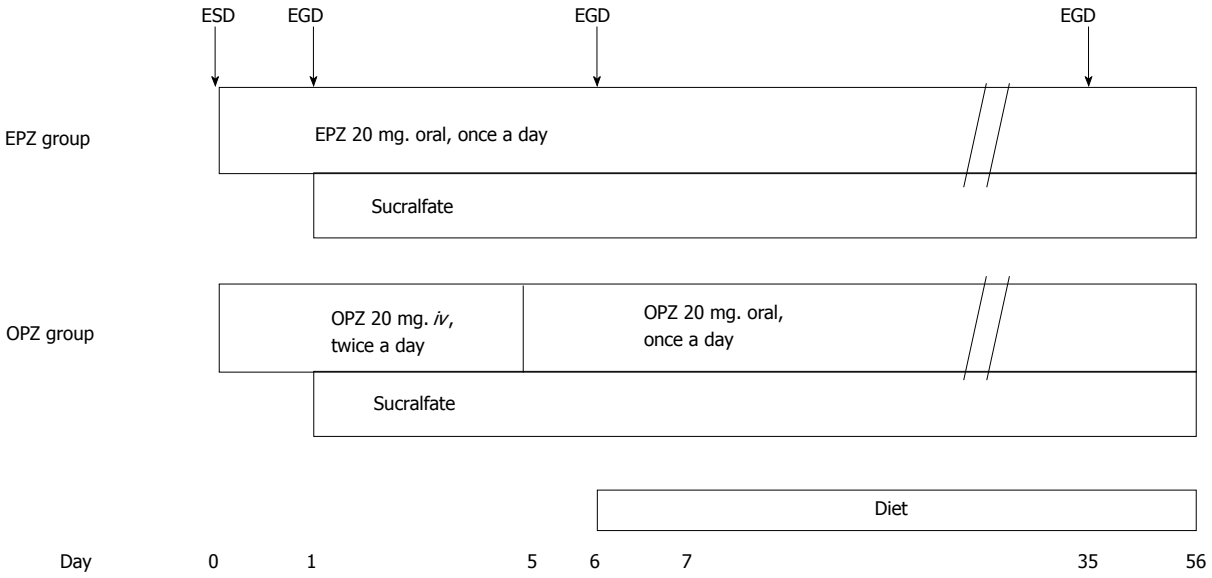


Figure 1 Treatment protocol for the two groups. EGD: Esophagogastroduodenoscopy; ESD: Endoscopic submucosal dissection; EPZ: Esomeprazole; OPZ: Omeprazole.

The variables and incidence of hemorrhage after ESD in the oral EPZ group were compared with those in the injectable OPZ group using the χ^2 test. Furthermore, propensity score matching was performed to control and reduce the selective bias[17-19]. Ten variables that could potentially influence the incidence of hemorrhage after ESD, listed below, were used to generate propensity scores using logistic regression: Patient age, patient sex, history of use of antiplatelet/anticoagulant drugs, location of the lesion, lesion depth, presence/absence of ulceration, diameter of the lesion, duration of operation, macroscopic type of the lesion, and the operator experience (beginners: Surgeons who had performed < 50 gastric ESDs; experts: Surgeons who had performed > 50 gastric ESDs). A propensity score-matched cohort was created by trying to match each patient given oral EPZ with a patient given injectable OPZ (a 1:1 match), using the nearest pair method. After matching, a coarse comparison of the matched cohorts was performed using χ^2 test. *P* values of < 0.05 were considered to indicate significance. Statistical analyses were performed using the JMP 10.0 software (SAS, North Carolina, United States).

RESULTS

Background characteristics of the patients

A total of 258 patients were enrolled in this study. Fifteen following reasons: Failure of resection of the lesion *en-bloc* (*n* = 8); presence of perforation (*n* = 5); interruption of the ESD (*n* = 1); previous history of gastrectomy (*n* = 1). Data of the remaining 243 patients were evaluated. Of the 243 patients, 172 who had undergone ESD before November 2012 received injectable OPZ, and the remaining 71 patients who had received ESD after November 2012 received oral EPZ (Figure 2). The data of 71 patients of the oral EPZ group and 172 patients of the injectable OPZ group were analyzed.

Among the 243 patients included in the analysis, 33 developed hemorrhage after the ESD (13.6%), with the hemorrhage being clinically significant in 10 of these cases (4.1%). Table 1 shows the baseline characteristics of the study population. A univariate analysis identified operator experience as the only risk factor for hemorrhage after ESD (beginner *vs* OR = 2.16; 95%CI: 1.03-4.55, *P* = 0.039). Hemorrhage after ESD was observed within 6 d of the procedure in all the cases.

Propensity score matching

A quasi-randomized experiment can be created using propensity score matching. That is, two subjects assigned to each group are equally likely to receive oral EPZ or injectable OPZ (Tables 2 and 3). Nearest-neighbor matches were performed using a caliper with 0.25 standard deviation of the propensity score (log odds scale). The predictive performance of the treatment model was evaluated using the χ^2 statistic that can take values from 0.5 for chance prediction to 1.0 for perfect prediction[20]. The propensity score allowed clear distinction between cases with and without hemorrhage after ESD, with a *c*-statistic of 0.77.

Among the matched samples, the incidence of hemorrhage after ESD was 15.4% (10/65) in the oral EPZ group and 16.9% (11/65) in the injectable OPZ group, with no statistically significant difference seen between the two groups (EPZ group *vs* OPZ group, OR = 0.89, 95%CI: 0.35-2.27, $P \geqslant 0.99$). The incidence of clinically significant hemorrhage was 6.2% (4/65) in the oral EPZ group and 4.6% (3/65) in the injectable OPZ group, with no significant difference of this parameter between the two groups either (EPZ group *vs* OPZ group, OR = 1.36, 95%CI: 0.29-6.31, $P \geqslant 0.99$). No significant differences in any of the other variables examined were found between the two groups.

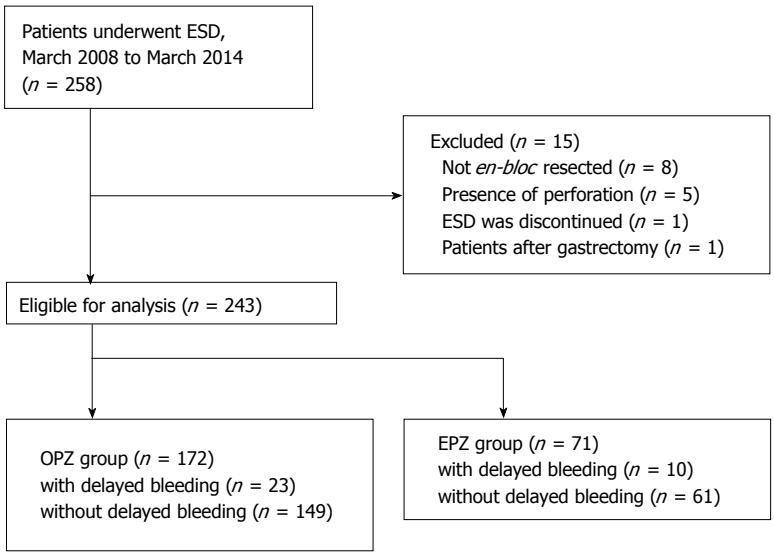


Figure 2 Selection of cases for study. ESD: Endoscopic submucosal dissection; EPZ: Esomeprazole; OPZ: Omeprazole.

Table 1 Background characteristics of the patients in relation to the bleeding status

	Hemorrhage after ESD		*P* value
	Negative	Positive	
Number	210	33	
Age (yr)	73.9 ± 8.0	71.7 ± 9.4	0.14
Gender (M/F)	151/59	8/25	0.65
Antiplatelet/anticoagulant drugs (-/+)	161/49	8/25	0.91
Hypertension (-/+)	123/87	20/13	0.83
Diabetes mellitus (-/+)	186/24	4/27	0.52
H. pylori infection (-/+)	90/120	13/20	0.89
Location (U/M/L)	28/96/86	2/15/16	0.45
Depth (m/sm)	190/20	5/28	0.35
Ulcer (-/+)	205/5	33/0	0.37
Diameter of the lesion (mm)	40.7 ± 15.3	40.4 ± 13.9	0.89
Duration of the operation (min)	106.9 ± 64.1	123.8 ± 98.5	0.2
Macroscopic type of the lesion (elevated or flat/combined/depressed)	130/29/51	5/10/2018	0.49
Pathological findings (Adenoma/Differentiated ca/Undifferentiated ca)	76/126/8	12/21/0	0.32
Lymphatic/venous invasion (-/+)	206/4	Jan-32	0.67
Anastomosis (-/+)	200/10	33/0	0.2
Operator type (expert/beginner)	129/81	14/19	0.0392
Bleeding during ESD (good/poor control)	164/46	9/24	0.49

P value calculated by the χ^2 test (Fisher's exact test or Pearson's test). ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.

DISCUSSION

EPZ is the first optical isomer developed as a PPI. Previous studies have demonstrated the efficacy of oral EPZ in the treatment of GERD[21,22]. Recently, Bunno *et al*[23] reported that oral EPZ was effective for ulcer healing after ESD. However, no studies have assessed the efficacy of oral EPZ for the control of hemorrhage after ESD. Recent studies have reported that oral EPZ therapy is a useful alternative to injectable PPI therapy to prevent recurrent hemorrhage in hemorrhagic gastric ulcer patients[24,25]. Laine *et al*[26], who compared oral and injectable lansoprazole, showed a difference in the intragastric pH only during the first hour after PPI administration, with no difference in the intragastric pH seen between the two groups at ⩾ 1.5 h after the drug administration. Javid *et al*[27] demonstrated an equivalent ability of injectable and high oral doses of various PPIs in suppressing gastric acid secretion, and no significant difference in effect among various PPIs given through different routes on the gastric pH ⩾ 6 for 72 h after successful endoscopic hemostasis. Our results were consistent with the findings of these previous studies. Oral EPZ therapy has the advantages of a lower cost and easier administration as compared to injectable PPI therapy, whereas injectable PPIs will still be needed for patients who cannot receive oral medications. Therefore, we conclude that oral EPZ therapy is a useful alternative to intravenous PPI therapy for the prevention of hemorrhage after ESD.

Table 2 Background characteristics of the patients according to the treatment group before the propensity score matching

	EPZ group	OPZ group	*P* value
Number	71	172	
Age (yr)	75.3 ± 7.1	72.9 ± 8.5	0.0361
Gender (M/F)	52/19	124/48	0.86
Antiplatelet/anticoagulant drugs (-/+)	50/21	136/36	0.15
Hypertension (-/+)	40/31	103/69	0.61
Diabetes Mellitus (-/+)	Sep-62	151/21	0.92
H. pylori infection (-/+)	29/42	55/117	0.19
Location (U/M/L)	10/34/27	20/77/75	0.7
Depth (m/sm)	57/14	161/11	0.0019
Ulcer (-/+)	71/0	167/5	0.15
Diameter of the lesion (mm)	42.2 ± 17.2	40.14 ± 14.1	0.31
Duration of the operation (min)	115.9 ± 87.3	106.4 ± 61.1	0.34
Macroscopic type of the lesion (elevated or flat/combined/depressed)	46/16/9	102/18/52	0.003
Pathological findings (Adenoma/Differentiated ca/Undifferentiated ca)	26/42/3	62/105/5	0.86
Lymphatic/venous invasion (-/+)	Jan-70	168/4	0.65
Anastomosis (-/+)	Mar-68	163/9	0.74
Operator type (expert/beginner)	31/40	112/60	0.002
Bleeding during ESD (good/poor control)	55/16	134/38	0.94
Hemorrhage after ESD (-/+)	149/23	Oct-61	0.88
Clinically significant bleeding (-/+)	165/7	Mar-68	0.96

P value calculated by the χ^2 test (Fisher's exact test or Pearson's test). EPZ: Esomeprazole; OPZ: Omeprazole; ESD: Endoscopic submucosal dissection.

Table 3 Background characteristics of the patients according to the treatment group after the propensity score matching

	EPZ group	OPZ group	*P* value
Number	65	65	
Age (yr)	75.2 ± 7.3	75.0 ± 7.5	0.9
Gender (M/F)	46/19	44/21	0.85
Antiplatelet/anticoagulant drugs (-/+)	46/19	44/21	0.85
Hypertension (-/+)	37/28	33/32	0.6
Diabetes Mellitus (-/+)	Aug-57	Dec-53	0.47
H. pylori infection (-/+)	26/39	23/42	0.72
Location (U/M/L)	5/33/27	10/24/31	0.19
Depth (m/sm)	Sep-56	Jun-59	0.58
Ulcer (-/+)	65/0	65/0	0
Diameter of the lesion (mm)	41.9 ± 18.5	39.6 ± 12.1	0.4
Duration of the operation (min)	110.6 ± 85.7	102.0 ± 54.9	0.5
Macroscopic type of the lesion (elevated or flat/combined/depressed)	42/14/9	10/8/1947	0.6
Pathological findings (Adenoma/Differentiated ca/Undifferentiated ca)	26/37/2	29/35/1	0.76
Lymphatic/venous invasion (-/+)	Jan-64	Feb-63	⩾ 0.99
Anastomosis (-/+)	Mar-62	Mar-62	⩾ 0.99
Operator type (expert/beginner)	29/36	27/38	0.86
Bleeding during ESD (good/poor control)	51/14	49/16	0.84
Hemorrhage after ESD (-/+)	Oct-55	Nov-54	⩾ 0.99
Clinically significant bleeding (-/+)	Apr-61	Mar-62	⩾ 0.99

P value calculated by the χ^2 test (Fisher's exact test or Pearson's test). EPZ: Esomeprazole; OPZ: Omeprazole; ESD: Endoscopic submucosal dissection.

Previous studies have reported the incidence and risk factors for hemorrhage after ESD, although the results are conflicting. We also assessed the risk factors for hemorrhage after ESD, and our analysis identified only the operator experience as a significant predictor of hemorrhage after ESD. Adequate coagulation of the vessels at the ulcer base after ESD is important to prevent delayed hemorrhage. As some experience is required for such coagulation, the incidence of hemorrhage after ESD differs between beginners and experts. A previous study also identified the operator experience as a significant risk factor for hemorrhage after ESD[11]. On the other hand, several studies have reported the absence of any significant effect of the operator experience on the risk of hemorrhage after ESD[6-10,12-14]. These differences in the outcomes were likely caused by the diversity of the ESD procedures and treatments employed. Further investigation is required to clarify the unified risk factors for hemorrhage after ESD.

Our study had some limitations. First of all, injectable EPZ is not available at our hospital; therefore, we compared oral esomeprazole with injectable OPZ. Second, we could not carry out a non-inferiority study, because the number of cases was small. Third, hemorrhage after

ESD is usually defined as bleeding, including hematemesis or melena, that necessitates endoscopic treatment and has been reported to occur in 1.3% to 11.9% of patients undergoing ESD[28]. We observed only 10 cases (10/243) with hemorrhage after ESD fulfilling this conventional definition, which made a reasonable comparison between oral EPZ and injectable OPZ difficult. Therefore, in this study, we defined hemorrhage after ESD as described in the text above. This was the reason why the frequency of hemorrhage after ESD was relatively high in this study, while the frequency of clinically significant hemorrhage was comparable to that reported from other studies. Fourth, this study was a 6-year clinical study. During this period, ESD has gradually become more and more popular. Individual learning curves, introduction of new devices, and establishment of education programs over the last few years make reasonable comparisons difficult.

In conclusion, in the present study, we assessed the frequency of hemorrhage after ESD after oral EPZ and injectable OPZ treatments. No difference was seen in the incidence of hemorrhage after ESD between the oral EPZ and injectable OPZ groups. This is the first study to investigate the effectiveness of oral EPZ therapy to prevent hemorrhage after ESD. Further large-scale trials are necessary to clarify the effectiveness of oral EPZ therapy. Oral PPI therapy shows a clear cost benefit and is easier to administer as compared to injectable PPI therapy. Thus, we conclude that oral EPZ therapy is a useful alternative to intravenous PPI therapy for the prevention of hemorrhage after ESD.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is technically difficult and is associated with a high risk of adverse events. Among the adverse events, hemorrhage is a frequently encountered and serious problem. Proton pump inhibitors (PPIs) have been reported to be effective for controlling hemorrhage after ESD. In this study, the authors compared the efficacy of oral effectiveness of oral esomeprazole (EPZ) therapy with that of injectable injectable omeprazole (OPZ) therapy for the prevention of hemorrhage after ESD.

Research frontiers

No comparison of the efficacy of oral PPI therapy *vs* injectable PPI therapy for the control of hemorrhage after ESD has been carried out previously. Therefore, whether oral PPI therapy or injectable PPI therapy is preferable for the prevention of hemorrhage after ESD remains uncertain. The results of this study contributed to clarifying the efficacy of oral EPZ therapy *vs* injectable OPZ therapy for the prevention of hemorrhage after ESD.

Innovations and breakthroughs

A quasi-randomized experiment was created using propensity score matching. Among the matched samples, the incidence of hemorrhage after ESD was 15.4% (10/65) in the oral EPZ group and 16.9% (11/65) in the injectable OPZ group. No statistically significant difference was seen between these groups.

Applications

This study suggests that oral EPZ therapy is a useful alternative to intravenous PPI therapy for the prevention of hemorrhage after ESD. Oral PPI therapy shows a clear cost benefit and is easier to administer as compared to injectable PPI therapy.

Terminology

ESD: An endoscopic technique allows *en-bloc* resection even for large or ulcerated gastric tumors.

Peer-review

The study is very well described and the results are clear. In this study, the authors investigated to compare EPZ *vs* intravenous omeprazole therapy to prevent hemorrhage after ESD using a quasi-randomized analysis with propensity score matching.

REFERENCES

1 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]

2 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]

3 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]

4 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]

5 **Fujishiro M**. Endoscopic submucosal dissection for gastric cancer. *Curr Treat Options Gastroenterol* 2008; **11**: 119-124 [PMID: 18321439]

6 **Mannen K**, Tsunada S, Hara M, Yamaguchi K, Sakata Y, Fujise T, Noda T, Shimoda R, Sakata H, Ogata S, Iwakiri R, Fujimoto K. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. *J Gastroenterol* 2010; **45**: 30-36 [PMID: 19760133 DOI: 10.1007/s00535-009-0137-4]

7 **Takizawa K**, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy* 2008; **40**: 179-183 [PMID: 18322872 DOI: 10.1055/s-2007-995530]

8 **Okada K**, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]

9 **Jang JS**, Choi SR, Graham DY, Kwon HC, Kim MC, Jeong JS, Won JJ, Han SY, Noh MH, Lee JH, Lee SW, Baek YH, Kim MJ, Jeong DS, Kim SK. Risk factors for immediate and delayed bleeding associated with endoscopic submucosal dissection of gastric neoplastic lesions. *Scand J Gastroenterol* 2009; **44**: 1370-1376 [PMID: 19891589 DOI: 10.3109/00365520903194609]

10 **Jeon SW**, Jung MK, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH. Predictors of immediate bleeding during endoscopic submucosal dissection in gastric lesions. *Surg Endosc* 2009; **23**: 1974-1979 [PMID: 18553202 DOI: 10.1007/s00464-009-0464-9]

11 **Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838 DOI: 10.3748/wjg.v16.i23.2913]

12 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]

13 **Nakamura M**, Nishikawa J, Hamabe K, Nishimura J, Satake M, Goto A, Kiyotoki S, Saito M, Fukagawa Y, Shirai Y, Okamoto T, Sakaida I. Risk factors for delayed bleeding from endoscopic submucosal

dissection of gastric neoplasms. *Scand J Gastroenterol* 2012; **47**: 1108-1114 [PMID: 22783937 DOI: 10.3109/00365521.2012.699550]
14 **Higashiyama M**, Oka S, Tanaka S, Sanomura Y, Imagawa H, Shishido T, Yoshida S, Chayama K. Risk factors for bleeding after endoscopic submucosal dissection of gastric epithelial neoplasm. *Dig Endosc* 2011; **23**: 290-295 [PMID: 21951088 DOI: 10.1111/j.1443-1661.2011.01151.x]
15 **Uedo N**, Takeuchi Y, Yamada T, Ishihara R, Ogiyama H, Yamamoto S, Kato M, Tatsumi K, Masuda E, Tamai C, Yamamoto S, Higashino K, Iishi H, Tatsuta M. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol* 2007; **102**: 1610-1616 [PMID: 17403076 DOI: 10.1111/j.1572-0241.2007.01197.x]
16 **McKeage K**, Blick SK, Croxtall JD, Lyseng-Williamson KA, Keating GM. Esomeprazole: a review of its use in the management of gastric acid-related diseases in adults. *Drugs* 2008; **68**: 1571-1607 [PMID: 18627213]
17 **Rosenbaum PR**, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**: 41-55
18 **Rosenbaum PR**, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984; **79**: 516-545
19 **Rosenbaum PR**, Rubin DB. The bias due to incomplete matching. *Biometrics* 1985; **41**: 103-116 [PMID: 4005368]
20 **Ash AS**, Shwartz M. Evaluating the performance of risk-adjustment methods: Dichotomous outcomes. In: Risk Adjustment for Measuring Health Care Outcomes. 2nd edition, edited by Iezzoni LI, Chicago, Health Administration Press, 1997
21 **Johnson DA**, Benjamin SB, Vakil NB, Goldstein JL, Lamet M, Whipple J, Damico D, Hamelin B. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol* 2001; **96**: 27-34 [PMID: 11197282 DOI: 10.1111/j.1572-0241.2001.03443.x]
22 **Richter JE**, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, Marino V, Hamelin B, Levine JG; Esomeprazole Study Investigators. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol* 2001; **96**: 656-665 [PMID: 11280530 DOI: 10.1111/j.1572-0241.2001.3600_b.x]
23 **Bunno M**, Gouda K, Yamahara K, Kawaguchi M. A Case-Control Study of Esomeprazole Plus Rebamipide vs. Omeprazole Plus Rebamipide on Post-ESD Gastric Ulcers. *Jpn Clin Med* 2013; **4**: 7-13 [PMID: 23966811 DOI: 10.4137/JCM.S11320]
24 **Sung JJ**, Suen BY, Wu JC, Lau JY, Ching JY, Lee VW, Chiu PW, Tsoi KK, Chan FK. Effects of intravenous and oral esomeprazole in the prevention of recurrent bleeding from peptic ulcers after endoscopic therapy. *Am J Gastroenterol* 2014; **109**: 1005-1010 [PMID: 24777150 DOI: 10.1038/ajg.2014.105]
25 **Yen HH**, Yang CW, Su WW, Soon MS, Wu SS, Lin HJ. Oral versus intravenous proton pump inhibitors in preventing re-bleeding for patients with peptic ulcer bleeding after successful endoscopic therapy. *BMC Gastroenterol* 2012; **12**: 66 [PMID: 22681960 DOI: 10.1186/1471-230X-12-66]
26 **Laine L**, Shah A, Bemanian S. Intragastric pH with oral vs intravenous bolus plus infusion proton-pump inhibitor therapy in patients with bleeding ulcers. *Gastroenterology* 2008; **134**: 1836-1841 [PMID: 18423628 DOI: 10.1053/j.gastro.2008.03.006]
27 **Javid G**, Zargar SA, U-Saif R, Khan BA, Yatoo GN, Shah AH, Gulzar GM, Sodhi JS, Khan MA. Comparison of p.o. or i.v. proton pump inhibitors on 72-h intragastric pH in bleeding peptic ulcer. *J Gastroenterol Hepatol* 2009; **24**: 1236-1243 [PMID: 19682194 DOI: 10.1111/j.1440-1746.2009.05900.x]
28 **Park CH**, Lee SK. Preventing and controlling bleeding in gastric endoscopic submucosal dissection. *Clin Endosc* 2013; **46**: 456-462 [PMID: 24143302 DOI: 10.5946/ce.2013.46.5.456]

P- Reviewer: Shu X, Suchanek S, Sugimoto M **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2017 October 16; 9(10): 521-528

DOI: 10.4253/wjge.v9.i10.521

ISSN 1948-5190 (online)

CASE REPORT

Two case reports of acute upper gastrointestinal bleeding from duodenal ulcers after Roux-en-Y gastric bypass surgery: Endoscopic diagnosis and therapy by single balloon or push enteroscopy after missed diagnosis by standard esophagogastroduodenoscopy

Seifeldin Hakim, Srinivas R Rami Reddy, Mihaela Batke, Gregg Polidori, Mitchell S Cappell

Seifeldin Hakim, Srinivas R Rami Reddy, Mihaela Batke, Gregg Polidori, Mitchell S Cappell, Division of Gastroenterology and Hepatology, Department of Medicine, William Beaumont Hospital, Royal Oak, MI 48073, United States

Mitchell S Cappell, Oakland University William Beaumont School of Medicine, Royal Oak, MI 48073, United States

Author contributions: Hakim S and Cappell MS are equal primary authors; Hakim S helped in reviewing and editing the two case reports, and wrote a preliminary version of the Introduction, and Discussion sections; Cappell MS was the mentor for Hakim S and Reddy SRR for this paper; Cappell MS supervised the writing of the entire paper, including writing parts of the Introduction and Discussion sections, and thoroughly edited the entire paper; Batke M was the attending clinician treating patient 1, wrote up a preliminary version of this case report, and reviewed the rest of the paper; Polidori G was the attending treating patient 2, wrote up a preliminary version of this case report, and reviewed the rest of the paper; Reddy SRR was the GI fellow treating patients 1 and 2, and assisted in the writing of the 2 case reports.

Institutional review board statement: William Beaumont Hospital IRB approved/exempted study on 12/16/16.

Informed consent statement: Exempted.

Conflict-of-interest statement: None. In particular, Dr. Cappell, as a consultant of the United States Food and Drug Administration (FDA) Advisory Committee for Gastrointestinal Drugs, affirms that this paper does not discuss any proprietary, confidential, pharmaceutical data submitted to the FDA; Dr. Cappell is also a member of the speaker's bureau for AstraZeneca and Daiichi Sankyo, co-marketers of Movantik. This work does not discuss any drug manufactured or marketed by AstraZeneca or Daiichi Sankyo.

Manuscript source: Unsolicited manuscript

Correspondence to: Mitchell S Cappell, MD, PhD, Director, Division of Gastroenterology and Hepatology, Department of Medicine, William Beaumont Hospital, MOB# 602, 3535 West Thirteen Mile Road, Royal Oak, MI 48073, United States. mitchell.cappell@beaumont.edu
Telephone: +1-248-5511227
Fax: +1-248-5517581

Received: January 9, 2017
Peer-review started: January 11, 2017
First decision: February 20, 2017
Revised: May 20, 2017
Accepted: June 12, 2017
Article in press: June 13, 2017
Published online: October 16, 2017

Abstract

The diagnosis and opportunity for endoscopic therapy of gastric or duodenal lesions may be missed at esophagogastroduodenoscopy (EGD) because of technical difficulty in intubating at EGD the postoperatively excluded stomach and proximal duodenum in patients status post Roux-en-Y gastric bypass (RYGB). Two cases are reported of acute upper gastrointestinal bleeding 10 or 11 years status post

RYGB, performed for morbid obesity, in which the EGD was non-diagnostic due to failure to intubate the excluded stomach and proximal duodenum, whereas subsequent push enteroscopy or single balloon enteroscopy were diagnostic and revealed 4-cm-wide or 5-mm-wide bulbar ulcers and even permitted application of endoscopic therapy. These case reports suggest consideration of push enteroscopy, or single balloon enteroscopy, where available, in the endoscopic evaluation of acute UGI bleeding in patients status post RYGB surgery when the EGD was non-diagnostic because of failure to intubate these excluded segments.

Key words: Morbid obesity; Bariatric surgery; Roux-en-Y gastric bypass surgery; Upper gastrointestinal bleeding; Esophagogastroduodenoscopy; Push enteroscopy; Single balloon enteroscopy; Therapeutic endoscopy; Double balloon enteroscopy

Core tip: After Roux-en-Y-gastric-bypass (RYGB) surgery, the surgically excluded distal stomach/duodenum may be difficult to intubate and examine during esophagogastroduodenoscopy (EGD). Two cases are reported of acute upper gastrointestinal (UGI) bleeding many years after RYGB surgery, in which EGD was non-diagnostic due to failure to intubate these excluded segments. However, single balloon or push enteroscopy successfully permitted this intubation, enabling endoscopic diagnosis and therapy of bulbar ulcers at high risk of rebleeding. These case reports suggest using single balloon or push enteroscopy to endoscopically evaluate acute UGI bleeding in patients status-post-RYGB-surgery when EGD was non-diagnostic because of failure to intubate the excluded gastroduodenal segments.

Hakim S, Reddy SRR, Batke M, Polidori G, Cappell MS. Two case reports of acute upper gastrointestinal bleeding from duodenal ulcers after Roux-en-Y gastric bypass surgery: Endoscopic diagnosis and therapy by single balloon or push enteroscopy after missed diagnosis by standard esophagogastroduodenoscopy. *World J Gastrointest Endosc* 2017; 9(10): 521-528 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i10/521.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i10.521

INTRODUCTION

Anastomotic ulcers are the most common cause of upper gastrointestinal (UGI) bleeding after Roux-en-Y gastric bypass (RYGB), the most popular form of bariatric surgery[1], but such patients can also bleed from ordinary gastric or duodenal (peptic) ulcers[2]. Ulcers in the proximal duodenum or stomach may, however, be missed at esophagogastroduodenoscopy (EGD) after RYGB surgery because deep intubation of the proximal afferent limb is technically difficult at EGD. Two patients with UGI bleeding status post RYGB surgery are reported who had non-diagnostic EGDs because of this technical difficulty, but then had 4-cm-wide or 5-mm-wide bulbar ulcers diagnosed and endoscopically treated after successfully intubating the proximal duodenum by push enteroscopy or single balloon enteroscopy. This work alerts physicians about this potential limitation of EGD in patients status post RYGB surgery, and suggests use of push enteroscopy or single balloon enteroscopy as alternatives for endoscopic diagnosis and therapy.

Methods

The literature was systematically reviewed *via* PubMed using the following medical subject headings or keys words: ("Roux-en-Y gastric bypass") AND ("duodenal ulcer" or "gastric ulcer" or "missed ulcer" or "peptic ulcer" or "esophagogastroduodenoscopy" or "push enteroscopy" or "single balloon enteroscopy" or "double balloon enteroscopy" or "therapeutic endoscopy") OR ("excluded segment" and "esophagogastroduodenoscopy") OR ("bariatric surgery" and "endoscopy" and "upper gastrointestinal bleeding"). The term esophagogastroduodenoscopy (EGD) is used to describe what is technically esophagogastrojejunoscopy (EGJ) in patients status post RYGB, in accordance with common usage. The IRB at William Beaumont Hospital, Royal Oak, approved/exempted this study on December 16, 2016.

CASE REPORT

Case 1

A 44-year-old woman with prior RYGB 11 years earlier for morbid obesity presented to a community hospital with recurrent melena, weakness, and orthostatic dizziness for 1 wk. She had been taking non-steroidal anti-inflammatory drugs (NSAIDs) about two days per month for several months, but was not taking proton pump inhibitors (PPIs). She was a non-smoker and non-alcoholic. Physical examination revealed stable vital signs, pallor, and a benign abdominal examination. Rectal examination revealed melena and no visible hemorrhoids. On admission the hemoglobin (Hgb) was 4.1 g/dL. She was intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered PPI. EGD did not reveal any source of UGI bleeding, but the excluded proximal duodenum and stomach were not intubated and viewed. Colonoscopy did not reveal any etiology of lower GI bleeding. The patient was discharged with Hgb = 8.0 g/dL.

The patient was readmitted 1 d later to the same hospital, and then transferred to William Beaumont Hospital, a tertiary care hospital, for recurrent GI bleeding, with Hgb decline to 5.8 g/dL. Physical examination revealed stable vital signs, pallor, and a benign abdominal examination. Rectal examination revealed dark red blood and no visible hemorrhoids.

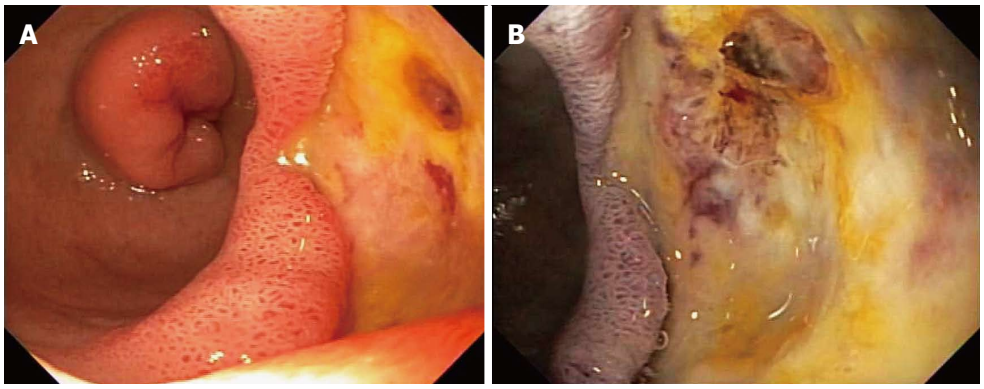


Figure 1 Endoscopic findings and therapy during single balloon enteroscopy in Case 1. A: Diagnostic findings. Single balloon enteroscopy performed in a 44-year-old woman, status post Roux-en-Y gastric bypass (RYGB) surgery 11 years earlier for morbid obesity, who presented with acute melena and a hemoglobin decline to 5.8 g/dL demonstrates a 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb. Note the retrograde view of the duodenal bulb with the pylorus seen in the distance. Esophagogastroduodenoscopy performed 3 d earlier for melena had revealed no upper gastrointestinal lesions, but the afferent limb of the Roux-en-Y, including the excluded proximal duodenum and stomach, had not been intubated and visualized because of technical difficulties at esophagogastroduodenoscopy; B: Endoscopic therapy. Single balloon enteroscopy showing the ablated bulbar ulcer after dual therapy of dilute epinephrine injection and heater probe thermocoagulation.

Laboratory tests revealed a normal mean corpuscular volume, platelet count, and coagulation panel. Serum blood urea nitrogen:creatinine (BUN:Cr) ratio = 36. Liver function tests were within normal limits, except for albumin = 1.6 g/dL. She was medically stabilized with transfusions of packed erythrocytes. Abdominal computed tomography (CT) with intravenous contrast was within normal limits. Single balloon enteroscopy revealed a non-bleeding, 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb and no other lesions (Figure 1A). The visible vessel was ablated by injection of 10 mL of dilute epinephrine 1:10000 and by heater probe thermocoagulation using coaptation with 13 pulses of 25 W for one second each (Figure 1B). The visible vessel was almost completely flattened by the thermocoagulation. After 72 h the patient had another episode of melena and the Hgb acutely declined from 9.5 to 6.5 g/dL. A technetium-labeled erythrocyte (bleeding) scan and an abdominal arteriogram did not reveal an actively bleeding source. Exploratory laparotomy revealed a giant, posterior, bulbar ulcer, which was oversewn. A Warthin-Starry stain of gastric biopsies did not reveal *Helicobacter pylori* (*H. pylori*). Serology for IgG antibodies against *H. pylori* was negative (low titer). No significant postoperative complications occurred. The patient is doing well at 3 mo follow-up, with no further GI bleeding.

Case 2

A 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. She was taking ibuprofen about 800 mg/d for about 2 d per week for arthralgia, but had stopped about 3 mo ago. She was not taking PPIs, did not drink alcohol, and had stopped smoking cigarettes (1 pack/d) 12 years earlier. Physical examination on admission revealed stable vital signs, pallor, and a normal abdominal examination. Rectal examination revealed melena and no visible hemorrhoids. Laboratory analysis revealed Hgb = 7.4 g/dL (baseline recent Hgb = 13.3 g/dL), evident iron deficiency anemia with ferritin = 25 ng/mL, platelet count = 62000/L, and serum BUN:Cr ratio = 100. Liver function tests and coagulation panel were within normal limits. She was intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered a PPI. EGD revealed no lesions, including no anastomotic ulcers, but the afferent limb was not intubated. Colonoscopy revealed no lesions. Both computed tomographic enterography and capsule endoscopy were within normal limits. Bleeding slowly resolved and she was discharged with Hgb = 8.0 gm/dL.

The patient was readmitted 3 d later for recurrent melena. Laboratory analysis revealed Hgb = 5.1 g/dL, platelets = 201000/L, and BUN:Cr ratio = 40. A technetium labeled erythrocyte (bleeding) scan did not reveal active GI bleeding. Push enteroscopy with intubation of the afferent limb revealed a 5-mm-wide acute bulbar ulcer with a visible vessel that was oozing blood, and an otherwise normal examination (Figure 2A). The visible vessel was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation (APC) (Figure 2B). Serologic tests for IgG antibodies against *H. pylori* were negative (low titer). The patient had one further, minor, episode of melena, after which the bleeding resolved, and the patient was discharged. She has had no further GI bleeding during 3 mo of follow-up.

DISCUSSION

The prevalence of obesity in adults is currently 13% worldwide, and 34%-36% in the United States[3]. From 1960 to 2008 the prevalence of morbid obesity [body mass index (BMI) > 40 kg/m^2 or > 35 kg/m^2

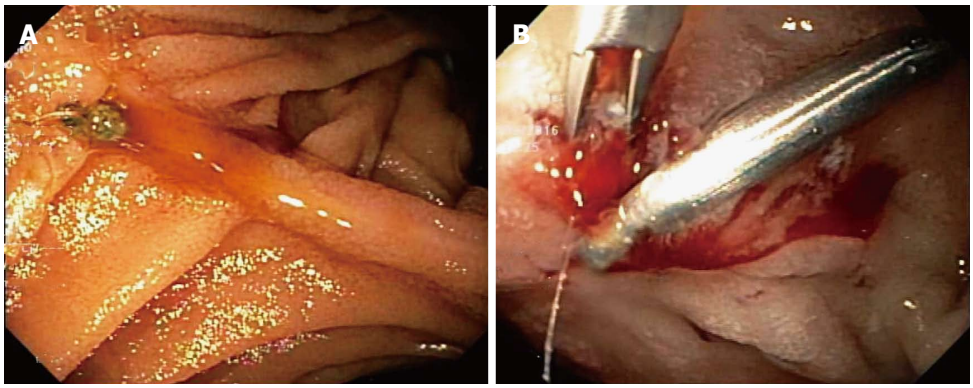


Figure 2 Endoscopic findings and therapy during push enteroscopy in Case 2. A: Diagnostic findings. Push enteroscopy performed in a 64-year-old woman status post RYGB surgery 10 years earlier for morbid obesity who presented with acute melena and a hemoglobin of 5.1 g/dL demonstrates a 5-mm-wide bulbar ulcer, which is actively oozing blood. EGD performed 5 d earlier for melena had revealed no upper gastrointestinal lesions, but the afferent limb of the Roux-en-Y, including the excluded proximal duodenum and stomach, had not been intubated and visualized because of technical difficulties at EGD; B: Endoscopic therapy. Push enteroscopy showing the bulbar ulcer after endoscopic treatment with dilute epinephrine, argon plasma coagulation, and hemoclips. RYGB: Roux-en-Y gastric bypass; EGD: Esophagogastroduodenoscopy.

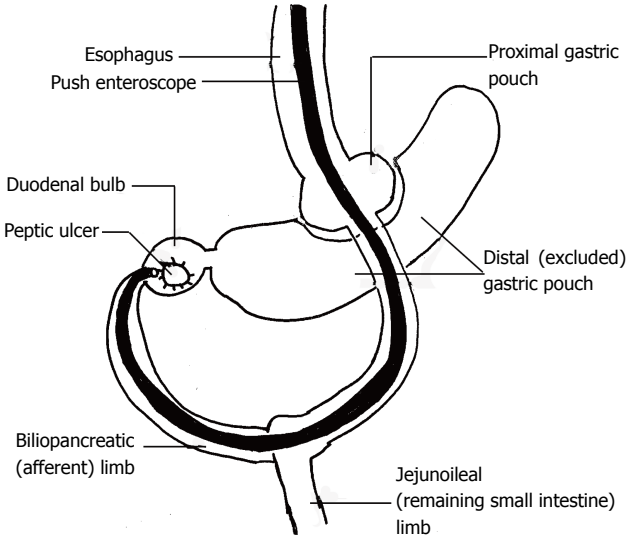


Figure 3 Sketch showing coronal axis of upper gastrointestinal tract during intubation of afferent (biliopancreatic) limb using a push enteroscope in a patient status post Roux-en-Y gastric bypass for morbid obesity. After Roux-en-Y gastric bypass (RYGP) direct continuity between the proximal and distal stomach is severed and the stomach is surgically divided and reconstructed to form two pouches: A small proximal gastric pouch that connects directly to the proximal jejunum *via* a surgical anastomosis (efferent limb) and a large distal pouch that connects retrograde only to the duodenum *via* the duodenal bulb (afferent limb). Surgical reconstruction of a small proximal gastric pouch promotes weight loss by causing early satiety due to limited proximal gastric pouch capacity, and by causing decreased appetite by reducing ghrelin synthesis. The sketch shows that the afferent (biliopancreatic) limb is hard to reach and intubate using a routine esophagogastroduodenoscope after RYGP because of the long distance traversed (through the jejunum) to reach the afferent limb, and sharp angulation at the anastomosis between the afferent and efferent limbs. Failure to intubate the afferent limb results in missing lesions in this limb, as occurred in the 2 currently reported cases in which duodenal bulb ulcers with high risk stigmata of recent hemorrhage were missed.

with significant obesity-related disorders) increased from 0.9% to 6%, and the prevalence of obesity (BMI > 30 kg/m^2) increased from 13.4% to 34.3% in the United States[4]. This epidemic of obesity has led to a surge in the number of bariatric surgeries, from 13365 annually in 1998 to 205000 annually in 2008 in the United States[5,6]. The direct annual costs of bariatric surgery are > 10 billion dollars per annum in the United States[7]. RYGB is the most common and most effective bariatric surgery performed in the United States[5,8].

Anastomotic ulcers are a common, important cause of UGI bleeding after RYGB, which most commonly occur in patients actively smoking or taking NSAIDs[9]. Such ulcers are usually easily detected and readily treated at EGD[10]. Contrariwise, bleeding from ordinary duodenal or gastric ulcers is rarely reported after RYGB, with only 22 reported cases[2,11-13]. Proposed mechanisms for these ulcers after RYGB include: An acidic environment within the excluded segment[14,15], deprivation of the buffering effect of ingested food in the excluded segment[16], bile acid reflux into the excluded stomach and duodenal bulb, excessive alcohol consumption, frequent NSAID use, and *H. pylori* infection[5,12]. In both reported cases, excessive alcohol consumption, frequent NSAID use, recent cigarette smoking, and *H. pylori* infection were excluded as risk factors for the peptic ulcers or GI bleeding by patient history and laboratory tests.

Diagnosis of ulcers in the excluded segment after RYGB is challenging because intubating the excluded stomach and proximal duodenum (afferent limb) is technically difficult due to sharp bowel angulation, deep intubation to reach the excluded segment (afferent limb) through the jejunum, endoscopic looping, and inability to adequately distend the gastric remnant with air (Figure 3). However, intubation of only the efferent limb at EGD would result in missing lesions in the afferent limb. CT or magnetic resonance imaging (MRI) virtual gastroduodenoscopy can provide excellent intra-luminal views, but cannot provide a tissue diagnosis[17]. Percutaneous endoscopic gastrostomy has been successfully used to endoscopically access the excluded segments[1]. Alternatively, patients have undergone intraoperative endoscopy or gastrostomy to identify and treat bleeding duodenal ulcers after RYGB surgery. Some authors have even suggested placing

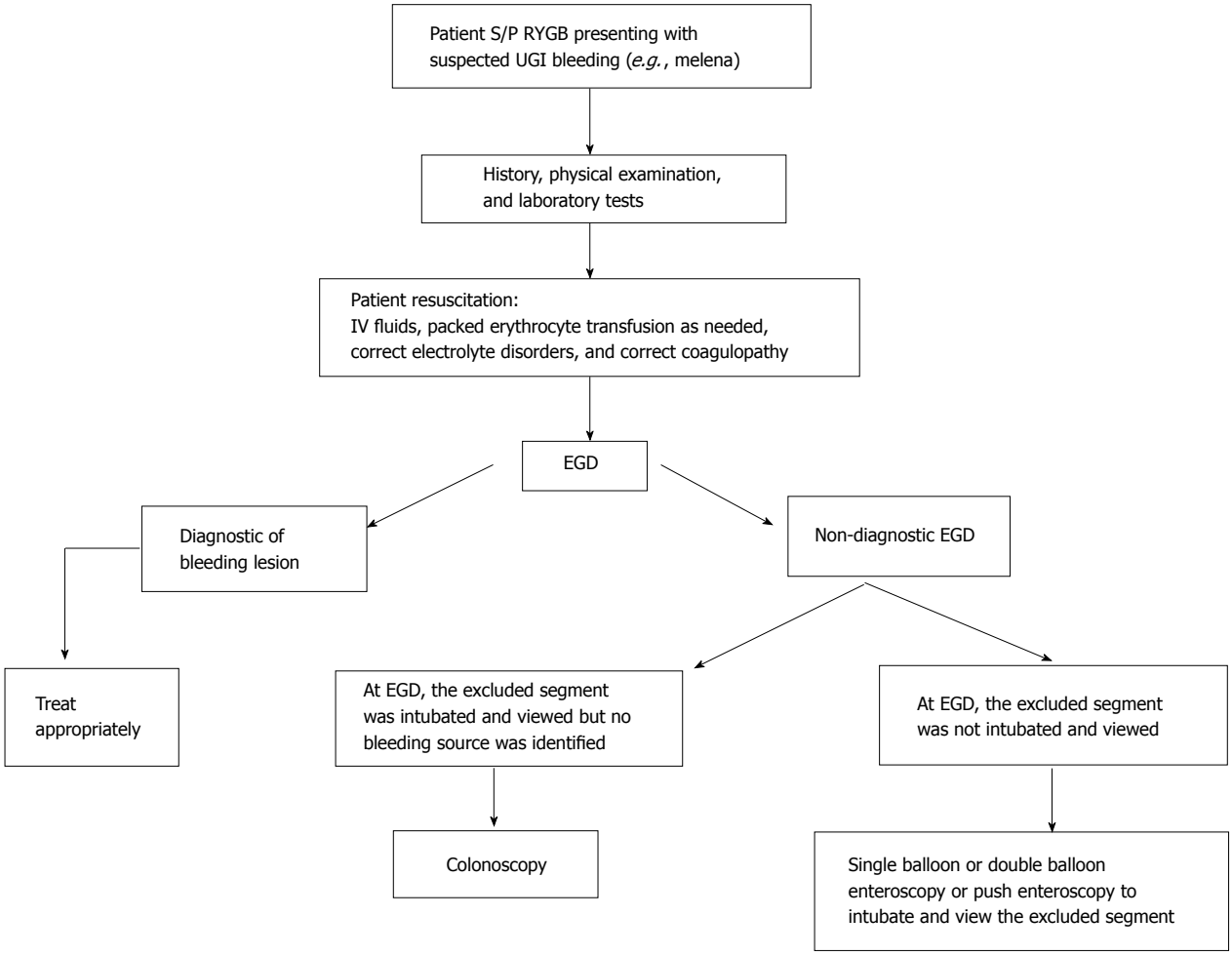


Figure 4 Flow diagram showing a proposed diagnostic/therapeutic algorithm for patients status post Roux-en-Y gastric bypass surgery presenting with acute gastrointestinal bleeding that is highly likely from an upper gastrointestinal source (*e.g.*, patient presenting with melena). The important difference in this algorithm from a general patient with UGI bleeding (who is not status post RYGB) is the addition of push enteroscopy, single balloon enteroscopy, or possibly double balloon enteroscopy if the EGD was non-diagnostic but the excluded stomach and duodenum (afferent limb) had not been intubated and viewed at EGD. Alternative management algorithms include: (1) performing push enteroscopy or single balloon enteroscopy initially instead of EGD in patients status post RYGB; or (2) performing colonoscopy before performing push enteroscopy or single balloon enteroscopy (or double balloon enteroscopy) after a non-diagnostic EGD. RYGB: Roux-en-Y gastric bypass; EGD: Esophagogastroduodenoscopy.

a gastrostomy tube within a radiopaque silastic ring during primary RYGB surgery to facilitate subsequent percutaneous endoscopic access to the excluded stomach[1].

There are no standard recommendations in RYGB patients who present with obscure GI bleeding. Eid *et al*[9] recommended that examination of the bypassed stomach and duodenum should be attempted before performing colonoscopy to evaluate for a lower GI source and before performing capsule endoscopy to evaluate for a small bowel source. This work adds to the literature by suggesting the diagnostic and therapeutic benefits of push enteroscopy or single balloon enteroscopy if EGD was non-diagnostic and the excluded segments were not intubated at EGD in patients status post RYGB surgery (Figure 4). These alternative endoscopies can be performed either before or after colonoscopy and capsule endoscopy, depending on the likelihood of the patient having had an UGI bleed. Push enteroscopy or single balloon enteroscopy can even be done initially instead of EGD in patients status post RYGP to increase the diagnostic yield and therapeutic efficacy of the initial endoscopy. Push enteroscopy, however, can sometimes fail to reach the desired area. Double balloon enteroscopy is a promising alternative technique that requires an experienced endoscopist and is currently offered primarily at tertiary care centers. Double balloon enteroscopy was approximately 83% successful in intubating the excluded segment in a study of 6 patients status post RYGB[18,19]. Cappell *et al*[20] in 1992 reported 3 cases in 2 patients of severely symptomatic gastric ulcers within the surgically excluded gastric segment in patients status post vertical banded gastroplasty that were missed at EGD and only diagnosed at laparotomy. Whereas the ulcers in the surgically excluded segment status post vertical banded gastroplasty were endoscopically inaccessible, the currently reported ulcers in the excluded segment status post RYGB are often accessible using push enteroscopy

or single balloon enteroscopy.

Angiography with embolization should be considered in actively bleeding and hemodynamically unstable patients. Emergency surgery, possibly including resection of the bypassed stomach, should be considered for patients with refractory bleeding, but such surgery without prior endoscopic localization of the bleeding site increases the surgical failure rate[9]. Some authorities even suggest resection of the excluded stomach, which can be performed during the initial bypass surgery[21]. Advantages of this resection include: (1) decreased acid production because of resection of most of the gastrin-releasing part of the stomach; (2) removal of difficult to access parts of the stomach; and (3) avoiding gastro-gastric fistulization. Disadvantages of this resection include: (1) risk of duodenal stump leakage; (2) risk of intraoperative or postoperative bleeding; (3) potential abscess formation from necrosis of omental fat; (4) bacterial overgrowth in the biliopancreatic blind pouch; and (5) nutrient deficiencies, including vitamin B12 deficiency. Due to the rarity of bleeding or perforation from peptic ulcers in the excluded segment after RYGB, surgical treatment should be individualized[21,22].

RYGB patients also face potentially delayed diagnosis of GI cancers in the excluded segment due to technically difficult endoscopic access, but RYGB patients have a lower incidence of gastric cancer as compared to the general population[18,23]. Five cases have been reported in the excluded segment of gastric adenocarcinoma, most of which were advanced cancers[18,24], and several cases of lymphoma or gastrointestinal stromal tumors have been reported[25]. Another problem in diagnosing these cancers are the limitations of virtual gastroduodenoscopy, including: (1) lack of visualization of fine mucosal detail, especially vascularity; (2) missing small, flat lesions; (3) confusion of residual intragastric food with a gastric mass; and (4) inability to obtain biopsy specimens for histological diagnosis[17]. Voellimger *et al*[26] suggested that resection of the bypassed stomach should be considered during the primary RYGB operation in patients with precancerous gastroduodenal lesions.

This study is limited by reporting only 2 cases and the retrospective methodology.

Despite the two currently reported diagnostic successes, these advanced endoscopic techniques may be non-diagnostic because of absence of lesions in the excluded segments or potential inability to sometimes intubate the excluded segments with these enteroscopes. Furthermore, endoscopic therapy of ulcers with stigmata of recent hemorrhage (SRH) may not necessarily prevent recurrent bleeding; one of the currently reported patients required surgery for re-bleeding despite the therapeutic endoscopy. Nonetheless, endoscopic therapy of ulcers with high risk SRH significantly reduces the risk of rebleeding and is therefore recommended despite occasional therapeutic failures[27]. This work should prompt a large, prospective, study to determine the technical success rate of single or double balloon enteroscopy *vs* standard EGD in intubating the excluded gastroduodenal segment (afferent limb) in patients status post RYGB.

In conclusion, intubation of the excluded stomach and duodenum at EGD is technically difficult in patients status post RYGB, and therefore the diagnosis and opportunity for endoscopic therapy of gastric or duodenal lesions may be missed. Two cases are reported of UGI bleeding 10 or 11 years status post RYGB in which the EGD was non-diagnostic due to failure to intubate the excluded stomach and proximal duodenum, whereas single balloon enteroscopy or push enteroscopy successfully diagnosed duodenal ulcers and provided for endoscopic treatment of these ulcers. These case reports suggest consideration of push enteroscopy, or single balloon enteroscopy, where available, in the evaluation of acute UGI bleeding in patients status post RYGB surgery when EGD was non-diagnostic because of failure to intubate these excluded segments. The results of this study require confirmation by a large study that is preferentially prospective, randomized, and controlled.

COMMENTS

Case characteristics

In case 1, a 44-year-old woman with prior Roux-en-Y gastric bypass (RYGB) 11 years earlier for morbid obesity presented with melena, weakness, and orthostatic dizziness for 1 wk. She had been taking non-steroidal anti-inflammatory drugs (NSAIDs) about two days per month for several months, but was not taking proton pump inhibitors (PPIs). She was a non-smoker and non-alcoholic. Physical examination revealed stable vital signs, pallor, and a benign abdominal examination. Rectal examination revealed melena and no visible hemorrhoids. In case 2, a 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. She was taking ibuprofen about 800 mg/d for about 2 d per week for arthralgia, but had stopped about 3 mo ago. She was not taking PPIs, did not drink alcohol, and had stopped smoking cigarettes (1 pack/d) 12 years earlier. Physical examination on admission revealed stable vital signs, pallor, and a normal abdominal examination. Rectal examination revealed melena and no visible hemorrhoids.

Clinical diagnosis

In case 1, the clinical history of melena, weakness, and orthostatic dizziness strongly suggests acute gastrointestinal bleeding. Melena strongly suggests acute upper GI bleeding, but lower GI bleeding cannot be completely excluded by this history. The symptoms of weakness and orthostatic dizziness suggest that the bleeding caused hypovolemia and was therefore physiologically significant and severe. In case 2, the clinical history of melena suggests acute upper GI bleeding, although occasionally melena may occur secondary to lower GI bleeding. The symptoms of dyspnea, fatigue, and syncope all suggest severe GI bleeding that is causing symptoms of end-organ injury or insufficiency from hypovolemia: Syncope from insufficient cerebral blood perfusion; and dyspnea and fatigue from profound anemia with decreased oxygen-carrying capacity of the blood.

Differential diagnosis

In case 1, the history of prior RYGB surgery in a patient presenting with melena suggests possible bleeding from an anastomotic (marginal) ulcer, but other common causes of upper GI bleeding are in the differential diagnosis, including ordinary peptic ulcer disease, hemorrhagic gastritis, hemorrhagic reflux gastritis, as well as relatively uncommon lesions. Bleeding from esophageal varices is unlikely because of no history of chronic liver disease, absence of stigmata of chronic liver disease, and normal biochemical parameters of liver function. Also lower GI lesions must be considered in the differential diagnosis of patients presenting with melena when the EGD is non-diagnostic. The patient lacked potential risk factors for peptic ulcers or other causes of upper

GI bleeding including known *H. pylori* infection, frequent NSAID use, smoking cigarettes, or alcoholism. In case 2, the melena suggests likely upper GI bleeding. Most prominent in the differential diagnosis in a patient status post RYGB with melena is an anastomotic (marginal) ulcer. However, other common causes of upper GI bleeding are in the differential diagnosis, including ordinary peptic ulcer disease, hemorrhagic gastritis, hemorrhagic reflux gastritis, as well as relatively uncommon lesions. Bleeding from esophageal varices is unlikely because of no history of chronic liver disease, absence of stigmata of chronic liver disease on physical examination, and normal biochemical parameters of liver function. Also lower GI lesions must be considered in the differential diagnosis of patients presenting with melena when the EGD is non-diagnostic. The patient lacked risk factors for peptic ulcer disease or other causes of upper GI bleeding including known *H. pylori* infection, recent NSAID use, recently smoking cigarettes, and alcoholism.

Laboratory diagnosis

In case 1, on admission the hemoglobin level was 4.1 g/dL. This profound anemia demonstrated the importance of relatively rapidly transfusing the patient to prevent end organ injury from hypovolemia, and the patient was transfused 4 units of packed erythrocytes. A coagulopathy was not contributing to the bleeding as the coagulation profile was normal. The blood urea nitrogen: creatinine ratio was 36, consistent with upper rather lower GI bleeding. These findings are consistent with severe, upper GI bleeding. In case 2, laboratory analysis revealed hemoglobin = 7.4 g/dL (recent baseline hemoglobin = 13.3 g/dL), evident iron deficiency anemia with ferritin = 25 ng/mL, platelet count = 62000/L, and serum BUN:Cr ratio = 100. Liver function tests and coagulation panel were within normal limits. The current very low hemoglobin level that has recently declined from a normal hemoglobin level suggests acute, severe, GI bleeding. The iron deficiency anemia suggests the bleeding has been sufficiently long and severe to deplete iron stores. Melena usually arises from an upper GI source, but can occasionally result from a lower GI source, especially when associated with hematochezia. The highly elevated BUN: creatinine ratio strongly suggests that the melena is from upper rather than lower GI bleeding.

Imaging diagnosis

In case 1, EGD did not reveal any source of UGI bleeding, but the excluded duodenum and distal stomach were not intubated and examined. This was due to the difficulty in intubating the afferent limb status post RYGB surgery because of the long intubation needed to reach the afferent limb and acute angulation at the anastomosis to the afferent limb. Colonoscopy was performed because the EGD was non-diagnostic and did not reveal any etiology of lower GI bleeding. The patient experienced recurrent GI bleeding, with hemoglobin decline to 5.8 g/dL for which the patient was again medically stabilized. Abdominal computerized tomography with intravenous contrast was within normal limits. Single balloon enteroscopy, with intubation of the afferent limb, revealed a non-bleeding, 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb and no other lesions. The diagnosis of a giant duodenal ulcer by single balloon enteroscopy after a non-diagnostic EGD due to failure to intubate the afferent limb at EGD is notable. In case 2, EGD did not reveal any source of UGI bleeding, including no anastomotic ulcers, but the excluded duodenum and distal stomach (afferent limb) status post RYGB surgery was not intubated and examined. This was due to the difficulty in intubating the afferent limb status post RYGB surgery because of the long intubation needed to reach the afferent limb and acute angulation at the afferent limb anastomosis. Colonoscopy was performed because of the history of melena and a non-diagnostic EGD, but did not reveal any etiology of lower GI bleeding. Both computed tomographic enterography and capsule endoscopy were within normal limits. Bleeding slowly resolved and she was discharged with hemoglobin level of 8.0 g/dL. The patient was readmitted 3 d later for recurrent melena with a hemoglobin level of 5.1 g/dL. A technetium labeled erythrocyte (bleeding) scan did not reveal active GI bleeding. Push enteroscopy revealed a 5-mm-wide acute bulbar ulcer with a visible vessel that was oozing blood, and an otherwise normal examination. The visible vessel was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation.

Pathological diagnosis

In case 1, giant duodenal ulcer in excluded gastroduodenal segment in afferent limb after RYGB surgery which was diagnosed by single-balloon enteroscopy and confirmed at surgery. The lesion was not resected and therefore the diagnosis was by endoscopic and intraoperative examination without a pathologic diagnosis. In case 2, peptic ulcer in the duodenal bulb in the excluded gastroduodenal segment (afferent limb) after RYGB surgery, as diagnosed by enteroscopy. The bulbar ulcer was not resected and therefore the diagnosis was by enteroscopy, without a pathologic diagnosis.

Treatment

In case 1, the visible vessel was ablated at single-balloon enteroscopy by injection of dilute epinephrine and by heater probe thermocoagulation. However, the patient had another episode of melena and the hemoglobin acutely declined from 9.5 g/dL to 6.5 g/dL 72 h after therapeutic single balloon enteroscopy. Failure despite use of two methods of endoscopic hemostasis (dilute epinephrine injection and heater probe thermocoagulation) was most likely related to the exceedingly large size of the duodenal ulcer (4 cm diameter). A technetium-labeled erythrocyte (bleeding) scan and an abdominal arteriogram did not reveal an actively bleeding source. Exploratory laparotomy revealed a giant, posterior, bulbar ulcer (which had been detected at single-balloon enteroscopy), which was oversewn. The patient was discharged with no further bleeding during the hospitalization or for three months of follow-up. In case 2, the patient received intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered a PPI. The duodenal ulcer lesion was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation (APC) because it was oozing blood at the endoscopy. The patient had one further, self-limited, episode of melena, after which the bleeding resolved, and the patient was discharged. She has had no further GI bleeding during 3 mo of follow-up.

Related reports

This work reports two cases of duodenal ulcers occurring after RYGB, supplementing 22 prior case reports of peptic ulcers after RYGB.

Term explanations

RYGB is an acronym for Roux-en-Y gastric bypass surgery, a popular form of bariatric surgery, in which a large part of the stomach and the duodenum is surgically excluded from the normal stream of food. This surgery leads to weight loss from decreased assimilation and absorption of food, from early satiety because of the very small residual stomach pouch, and from decreased production of ghrelin which acts as a "hunger hormone". The afferent limb (also called the biliopancreatic limb) is composed of the duodenum which is excluded from the alimentary track after RYGB. The gastrojejunal (alimentary) limb connects directly from the proximal gastric pouch to the jejunoileum after RYGB surgery. After RYGB surgery the distal gastric pouch, duodenal bulb and rest of the duodenum are excluded from continuity with the rest of the alimentary tract.

Experiences and lessons

These two cases report bleeding giant or moderately-sized duodenal ulcers being missed at routine EGD performed for acute upper GI bleeding because of inability to intubate the afferent limb (excluded segment) due to acute angulation and the need for deep intubation. This finding has been previously reported in case reports. This work reports that the afferent limb was successfully intubated by either a single balloon enteroscope or push enteroscope. This work further confirms the findings in previous isolated case reports. Use of these specialized endoscopes (enteroscopes) permitted the diagnosis of the etiology of the acute upper GI bleeding as peptic ulcers, permitted identification of high-risk stigmata of recent hemorrhage (SRH) consisting of either a visible vessel or active oozing of blood, and permitted performance of therapeutic endoscopy for hemostasis. Although recurrent GI bleeding from only one of the two high risk peptic ulcers was prevented by the endoscopic therapy and the second patient required GI surgery for recurrent GI bleeding, these two cases illustrate the usefulness of specialized enteroscopes rather than standard esophagogastroduodenoscopes to intubate, examine, and diagnose lesions in the excluded gastroduodenal segment (afferent limb) status post RYGB surgery. This work adds to the literature by emphasizing the potential diagnostic and therapeutic benefits of push enteroscopy or single balloon enteroscopy if EGD was non-diagnostic in patients status-post RYGB surgery. This work points out the need for a prospective, large study comparing the diagnostic yield of enteroscopy *vs* EGD in patients with upper GI bleeding

status post RYGB surgery.

Peer-review

The authors report two cases with acute UGIB following Roux-en-Y gastric bypass where the diagnosis and treatment were performed successfully with enteroscopy. This report treats interesting cases.

REFERENCES

1 **Ceppa FA**, Gagné DJ, Papasavas PK, Caushaj PF. Laparoscopic transgastric endoscopy after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2007; **3**: 21-24 [PMID: 17116423 DOI: 10.1016/j.soard.2006.08.018]

2 **Iskandar ME**, Chory FM, Goodman ER, Surick BG. Diagnosis and Management of Perforated Duodenal Ulcers following Roux-En-Y Gastric Bypass: A Report of Two Cases and a Review of the Literature. *Case Rep Surg* 2015; **2015**: 353468 [PMID: 25949843 DOI: 10.1155/2015/353468]

3 **Arroyo-Johnson C**, Mincey KD. Obesity Epidemiology Worldwide. *Gastroenterol Clin North Am* 2016; **45**: 571-579 [PMID: 27837773 DOI: 10.1016/j.gtc.2016.07.012]

4 **Fryar CD**, Carroll MD, Ogden CL. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, 1960-1962 Through 2011-2012. Available from: URL: https: //www.cdc.gov/nchs/data/hestat/obesity_adult_11_12/obesity_adult_11_12.htm

5 **Zerey M**, Sigmon LB, Kuwada TS, Heniford BT, Sing RF. Bleeding duodenal ulcer after roux-en-Y gastric bypass surgery. *J Am Osteopath Assoc* 2008; **108**: 25-27 [PMID: 18258698]

6 **Trainer S**, Benjamin T. Elective surgery to save my life: rethinking the "choice" in bariatric surgery. *J Adv Nurs* 2017; **73**: 894-904 [PMID: 27779770 DOI: 10.1111/jan.13193]

7 **Steinbrook R**. Surgery for severe obesity. *N Engl J Med* 2004; **350**: 1075-1079 [PMID: 15014179 DOI: 10.1056/NEJMp048029]

8 **Santry HP**, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. *JAMA* 2005; **294**: 1909-1917 [PMID: 16234497 DOI: 10.1001/jama.294.15.1909]

9 **Eid JJ**, Radecke JM, Murr MM. Gastrointestinal bleeding from the excluded stomach: a proposed algorithmic approach to management. *Surg Obes Relat Dis* 2015; **11**: e11-e14 [PMID: 25449066 DOI: 10.1016/j.soard.2014.09.008]

10 **Jamil LH**, Krause KR, Chengelis DL, Jury RP, Jackson CM, Cannon ME, Duffy MC. Endoscopic management of early upper gastrointestinal hemorrhage following laparoscopic Roux-en-Y gastric bypass. *Am J Gastroenterol* 2008; **103**: 86-91 [PMID: 17941960 DOI: 10.1111/j.1572-0241.2007.01588.x]

11 **Ivanecz A**, Sremec M, Ceranić D, Potrč S, Skok P. Life threatening bleeding from duodenal ulcer after Roux-en-Y gastric bypass: Case report and review of the literature. *World J Gastrointest Endosc* 2014; **6**: 625-629 [PMID: 25512773 DOI: 10.4253/wjge.v6.i12.625]

12 **Mittermair R**, Renz O. An unusual complication of gastric bypass: perforated duodenal ulcer. *Obes Surg* 2007; **17**: 701-703 [PMID: 17658034]

13 **Macgregor AM**, Pickens NE, Thoburn EK. Perforated peptic ulcer following gastric bypass for obesity. *Am Surg* 1999; **65**: 222-225 [PMID: 10075296]

14 **Mason EE**, Munns JR, Kealey GP, Wangler R, Clarke WR, Cheng HF, Printen KJ. Effect of gastric bypass on gastric secretion. *Am J Surg* 1976; **131**: 162-168 [PMID: 1251957]

15 **Flickinger EG**, Sinar DR, Pories WJ, Sloss RR, Park HK, Gibson JH. The bypassed stomach. *Am J Surg* 1985; **149**: 151-156 [PMID: 3966631]

16 **Bjorkman DJ**, Alexander JR, Simons MA. Perforated duodenal ulcer after gastric bypass surgery. *Am J Gastroenterol* 1989; **84**: 170-172 [PMID: 2916529]

17 **Silecchia G**, Catalano C, Gentileschi P, Elmore U, Restuccia A, Gagner M, Basso N. Virtual gastroduodenoscopy: a new look at the bypassed stomach and duodenum after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Obes Surg* 2002; **12**: 39-48 [PMID: 11868296 DOI: 10.1381/096089202321144568]

18 **Tagaya N**, Kasama K, Inamine S, Zaha O, Kanke K, Fujii Y, Kanehira E, Hiraishi H, Kubota K. Evaluation of the excluded stomach by double-balloon endoscopy after laparoscopic Roux-en-Y gastric bypass. *Obes Surg* 2007; **17**: 1165-1170 [PMID: 18074489]

19 **Sakai P**, Kuga R, Safatle-Ribeiro AV, Faintuch J, Gama-Rodrigues JJ, Ishida RK, Furuya CK, Yamamoto H, Ishioka S. Is it feasible to reach the bypassed stomach after Roux-en-Y gastric bypass for morbid obesity? The use of the double-balloon enteroscope. *Endoscopy* 2005; **37**: 566-569 [PMID: 15933931 DOI: 10.1055/s-2005-861444]

20 **Cappell MS**, Miller SH. Gastric lesions in the excluded gastric segment undetected by endoscopy or radiography in patients status post vertical banded gastroplasty. *Am J Gastroenterol* 1992; **87**: 639-644 [PMID: 1595654]

21 **Csendes A**, Burdiles P, Papapietro K, Diaz JC, Maluenda F, Burgos A, Rojas J. Results of gastric bypass plus resection of the distal excluded gastric segment in patients with morbid obesity. *J Gastrointest Surg* 2005; **9**: 121-131 [PMID: 15623453 DOI: 10.1016/j.gassur.2004.05.006]

22 **Gypen BJ**, Hubens GJ, Hartman V, Balliu L, Chapelle TC, Vaneerdeweg W. Perforated duodenal ulcer after laparoscopic gastric bypass. *Obes Surg* 2008; **18**: 1644-1646 [PMID: 18443886 DOI: 10.1007/s11695-008-9530-y]

23 **Wingo PA**, Ries LA, Giovino GA, Miller DS, Rosenberg HM, Shopland DR, Thun MJ, Edwards BK. Annual report to the nation on the status of cancer, 1973-1996, with a special section on lung cancer and tobacco smoking. *J Natl Cancer Inst* 1999; **91**: 675-690 [PMID: 10218505]

24 **Watkins BJ**, Blackmun S, Kuehner ME. Gastric adenocarcinoma after Roux-en-Y gastric bypass: access and evaluation of excluded stomach. *Surg Obes Relat Dis* 2007; **3**: 644-647 [PMID: 17950044 DOI: 10.1016/j.soard.2007.06.008]

25 **de Roover A**, Detry O, de Leval L, Coimbra C, Desaive C, Honoré P, Meurisse M. Report of two cases of gastric cancer after bariatric surgery: lymphoma of the bypassed stomach after Roux-en-Y gastric bypass and gastrointestinal stromal tumor (GIST) after vertical banded gastroplasty. *Obes Surg* 2006; **16**: 928-931 [PMID: 16839496 DOI: 10.1381/096089206777822142]

26 **Voellinger DC**, Inabnet WB. Laparoscopic Roux-en-Y gastric bypass with remnant gastrectomy for focal intestinal metaplasia of the gastric antrum. *Obes Surg* 2002; **12**: 695-698 [PMID: 12448395 DOI: 10.1381/096089202321019710]

27 **Cappell MS**. Therapeutic endoscopy for acute upper gastrointestinal bleeding. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 214-229 [PMID: 20212504 DOI: 10.1038/nrgastro.2010.24]

P- Reviewer: Chen CH, Chiba H, Thomopoulos KC
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2017 October 16; 9(10): 529-534

DOI: 10.4253/wjge.v9.i10.529

ISSN 1948-5190 (online)

CASE REPORT

Cap polyposis refractory to *Helicobacter pylori* eradication treated with endoscopic submucosal dissection

Masaki Murata, Mitsushige Sugimoto, Hiromitsu Ban, Taketo Otsuka, Toshiro Nakata, Masahide Fukuda, Osamu Inatomi, Shigeki Bamba, Ryoji Kushima, Akira Andoh

Masaki Murata, Taketo Otsuka, Toshiro Nakata, Osamu Inatomi, Shigeki Bamba, Akira Andoh, Department of Gastroenterology, Shiga University of Medical Science Hospital, Otsu 520-2192, Japan

Mitsushige Sugimoto, Hiromitsu Ban, Division of Digestive Endoscopy, Shiga University of Medical Science Hospital, Otsu 520-2192, Japan

Masahide Fukuda, Ryoji Kushima, Department of Clinical Laboratory Medicine, Shiga University of Medical Science Hospital, Otsu 520-2192, Japan

Author contributions: Murata M, Sugimoto M, Ban H, Otsuka T, Nakata T, Fukuda M, Inatomi O, Bamba S, Kushima R and Andoh A collected and analyzed the patient's clinical data and wrote the paper.

Institutional review board statement: Approval of this case report was not given in advance by the Institutional Review Board of Shiga University of Medical Science.

Informed consent statement: A patient of this case provided informed written consent prior to the endoscopic procedure and treatment.

Conflict-of-interest statement: No conflict of interest to declare.

Manuscript source: Invited manuscript

Correspondence to: Mitsushige Sugimoto, MD, PhD, Division of Digestive Endoscopy, Shiga University of Medical Science Hospital, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan. sugimo@belle.shiga-med.ac.jp
Telephone: +81-77-5482618
Fax: +81-77-5482618

Received: April 6, 2017
Peer-review started: April 10, 2017
First decision: May 16, 2017
Revised: May 24, 2017
Accepted: June 30, 2017
Article in press: July 3, 2017
Published online: October 16, 2017

Abstract

Cap polyposis is a rare intestinal disorder. Characteristic endoscopic findings are multiple inflammatory polypoid lesions covered by caps of fibrous purulent exudate. Although a specific treatment has not been established, some studies have suggested that eradication therapy for *Helicobacter pylori* (*H. pylori*) is effective. We report a case of a 20-year-old man with cap polyposis presenting with hematochezia. Colonoscopy showed the erythematous polyps with white caps from the sigmoid colon to rectum. Histopathological findings revealed elongated, tortuous, branched crypts lined by hyperplastic epithelium with a mild degree of fibromusculosis in the lamina propria. Although *H. pylori* eradication was instituted, there was no improvement over six months. We then performed *en bloc* excision of the polyps by endoscopic submucosal dissection (ESD), which resulted in complete resolution of symptoms. ESD may be a treatment option for cap polyposis refractory to conservative treatments. We review the literature concerning treatment for cap polyposis and clinical outcomes.

Key words: Endoscopic submucosal dissection; Cap polyposis; Eradication therapy; *Helicobacter pylori*

Core tip: Although for cap polyposis, conservative treatment should be selected as first-line therapy, the optimal treatment of cap polyposis refractory to conservative treatment has not been established. Endoscopic submucosal dissection may be a treatment option for cases refractory to conservative treatment.

Murata M, Sugimoto M, Ban H, Otsuka T, Nakata T, Fukuda M, Inatomi O, Bamba S, Kushima R, Andoh A. Cap polyposis refractory to *Helicobacter pylori* eradication treated with endoscopic submucosal dissection. *World J Gastrointest Endosc* 2017; 9(10): 529-534 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i10/529.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i10.529

INTRODUCTION

Cap polyposis is a rare intestinal disorder with unique clinical, endoscopic, and histological findings. Clinical symptoms include mucoid and bloody diarrhea, abdominal pain, tenesmus, weight loss, and dysplasia. Endoscopy typically reveals multiple reddish, mucus-capped inflammatory polyps in the rectosigmoid area with normal mucosa interspersed between the polyps[1]. Pathologically, the surfaces of these inflammatory polyps are covered by a thick layer of fibrinopurulent exudate, hence the term "cap"[1]. However, the etiology of cap polyposis is unclear and its clinical course varies from spontaneous clinical and endoscopic remission without treatment[2-4] to persistent disease refractory to conservative treatment[5-7], requiring surgical resection. Little is known about its long-term course.

The optimal treatment for cap polyposis has not been established[2-16]. Some cases have been treated successfully by the avoidance of straining at defecation[8], antimicrobial agents (*i.e.,* metronidazole)[9], steroids[2], immunomodulators (*i.e.,* infliximab)[12], endoscopic therapy[13,14] and surgical resection[5-7]. Recently, the efficacy of *Helicobacter pylori* (*H. pylori*) eradication therapy for *H. pylori*-positive patients with cap polyposis has been reported[10,11,15,16], and in 2016 the Japanese Society for *Helicobacter* Research added cap polyposis as a possible *H. pylori*-associated disease in its treatment guidelines. However, no treatments for *H. pylori*-negative cap polyposis or *H. pylori*-positive cases refractory to eradication therapy have yet been established.

Here, we report a case of *H. pylori*-negative cap polyposis refractory to *H. pylori* eradication therapy that was successfully treated with endoscopic submucosal dissection (ESD). We also review the literature concerning conservative and endoscopic treatments for cap polyposis.

CASE REPORT

A 20-year-old Japanese man presented with a 1-year history of hematochezia and tenesmus. He denied straining at stool and had no history of anal prolapse. His past medical and family history were unremarkable. Laboratory tests revealed mild hypoproteinemia (serum albumin 3.9 g/L), but no hepatic or renal dysfunction, leukocytosis, elevation of C-reactive protein, or anemia. Colonoscopy revealed the characteristic appearance of cap polyposis, with approximately 20-30 erythematous variform inflammatory polyps with white caps of fibrinopurulent exudate from the sigmoid colon to the rectum (Figure 1A and B). Magnification endoscopy with narrow-band imaging showed amorphous exudate in the white caps overlying long branching tortuous crypts in the basal part of the polyps (Figure 1C and D). Endoscopic ultrasonography (EUS) with radial array scanning showed significant thickening of the mucosa without evidence of invasion into the submucosa (Figure 1E). Histologic findings from a polyp revealed elongated, tortuous, branched crypts lined with hyperplastic epithelium with inflammatory cell infiltration and a mild degree of fibromusculosis in the lamina propria (Figure 2). The surface of the polyps was covered by thick inflammatory granulation tissue with exudate (Figure 2). The intervening mucosa between lesions was histologically normal. Computed tomography and magnetic resonance imaging showed multiple elevated lesions thickening the walls of the sigmoid colon and rectum (Figure 3A and B). Barium enema showed multiple raised mucosal lesions without stenosis or sclerotic changes in the sigmoid colon and rectum (Figure 3C). The differential diagnosis included the mucosal prolapse syndrome, inflammatory polyps, colon cancer, malignant lymphoma, inflammatory bowel disease, and adenomatous polyposis. We diagnosed cap polyposis based on the endoscopic and histopathological characteristics.

The patient had no evidence of *H. pylori* infection by urea breath test, anti-*H. pylori* antibody, or endoscopic findings (*i.e.,* gastric mucosal atrophy or diffuse redness of gastric mucosa). However, according to previous evidence that *H. pylori* eradication therapy was effective for patients with cap polyposis[10,11,15,16], *H. pylori* eradication therapy with vonoprazan 20 mg, amoxicillin 750 mg and clarithromycin 200 mg twice daily for 7 d was initiated. Abdominal symptoms (*i.e.,* hematochezia and tenesmus), bowel habits, and endoscopic findings did not improve over the six months after therapy. Therefore, as conservative alternative treatment, we performed *en bloc* excision of the polyps with ESD (Figure 4). After resection, the patient's symptoms disappeared and he had no endoscopic evidence of recurrence for six months.

DISCUSSION

We report a case of a patient with cap polyposis refractory to *H. pylori* eradication therapy who then underwent *en bloc* excision of polyps by ESD with good results. This is the first report of the efficacy of ESD for treatment of cap polyposis. More studies of ESD as a treatment option for cap polyposis are needed to validate

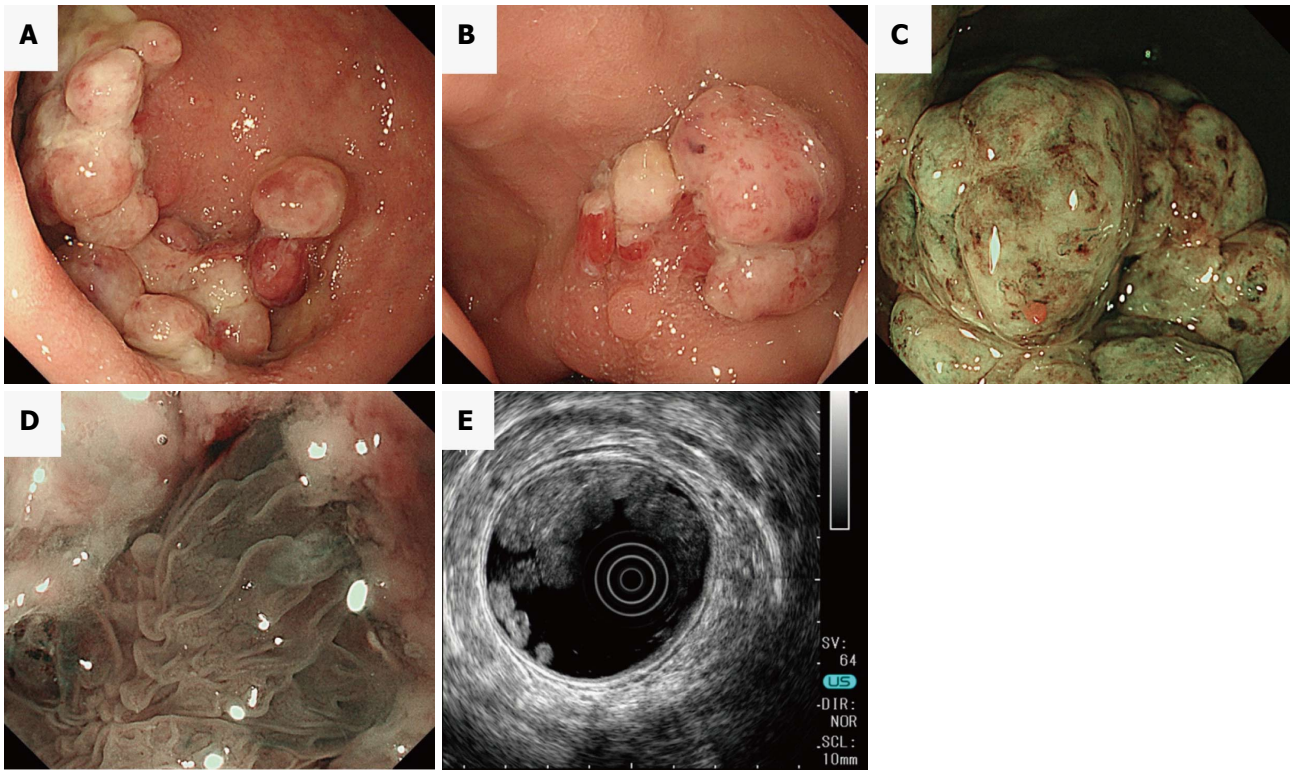


Figure 1 Endoscopic findings of multiple inflammatory polyps. A and B: Caps of fibrinopurulent exudate from the sigmoid colon to the rectum interspersed with normal colonic mucosa; C and D: Magnifying endoscopy shows an area in the cap of amorphous fibrinopurulent exudate and tortuous and long branching crypts under the cap; E: Endoscopic ultrasonography showed significant thickening of the colonic mucosa layers.

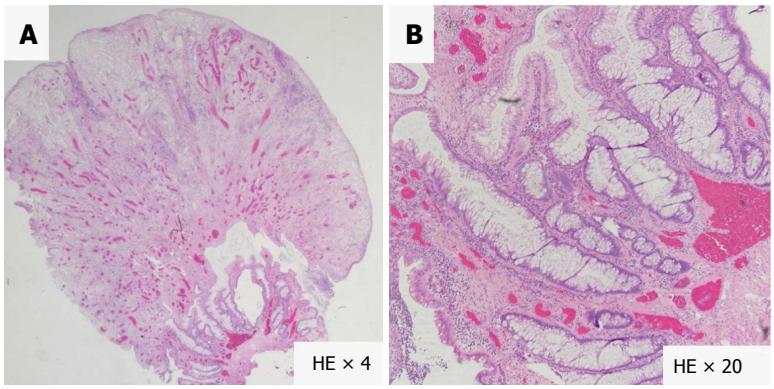


Figure 2 Microscopic findings of inflammatory polyps show elongated, tortuous, branched, and dilated crypts with epithelial hyperplasia, inflammatory granulation tissue and a mild degree of fibromusculosis in the lamina propria. Hematoxylin-Eosin stain, × 4 (A) and × 20 (B).

its use instead of surgical resection.

Diagnosis of cap polyposis

Cap polyposis can be difficult to diagnose. It can resemble mucosal prolapse syndrome (MPS). There has been a debate about whether cap polyposis is a specific form of inflammatory disorder or part of a spectrum of MPS[12]. MPS and cap polyposis share some clinical, endoscopic, and histological features. Both diseases show infiltration of inflammatory cells with elongated stroma and fibromuscular obliteration of the lamina propria. However, the fibromuscular obliteration is more marked in cap polyposis. MPS is usually confined to the rectum, but cap polyposis usually involves the sigmoid and/or descending colon as well as the rectum. EUS findings in cap polyposis show significant thickening of the mucosa[9], whereas MPS is characterized by smooth, diffuse thickening of the submucosa and minimal thickening of the lamina propria[17].

Cap polyposis and protein loss

Common clinical features of cap polyposis are hematochezia (82%), chronic straining (64%), and mucous diarrhea (46%)[1]. When mucous diarrhea is severe and/or continuous for long periods, excessive protein loss is observed as a result[1,5]. Direct loss of protein was

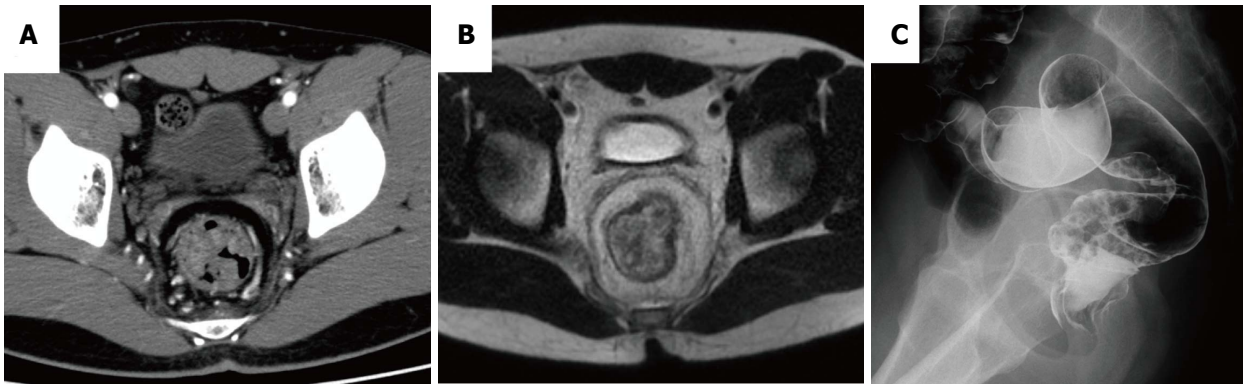


Figure 3 Multiple elevated lesions with wall thickening in the sigmoid colon. Rectum on computed tomography (A) and magnetic resonance imaging (B); Barium enema shows a collection of small sessile polyps in the sigmoid colon and rectum (C).

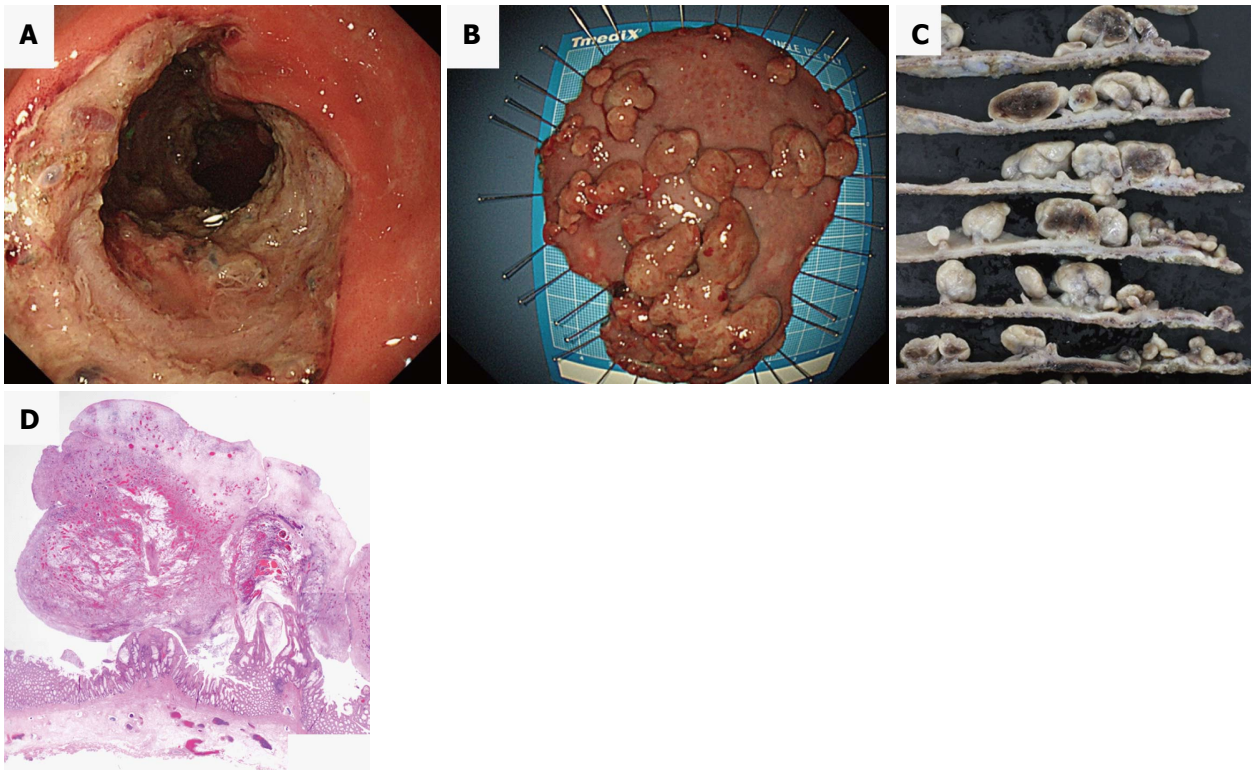


Figure 4 Endoscopic submucosal dissection. Post-dissection ulcers after endoscopic submucosal dissection at the sigmoid colon and rectum (A). Fresh specimen of cap polyposis after endoscopic submucosal dissection (B) and fixed specimen (C). The fixed specimen revealed bleeding into the polyps. Microscopic findings of inflammatory polyps [HE stain, × 4 (D)].

demonstrated in a case of cap polyposis by scintigraphy with technetium 99m-labeled diethylenetriaminepentaacetic acid complexed to human serum albumin[18]. In our case, blood tests revealed mild hypoproteinemia, with an albumin level 39 g/L, possibly secondary to protein loss from mucous diarrhea.

Cap polyposis and H. pylori infection

Cap polyposis has been attributed to colonic dysmotility, immune abnormalities, bacterial infection (*i.e., H. pylori*) or other unknown pathogens. Géhénot *et al*[19] suggested the possibility of bacterial infection, reporting on a cap polyposis patient who had no evidence of colonic dysmotility and who was successfully treated with metronidazole. Of the myriad gut microbiota, although *H. pylori* is not detected in mucosa obtained from cap polyposis lesions[10], most cases of cap polyposis with *H. pylori* infection have resolved after *H. pylori* eradication therapy[10,11,15,16,18]. *H. pylori* infection is well-known to cause not only gastroduodenal diseases, but also diseases such as idiopathic thrombocytopenic purpura and chronic idiopathic urticaria[20,21]. In addition, eradication therapy often induces regression of mucosa-associated lymphoid tissue (MALT) lymphoma in the rectum and thyroid[22]. Although an *H. pylori*-associated immune reaction may play a role in the development of some cases of cap

polyposis, there is no evidence for efficacy of *H. pylori* eradication therapy in *H. pylori*-negative cap polyposis patients, as in our case. Because the development of cap polyposis with active inflammation in the colonic mucosa may be related to other bacterial infections that are also sensitive to the antimicrobial agents used in *H. pylori* eradication therapy (*i.e.*, clarithromycin, amoxicillin, and metronidazole), we selected eradication therapy as the first-line treatment. Although eradication failed to cure the cap polyposis, further studies will be required to investigate whether other pathogens are related to this diagnosis, and whether their eradication can effect resolution.

Cap polyposis and endoscopic treatment

The efficacy of endoscopic treatment, such as polypectomy and endoscopic mucosal resection (EMR), for cap polyposis has been reported[12,14]. However, *en bloc* excision is difficult to perform with conventional EMR, and the use of surgical resection is more frequent[5-7]. Although there have been no reports of malignant transformation, surgical resection may be excessive for the treatment of cap polyposis. We consider ESD *en bloc* excision to be less invasive, and also can prevent recurrence.

ESD, an endoscopic procedure that originated in Japan and Korea in the late 1990s which has since spread rapidly to other nations, is now commonly used to treat gastrointestinal tumors[23,24]. ESD allows complete pathological assessment, proving this technique superior to polypectomy or conventional EMR to prevent recurrence[25]. To date, no case of cap polyposis treated with ESD has been reported. Our present case suggests that ESD may be an effective treatment for intractable cap polyposis, with lower invasiveness than surgical resection. Our patient remains under surveillance for recurrence.

Conclusion

For cap polyposis, conservative treatment should be selected as first-line therapy. In particular, we recommend eradication therapy for *H. pylori* infection. To our knowledge, however, the optimal treatment of cap polyposis refractory to conservative medical treatment has not been established. This is the first report of cap polyposis refractory to conservative medical treatment effectively treated with ESD. We believe that ESD is less invasive and more effective than surgical resection in cases refractory to conservative treatment. ESD may be a treatment option for cap polyposis cases refractory to conservative medical treatments, such as *H pylori* eradication, metronidazole, steroids, and infliximab. Further investigation is required.

COMMENTS

Case characteristics

A 20-year-old Japanese man with cap polyposis located in sigmoid colon and rectum refractory to *Helicobacter pylori* (*H. pylori*) eradication and resected with endoscopic submucosal dissection.

Clinical diagnosis

Cap polyposis.

Differential diagnosis

Although the differential diagnosis includes the mucosal prolapse syndrome (MPS), inflammatory polyps, colon cancer, malignant lymphoma, inflammatory bowel disease, and adenomatous polyposis, MPS is most possible disease as differentiation disease, because cap polyposis and MPS share some clinical, endoscopic, and histological features.

Laboratory diagnosis

Although mild hypoproteinemia was revealed, there was no hepatic or renal dysfunction, leukocytosis, elevation of C-reactive protein, or anemia.

Imaging diagnosis

Colonoscopy revealed the characteristic appearance of cap polyposis, with approximately 20-30 erythematous variform inflammatory polyps with white caps of fibrinopurulent exudate from the sigmoid colon to the rectum.

Pathological diagnosis

Pathological findings revealed elongated, tortuous, branched crypts lined with hyperplastic epithelium with inflammatory cell infiltration and a mild degree of fibromusculosis in the lamina propria in the polypoid lesion and thick inflammatory granulation tissue in the surface of the polyps.

Treatment

Because this case was refractory to *H. pylori* eradication as the first-line therapy, *en bloc* excision of polyposis with endoscopic submucosal dissection (ESD) was selected as second-line therapy.

Related reports

Previously, although endoscopic treatment including polypectomy and EMR, and conservative medical treatments including *H. pylori* eradication, metronidazole, steroids, and infliximab, had been reported, the optimal treatment for cap polyposis has not been established.

Experiences and lessons

ESD may be a treatment option for cap polyposis cases refractory to conservative treatments (*i.e., H. pylori* eradication, metronidazole, steroids, and infliximab).

Peer-review

The paper is well written.

REFERENCES

1 **Ng KH**, Mathur P, Kumarasinghe MP, Eu KW, Seow-Choen F. Cap polyposis: further experience and review. *Dis Colon Rectum* 2004; **47**: 1208-1215 [PMID: 15164251 DOI: 10.1007/s10350-004-0561-8]

2 **Chang HS**, Yang SK, Kim MJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Long-term outcome of cap polyposis, with special reference to the effects of steroid therapy. *Gastrointest Endosc* 2012; **75**: 211-216 [PMID: 22078102 DOI: 10.1016/j.gie.2011.08.027]

3 **Sasaki Y**, Takeda H, Fujishima S, Sato T, Nishise S, Abe Y, Ajioka Y, Kawata S, Ueno Y. Nine-year follow-up from onset to spontaneous complete remission of cap polyposis. *Intern Med* 2013; **52**: 351-354 [PMID: 23370743]

4 **Ohkawara T**, Kato M, Nakagawa S, Nakamura M, Takei M, Komatsu Y, Shimizu Y, Takeda H, Sugiyama T, Asaka M. Spontaneous resolution of cap polyposis: case report. *Gastrointest Endosc* 2003; **57**: 599-602 [PMID: 12665781 DOI: 10.1067/mge.2003.166]

5 **Gallegos M**, Lau C, Bradly DP, Blanco L, Keshavarzian A, Jakate SM. Cap polyposis with protein-losing enteropathy. *Gastroenterol Hepatol* (N Y) 2011; **7**: 415-420 [PMID: 21869875]

6 **Konishi T**, Watanabe T, Takei Y, Kojima T, Nagawa H. Confined progression of cap polyposis along the anastomotic line, implicating the role of inflammatory responses in the pathogenesis. *Gastrointest Endosc* 2005; **62**: 446-447; discussion 447 [PMID: 16111972 DOI: 10.1016/j.gie.2005.04.030]

7 **Campbell AP**, Cobb CA, Chapman RW, Kettlewell M, Hoang P, Haot BJ, Jewell DP. Cap polyposis--an unusual cause of diarrhoea. *Gut* 1993; **34**: 562-564 [PMID: 8491408]

8 **Oriuchi T**, Kinouchi Y, Kimura M, Hiwatashi N, Hayakawa T, Watanabe H, Yamada S, Nishihira T, Ohtsuki S, Toyota T. Successful treatment of cap polyposis by avoidance of intraluminal trauma: clues to pathogenesis. *Am J Gastroenterol* 2000; **95**: 2095-2098 [PMID: 10950064 DOI: 10.1111/j.1572-0241.2000.02277.x]

9 **Shimizu K**, Koga H, Iida M, Yao T, Hirakawa K, Hoshika K, Mikami Y, Haruma K. Does metronidazole cure cap polyposis by its antiinflammatory actions instead of by its antibiotic action? A case study. *Dig Dis Sci* 2002; **47**: 1465-1468 [PMID: 12141801]

10 **Akamatsu T**, Nakamura N, Kawamura Y, Shinji A, Tateiwa N, Ochi Y, Katsuyama T, Kiyosawa K. Possible relationship between Helicobacter pylori infection and cap polyposis of the colon. *Helicobacter* 2004; **9**: 651-656 [PMID: 15610079 DOI: 10.1111/j.1083-4389.2004.00273.x]

11 **Oiya H**, Okawa K, Aoki T, Nebiki H, Inoue T. Cap polyposis cured by Helicobacter pylori eradication therapy. *J Gastroenterol* 2002; **37**: 463-466 [PMID: 12108681 DOI: 10.1007/s005350200067]

12 **Bookman ID**, Redston MS, Greenberg GR. Successful treatment of cap polyposis with infliximab. *Gastroenterology* 2004; **126**: 1868-1871 [PMID: 15188181]

13 **Arimura Y**, Isshiki H, Hirayama D, Onodera K, Murakami K, Yamashita K, Shinomura Y. Polypectomy to eradicate cap polyposis with protein-losing enteropathy. *Am J Gastroenterol* 2014; **109**: 1689-1691 [PMID: 25287098 DOI: 10.1038/ajg.2014.227]

14 **Batra S**, Johal J, Lee P, Hourigan S. Cap Polyposis Masquerading as Inflammatory Bowel Disease in a Child. *J Pediatr Gastroenterol Nutr* 2016; Epub ahead of print [PMID: 27437929 DOI: 10.1097/MPG.0000000000001343]

15 **Takeshima F**, Senoo T, Matsushima K, Akazawa Y, Yamaguchi N, Shiozawa K, Ohnita K, Ichikawa T, Isomoto H, Nakao K. Successful management of cap polyposis with eradication of Helicobacter pylori relapsing 15 years after remission on steroid therapy. *Intern Med* 2012; **51**: 435-439 [PMID: 22333383]

16 **Suzuki H**, Sato M, Akutsu D, Sugiyama H, Sato T, Mizokami Y. A case of cap polyposis remission by betamethasone enema after antibiotics therapy including Helicobacter pylori eradication. *J Gastrointestin Liver Dis* 2014; **23**: 203-206 [PMID: 24949613]

17 **Hizawa K**, Iida M, Suekane H, Mibu R, Mochizuki Y, Yao T, Fujishima M. Mucosal prolapse syndrome: diagnosis with endoscopic US. *Radiology* 1994; **191**: 527-530 [PMID: 8153334 DOI: 10.1148/radiology.191.2.8153334]

18 **Nakagawa Y**, Nagai T, Okawara H, Nakashima H, Tasaki T, Soma W, Hisamatsu A, Watada M, Murakami K, Fujioka T. Cap polyposis (CP) which relapsed after remission by avoiding straining at defecation, and was cured by Helicobacter pylori eradication therapy. *Intern Med* 2009; **48**: 2009-2013 [PMID: 19952483]

19 **Géhénot M**, Colombel JF, Wolschies E, Quandalle P, Gower P, Lecomte-Houcke M, Van Kruiningen H, Cortot A. Cap polyposis occurring in the postoperative course of pelvic surgery. *Gut* 1994; **35**: 1670-1672 [PMID: 7828996]

20 **Take S**, Mizuno M, Ishiki K, Hamada F, Yoshida T, Yokota K, Okada H, Yamamoto K. Seventeen-year effects of eradicating Helicobacter pylori on the prevention of gastric cancer in patients with peptic ulcer; a prospective cohort study. *J Gastroenterol* 2015; **50**: 638-644 [PMID: 25351555 DOI: 10.1007/s00535-014-1004-5]

21 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]

22 **Kalpadakis C**, Pangalis GA, Vassilakopoulos TP, Kyriakaki S, Yiakoumis X, Sachanas S, Moschogiannis M, Tsirkinidis P, Korkolopoulou P, Papadaki HA, Angelopoulou MK. Clinical aspects of malt lymphomas. *Curr Hematol Malig Rep* 2014; **9**: 262-272 [PMID: 25240474 DOI: 10.1007/s11899-014-0218-1]

23 **Fujishiro M**. Endoscopic submucosal dissection for stomach neoplasms. *World J Gastroenterol* 2006; **12**: 5108-5112 [PMID: 16937520 DOI: 10.3748/wjg.v12.i32.5108]

24 **Ninomiya Y**, Oka S, Tanaka S, Nishiyama S, Tamaru Y, Asayama N, Shigita K, Hayashi N, Chayama K. Risk of bleeding after endoscopic submucosal dissection for colorectal tumors in patients with continued use of low-dose aspirin. *J Gastroenterol* 2015; **50**: 1041-1046 [PMID: 25682173 DOI: 10.1007/s00535-015-1053-4]

25 **Hull MJ**, Mino-Kenudson M, Nishioka NS, Ban S, Sepehr A, Puricelli W, Nakatsuka L, Ota S, Shimizu M, Brugge WR, Lauwers GY. Endoscopic mucosal resection: an improved diagnostic procedure for early gastroesophageal epithelial neoplasms. *Am J Surg Pathol* 2006; **30**: 114-118 [PMID: 16330950]

P- Reviewer: Zamani M **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Lu YJ

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.f6publishing.com

World J Gastrointest Endosc 2017 October 16; 9(10): 535-539

DOI: 10.4253/wjge.v9.i10.535

ISSN 1948-5190 (online)

CASE REPORT

Endoscopic ultrasound-guided pancreaticogastrostomy for symptomatic pancreatic duct obstruction caused by migrated pancreatic stent

Lei Lu, Hang-Bin Jin, Jian-Feng Yang, Xiao-Feng Zhang

Lei Lu, Hang-Bin Jin, Jian-Feng Yang, Xiao-Feng Zhang, Department of Gastroenterology, Hangzhou First People's Hospital, Nanjing Medical University, Hangzhou 310000, Zhejiang Province, China

Author contributions: All authors contributed to the acquisition of data, writing, and revision of this manuscript.

Institutional review board statement: This case report was reviewed and approved by the Hangzhou First People's Hospital Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Xiao-Feng Zhang, Department of Gastroenterology, Hangzhou First People's Hospital, Nanjing Medical University, Hangzhou 310000, Zhejiang Province, China. zxf837@tom.com
Telephone: +86-571-56006788

Received: March 24, 2017
Peer-review started: March 29, 2017
First decision: May 8, 2017
Revised: May 28, 2017
Accepted: June 30, 2017
Article in press: July 3, 2017

Published online: October 16, 2017

Abstract

Endoscopic pancreatic stenting has been widely used in various pancreatic conditions. With the increasing use of pancreatic stents, many complications have been recognized. Especially, proximal stent migration presents a serious condition because of subsequent pancreatic duct obstruction, impaired drainage, ductal dilation, and pancreatic pain. Although endoscopic retrieval is the preferred treatment for proximally migrated pancreatic stents, it is not always successful, resulting in conversion to surgery. To date, endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) has never been reported for treatment of pancreatic duct obstruction caused by proximally migrated pancreatic stent. We herein describe a case of pancreatic duct rupture and obstruction caused by proximally migrated pancreatic stent that was successfully treated by EUS-guided pancreaticogastrostomy while keeping the former stent *in situ* after failed endoscopic retrograde cholangiopancreatography. We believe that this report adds to the increasing evidence of symptomatic pancreatic duct obstruction being successfully treated by EUS-PD.

Key words: Endoscopic retrograde cholangiopancreatography; Pancreatic stent; Stent migration; Pancreatic duct obstruction; Endoscopic ultrasound-guided pancreatic duct drainage

Core tip: Stent migration is a rare complication of pancreatic stenting. Especially, proximal migration presents a serious condition because of subsequent pancreatic duct obstruction, impaired drainage, and pancreatic pain.

We described a case of symptomatic pancreatic duct obstruction caused by proximally migrated pancreatic stent that was successfully treated by endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) while keeping the former stent *in situ*. To the best of our knowledge, EUS-PD has never been reported for relief of pancreatic duct obstruction caused by proximally migrated pancreatic stent, and this report adds to the increasing evidence of the safety and effectiveness of EUS-PD.

Lu L, Jin HB, Yang JF, Zhang XF. Endoscopic ultrasound-guided pancreaticogastrostomy for symptomatic pancreatic duct obstruction caused by migrated pancreatic stent. *World J Gastrointest Endosc* 2017; 9(10): 535-539 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i10/535.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i10.535

INTRODUCTION

Endoscopic pancreatic stenting has become an accepted therapy for various pancreatic diseases, including pancreatic duct obstruction due to benign strictures, stones, or tumors, drainage of pancreatic pseudocysts, symptomatic pancreaticobiliary anomalies, and preventing post-ERCP pancreatitis (PEP)[1,2]. With the increasing use of pancreatic stents, various complications have been recognized, such as bleeding, infection, stent occlusion, duodenal perforation, stent fracture, and PEP. Especially, proximal stent migration is a rare complication and presents a serious condition because of subsequent pancreatic duct obstruction, impaired drainage, ductal dilation, and pancreatic pain[3]. Although endoscopic removal of proximally migrated stents can be quite effective, it is not always successful, resulting in conversion to surgery[4]. Endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) is a promising option for pancreatic duct decompression after failed endoscopic retrograde cholangiopancreatography (ERCP)[5], however, it has never been reported for relief of pancreatic duct obstruction caused by proximally migrated pancreatic stent. We herein report a case of a 78-year-old woman with symptomatic pancreatic duct obstruction caused by proximally migrated pancreatic stent that was recovered *via* EUS-guided pancreaticogastrostomy (EPG).

CASE REPORT

A 78-year-old woman was admitted to our hospital with epigastric discomfort of three months' history. On admission, she appeared ill, vitally stable, not jaundiced, and her abdomen was soft but mild tenderness over the epigastrium. Laboratory data were within the normal ranges. Abdominal computed tomography (CT) showed a bright linear object extending from the main pancreatic duct (MPD) and parenchyma into the lesser omental bursa along with a dilated distal MPD (Figure 1).

The patient's medical history revealed recurrent acute pancreatitis during the past 7 years. At 71 years of age, she experienced the first attack of acute pancreatitis. Further examination excluded the possibilities of biliary, alcoholic or hyperlipidemic causes. ERCP was then performed and demonstrated a stricture of the head segment of MPD. A positron emission tomography/computed tomography (PET-CT) was performed for further evaluation and no pancreatic mass was detected. For reliving the stricture of MPD, a pancreatic stent was inserted by ERCP and the patient achieved symptomatic relief at discharge. However, regular stent exchange was refused by the patient for fear of endoscopic procedure. Thereafter, she had several episodes of acute pancreatitis and occasional epigastric pain which were all managed conservatively. She could not remember which type of pancreatic stent was used after 7 years.

In view of her medical history and imaging findings, a possibility of pancreatic duct obstruction due to a proximally migrated pancreatic stent was considered and we attempted to drain the MPD to relieve her symptoms. Endoscopic transpapillary treatment was failed because of pyloric deformation preventing access to the second portion of the duodenum. After a brief discussion with the patient's family and obtaining their consent, we decided to perform endoscopic ultrasound-guided pancreaticogastrostomy (EPG) while keeping the former stent *in situ*. The dilated MPD was punctured transgastrically with a 19-gauge needle (Echotip 19A; Cook Medical Inc., United States) (Figure 2A), and a sample was aspirated for further testing. Under fluoroscopy, pancreatogram displayed the dilated pancreatic duct proximal to complete obstruction (Figure 2B). After introduction of a 0.035-inch guidewire (Jagwire, Boston Scientific) into the MPD, the EUS needle was removed (Figure 2C), and a 6 Fr cystotome (Cook Endoscopy) was used to dilate the tract. Finally, the pancreaticogastrostomy was then stented with a 6-Fr double pigtail stent (Figure 2D). The amylase concentration of the effusion was 72450 U/L, while CEA and CA-199 were within the normal range. The patient revealed great resolution of abdominal pain, which was confirmed by CT scanning performed after 1 wk (Figure 3). There were no adverse events, and the patient remains asymptomatic at present (five months after the EPG procedure). We planned to make the follow-up investigations (endoscopic ultrasonography) for the possible stent occlusion and pancreatic duct obstruction after 6 mo and then once a year. Stent exchange under EUS is planned if recurrent acute pancreatitis occur.

DISCUSSION

Stent migration is an infrequent complication of endoscopic pancreatic stenting. Distal stent migration has been reported in 7.5% of pancreatic stent placement[3]. This rarely presents a problem since the stent can clear from the intestine spontaneously. However, proximal stent migration can result in serious complications, including ductal damage, recurrent pancreatitis, impaction and subsequent difficulty to retrieve the migrated stent[3]. In

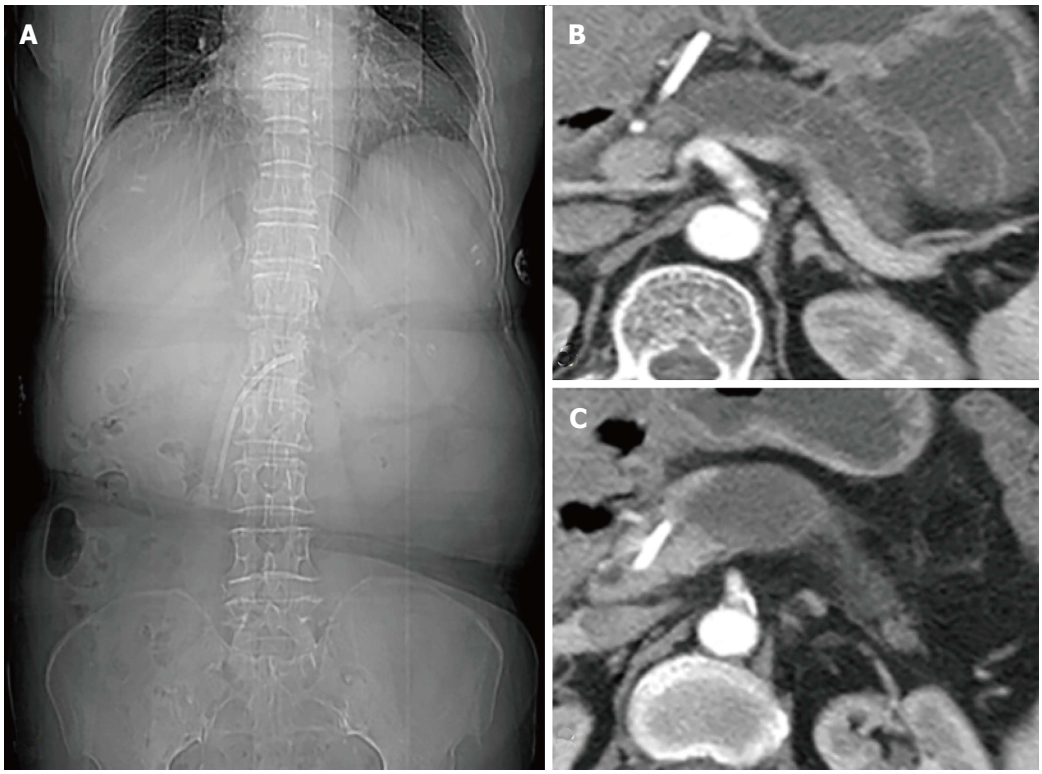


Figure 1 Abdominal computed tomography. A: Computed tomography image showing a pancreatic stent; B and C: An endoprosthesis extending from the main pancreatic duct (MPD) and parenchyma into the lesser omental bursa with a dilated distal MPD.

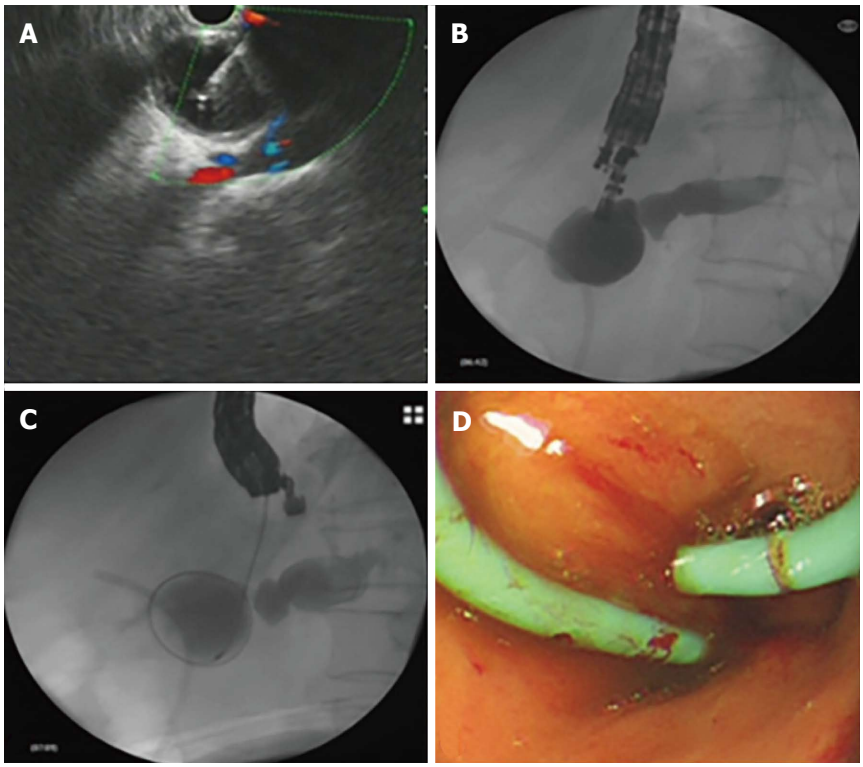


Figure 2 Endoscopic ultrasound-guided pancreaticogastrostomy. A: Endoscopic ultrasound-guided puncture; B and C: Contrast injection and cystotome advancement; D: Double pigtail stent placement.

the case presented, the proximal stent tip migrated into the lesser omental bursa, which resulted in duct distortion and obstruction, and eventually symptomatic pancreatic duct hypertension. This patient had never undergone stent

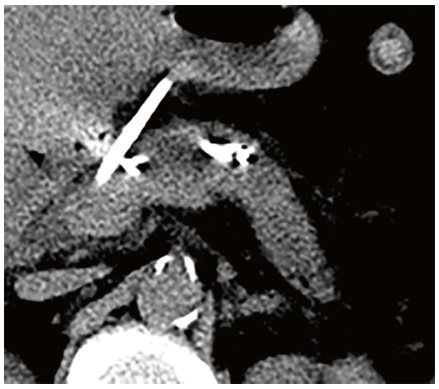


Figure 3 Successful decompression of the dilated main pancreatic duct.

revision or retrieval since its placement 7 years earlier. Her history of long term recurrent acute pancreatitis might indicate stent migration and subsequent pancreatic duct obstruction, however, which was unfortunately ignored during her previous hospitalization.

Currently, ERCP is the preferred procedure for treating pancreatic duct obstruction. However, it may not be feasible in approximately 3% to 10% of patients because of surgically altered anatomy, complete ductal obstructions, or disrupted ducts. In these cases, percutaneous radiologic intervention or surgical treatment is required[6]. However, both methods have been associated with significant morbidity and mortality rates. The development of EUS allowed the ability to visualize the pancreatic ductal system, and introduction of the therapeutic linear echoendoscope allowed access to the pancreatic duct with a needle in the case of ERCP failure. EUS-PD was first described by Bataille *et al*[7] in 2002. Following this report, several case series with satisfactory results have been published[8-10]. Technically, EUS-PD can either be performed *via* a rendezvous technique, combining EUS and ERCP, or *via* a transluminal technique. The former should be attempted in patients with accessible ampulla. Actually, in the present case, the echoendoscope cannot access the second part of duodenum because of pyloric deformation, and EUS-PD with transmural stenting seems to be the primary intervention.

To date, EUS-PD remains one of the most technically challenging endosonography interventions[11]. Success rates vary widely and adverse events occur in approximately 15% of reported cases[12]. Mainly, EUS-PD might be associated with complications such as pancreatitis, hemorrhage, stent migration, stent dysfunction, perforation, pneumoperitoneum, pancreatic juice leakage as well as abscess formation. Although there was no procedure related mortality, severe adverse events were noted when pancreatic drainage failed, and EUS-PD should be performed in endoscopic units experienced in therapeutic endoscopy[13].

Endoscopic retrieval is the primary treatment modality for proximally migrated pancreatic stents[4]. Matsumoto *et al*[4] reported that the successful endoscopic retrieval rate for proximally migrated pancreatic stents was approximately 80%. In the presented case, endoscopic transpapillary removal of the migrated stent was impossible because of pyloric deformation, and surgical intervention is too invasive for patients with benign cause. Once the pancreatic duct decompression was achieved, it does not seem necessary to remove the migrated pancreatic stent, which entails little damage to her health.

In conclusion, proximal migration of a pancreatic stent into the lesser omental bursa resulting in distortion and obstruction of the MPD, and symptomatic pancreatic duct dilation is a rare and catastrophic complication of pancreatic stenting. EUS-PD appears to be an effective and safe treatment for MPD decompression when conventional ERCP fails. This report adds to the increasing evidence of symptomatic pancreatic duct obstruction being successfully treated by EUS-PD.

COMMENTS

Case characteristics

A 78-year-old woman with endoscopic pancreatic duct stenting 7 years earlier presented with epigastric discomfort of three months' history.

Clinical diagnosis

The patient had a history of recurrent acute pancreatitis within 7 years. After admission to the hospital, CT scan showed a bright linear object extending from the main pancreatic duct (MPD) and parenchyma into the lesser omental bursa along with a dilated distal MPD.

Laboratory diagnosis

All laboratory data were within normal limits.

Imaging diagnosis

Computed tomography scan revealed a bright linear object extending from the MPD and parenchyma into the lesser omental bursa along with a dilated distal MPD.

Treatment

Endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) was performed after failed endoscopic retrieval.

Related reports

There is no related report about EUS-PD for pancreatic duct obstruction caused by proximally migrated pancreatic stent.

Experiences and lessons

Proximal stent migration is an infrequent complication of endoscopic pancreatic stenting and can sometimes result in serious complications including pancreatic duct obstruction, pancreatic pain and acute pancreatitis. Endoscopic retrieval is the primary treatment modality for proximal migrated pancreatic stents. EUS-PD is feasible and safe for pancreatic duct drainage, as well as symptomatic relief if endoscopic retrieval has failed.

Peer-review

The authors propose the migration of a proximal pancreatic duct stent, which cannot be removed by ERCP, as a new indication for EUS-PD. This interesting case report adds to the increasing evidence of the use of EUS-PD as an effective and safe treatment for pancreatic duct decompression.

REFERENCES

1 **Binmoeller KF**, Jue P, Seifert H, Nam WC, Izbicki J, Soehendra N. Endoscopic pancreatic stent drainage in chronic pancreatitis and a

dominant stricture: long-term results. *Endoscopy* 1995; **27**: 638-644 [PMID: 8903975 DOI: 10.1055/s-2007-1005780]
2 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864 [PMID: 15173799 DOI: 10.1016/S0016-5107(04)00353-0]
3 **Johanson JF**, Schmalz MJ, Geenen JE. Incidence and risk factors for biliary and pancreatic stent migration. *Gastrointest Endosc* 1992; **38**: 341-346 [PMID: 1607087 DOI: 10.1016/S0016-5107(92)70429-5]
4 **Matsumoto K**, Katanuma A, Maguchi H. Endoscopic removal technique of migrated pancreatic plastic stents. *J Hepatobiliary Pancreat Sci* 2014; **21**: E34-E40 [PMID: 24535753 DOI: 10.1002/jhbp.94]
5 **Kahaleh M**, Artifon EL, Perez-Miranda M, Gaidhane M, Rondon C, Itoi T, Giovannini M. Endoscopic ultrasonography guided drainage: summary of consortium meeting, May 21, 2012, San Diego, California. *World J Gastroenterol* 2015; **21**: 726-741 [PMID: 25624708 DOI: 10.3748/wjg.v21.i3.726]
6 **Fujii LL**, Topazian MD, Abu Dayyeh BK, Baron TH, Chari ST, Farnell MB, Gleeson FC, Gostout CJ, Kendrick ML, Pearson RK, Petersen BT, Truty MJ, Vege SS, Levy MJ. EUS-guided pancreatic duct intervention: outcomes of a single tertiary-care referral center experience. *Gastrointest Endosc* 2013; **78**: 854-864.e1 [PMID: 23891418 DOI: 10.1016/j.gie.2013.05.016]
7 **Bataille L**, Deprez P. A new application for therapeutic EUS: main pancreatic duct drainage with a "pancreatic rendezvous technique". *Gastrointest Endosc* 2002; **55**: 740-743 [PMID: 11979263 DOI: 10.1067/mge.2002.123621]
8 **Tessier G**, Bories E, Arvanitakis M, Hittelet A, Pesenti C, Le Moine O, Giovannini M, Devière J. EUS-guided pancreatogastrostomy and pancreatobulbostomy for the treatment of pain in patients with pancreatic ductal dilatation inaccessible for transpapillary endoscopic therapy. *Gastrointest Endosc* 2007; **65**: 233-241 [PMID: 17258981 DOI: 10.1016/j.gie.2006.06.029]
9 **Ergun M**, Aouattah T, Gillain C, Gigot JF, Hubert C, Deprez PH. Endoscopic ultrasound-guided transluminal drainage of pancreatic duct obstruction: long-term outcome. *Endoscopy* 2011; **43**: 518-525 [PMID: 21437853 DOI: 10.1055/s-0030-1256333]
10 **Oh D**, Park do H, Cho MK, Nam K, Song TJ, Lee SS, Seo DW, Lee SK, Kim MH. Feasibility and safety of a fully covered self-expandable metal stent with antimigration properties for EUS-guided pancreatic duct drainage: early and midterm outcomes (with video). *Gastrointest Endosc* 2016; **83**: 366-373
11 **Dhir V**, Isayama H, Itoi T, Almadi M, Siripun A, Teoh AYB, Ho KY. Endoscopic ultrasonography-guided biliary and pancreatic duct interventions. *Dig Endosc* 2017; **29**: 472-485 [PMID: 28118509 DOI: 10.1111/den.12818]
12 **Giovannini M**. EUS-guided pancreatic duct drainage: ready for prime time? *Gastrointest Endosc* 2013; **78**: 865-867 [PMID: 24237945 DOI: 10.1016/j.gie.2013.10.019]
13 **Itoi T**, Yasuda I, Kurihara T, Itokawa F, Kasuya K. Technique of endoscopic ultrasonography-guided pancreatic duct intervention (with videos). *J Hepatobiliary Pancreat Sci* 2014; **21**: E4-E9 [PMID: 24123911 DOI: 10.1002/jhbp.43]

P- Reviewer: Hijioka S, Nakai Y, Reeh M **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com