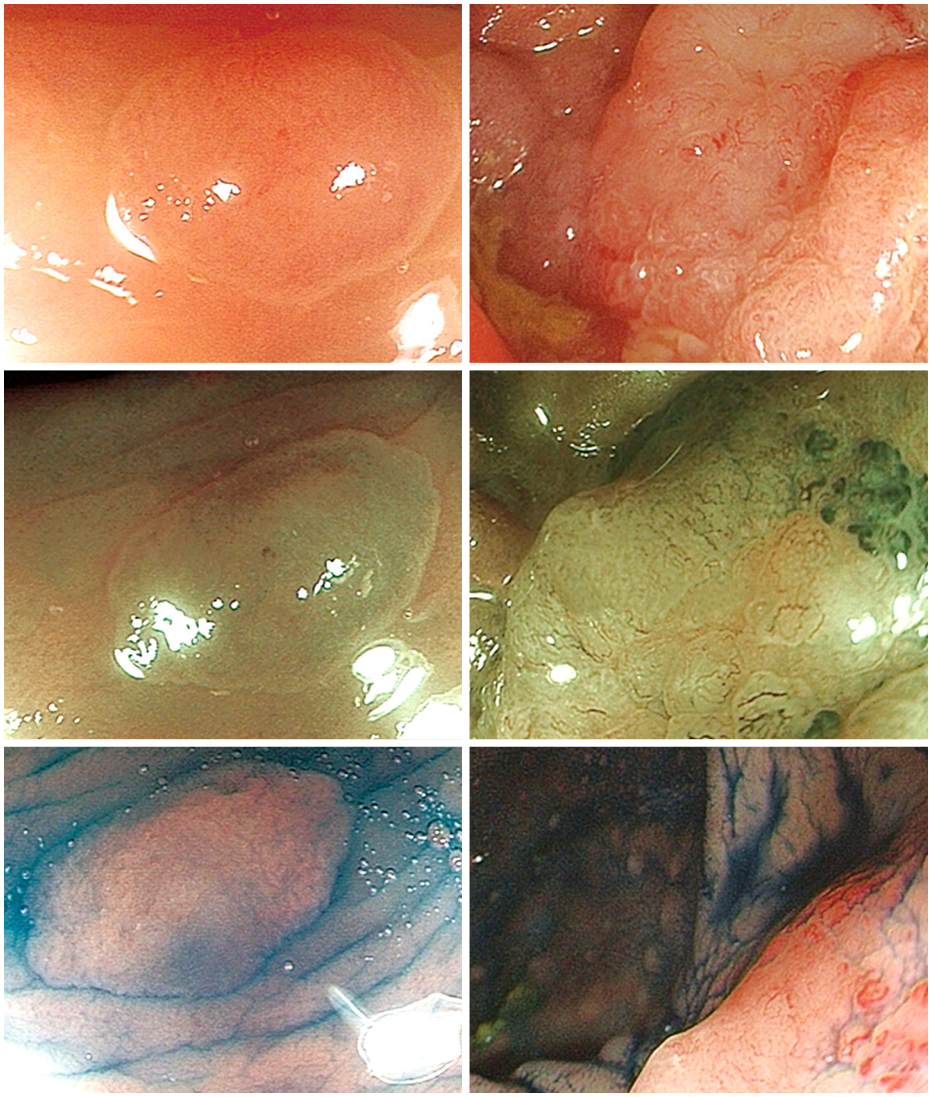
ISSN 1948-5190 (online)

World Journal of Gastrointestinal Endoscopy

World J Gastrointest Endosc 2009 October 15; 1(1): 1-75

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



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WJGE World Journal of Gastrointestinal Endoscopy

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

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WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 1 Number 1 October 15, 2009

World Journal of Gastrointestinal Endoscopy
Volume 1 Number 1 October 15, 2009

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

LAUNCH DATE
October 15, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
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Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
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Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price: 216.00 USD

PUBLICATION DATE
October 15, 2009

CSSN
ISSN 1948-5190 (online)

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World Journal of Gastrointestinal Endoscopy
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World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.1

World J Gastrointest Endosc 2009 October 15; 1(1): 1-2
ISSN 1948-5190 (online)

EDITORIAL

What is the purpose of launching *World Journal of Gastrointestinal Endoscopy*?

Lian-Sheng Ma

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Received: August 15, 2009 Revised: August 28, 2009
Accepted: September 4, 2009
Published online: October 15, 2009

Abstract

The first issue of *World Journal of Gastrointestinal Endoscopy* (*WJGE*), whose preparatory work was initiated on October 13, 2008, will be published on October 15, 2009. The *WJGE* Editorial Board has now been established and consists of 97 distinguished experts from 24 countries. Our purpose of launching *WJGE* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

Key words: Maximization of personal benefits; Editorial board members; Authors; Readers; Employees; *World Journal of Gastrointestinal Endoscopy*

Ma LS. What is the purpose of launching *World Journal of Gastrointestinal Endoscopy*? *World J Gastrointest Endosc* 2009; 1(1): 1-2 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/1.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.1

INTRODUCTION

I am very pleased to announce that the first issue of *World Journal of Gastrointestinal Endoscopy* (*World J Gastrointest Endosc*, *WJGE*, ISSN 1948-5190, DOI: 10.4253) will be published on October 15, 2009. Originally, the journal was titled *Gastrointestinal Endoscopy Review Letters* when preparatory work was initiated on September 23, 2008. The *WJGE* Editorial Board has now been established and consists of 97 distinguished experts from 24 countries.

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. To realize these desired attributes of a journal and create a well-recognized journal, the following four types of personal benefits should be maximized.

MAXIMIZATION OF PERSONAL BENEFITS

The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others.

Maximization of the benefits of editorial board members

The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they

have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution.

Maximization of the benefits of authors

Since *WJGE* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGE* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading.

Maximization of the benefits of readers

Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion[1].

Maximization of the benefits of employees

It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal[2,3]. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJGE* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

SCOPE

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

COLUMNS

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

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World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.3

World J Gastrointest Endosc 2009 October 15; 1(1): 3-6
ISSN 1948-5190 (online)

EDITORIAL

Occult and obscure gastrointestinal bleeding: Causes and diagnostic approach in 2009

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Received: December 8, 2008 Revised: February 10, 2009
Accepted: February 17, 2009
Published online: October 15, 2009

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Bresci G. Occult and obscure gastrointestinal bleeding: Causes and diagnostic approach in 2009. *World J Gastrointest Endosc* 2009; 1(1): 3-6 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/3.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.3

Abstract

Gastrointestinal bleeding can be obscure or occult (OGIB), the causes and diagnostic approach will be discussed in this editorial. The evaluation of OGIB consists on a judicious search of the cause of bleeding, which should be guided by the clinical history and physical findings. The standard approach to patients with OGIB is to directly evaluate the gastrointestinal tract by endoscopy, abdominal computed tomography, angiography, radionuclide scanning, capsule endoscopy. The source of OGIB can be identified in 85%-90%, no bleeding sites will be found in about 5%-10% of cases. Even if the bleedings originating from the small bowel are not frequent in clinical practice (7.6% of all digestive haemorrhages, in our casuistry), they are notoriously difficult to diagnose. In spite of progress, however, a number of OGIB still remain problematic to deal with at present in the clinical context due to both the difficulty in exactly identifying the site and nature of the underlying source and the difficulty in applying affective and durable diagnostic approaches so no single technique has emerged as the most efficient way to evaluate OGIB.

Key words: Occult gastrointestinal bleeding; Obscure gastrointestinal bleeding; Bleeding; Gastrointestinal endoscopy

INTRODUCTION

Gastrointestinal bleeding (GIB) is a bleeding that starts in the gastrointestinal tract, which extends from the mouth to the large bowel. The amount of bleeding can range from nearly undetectable to acute, massive, and life threatening. The nearly undetectable gastrointestinal bleeding is a commonly encountered primary care clinical challenge but often the cause is occult or obscure[1,2]. Occult GIB is defined as bleeding that is not visible to the subject while obscure GIB is defined as persistent or recurrent bleeding for which no definitive source has been identified by an initial evaluation. Obscure GIB may be occult, if not visible or overt if it manifests with a continued passage of visible blood[3-5]. The causes and diagnostic approach of the occult and obscure gastrointestinal bleeding (OGIB) will be discussed in this editorial.

ETHIOLOGY

The evaluation of OGIB consists on a judicious search of the cause of bleeding, which should be guided by the clinical history and physical findings.

There are several elements on the medical history and physical examination that can provide clues about the cause of OGIB and help define the aggressiveness with which a bleeding site should be sought. A history can reveal ingestion of medications known to cause

bleeding (e.g. aspirin, nonsteroidal anti-inflammatory drugs, anticoagulants). A family history might suggest a hereditary vascular problem. Other rare causes of bleeding may be detected on physical examination, including Plummer-Vinson syndrome, acquired immunodeficiency syndrome and other diseases with typical cutaneous manifestations[6,7]. A family history of cancer occurring at an early age, particularly colorectal or endometrial, may suggest the presence of hereditary nonpolyposis colorectal cancer. Their relative frequency has not been well defined in large trials but probably depends upon age[8]. Subjects younger than 40 may be more likely to have inflammatory bowel disease, a Meckel's diverticulum, Dieulafoy's lesion, or a small bowel tumor while older patients may be more likely to have bleeding from vascular lesions, erosions, or ulcers related to nonsteroidal anti-inflammatory drugs. OGIB may have an upper (oesophagus, stomach), middle (small intestine) or lower tract (colon, rectum) source and may be of different nature. Causes of obscure or occult gastrointestinal bleeding: (1) Upper tract source: Esophagus/stomach: Reflux esophagitis, Erosive gastritis/ulceration, Varices, Cameron's erosions within a hiatal hernia, Dieulafoy's lesion, Gastric antral vascular ectasia; Portal gastropathy Small intestine: Duodenitis, Celiac sprue, Meckel's diverticulum, Crohn's disease; (2) Lower tract source: Colon: Diverticula, Ischemic colitis, Ulcerative colitis, other colitis, infection (e.g. hookworm, whipworm, Strongyloides, ascariasis, tuberculous enterocolitis, amebiasis, cytomegalovirus); (3) Rectum: Fissure, Hemorrhoids; (4) Any gastrointestinal source: Vascular ectasia/angiodysplasia, Carcinoma, Vasculitis, Aortoenteric fistula, Kaposi's sarcoma, lymphoma, leiomyoma, leiomyosarcoma, carcinoid tumors, Osler-Weber-Rendu syndrome, Amyloidosis, anti-inflammatory drugs, Radiation-induced mucosal injury; and (5) No source found. Recurrent hematemesis indicates bleeding above the ligament of Treitz while recurrent passage of bright red blood per rectum or melena suggests a lower GI cause. however OGIB is usually asymptomatic and occurs only with a positive fecal occult blood test (FOBT) and/or iron deficiency anemia, without visible fecal blood. Iron deficiency anemia, the result of chronic blood loss, is the most common form of anemia encountered in the world.

DIAGNOSIS

Iron deficiency anemia is most common in children and women of child-bearing age and/or who have become pregnant. From the perspective of the gastrointestinal tract, current dogma is that in men and postmenopausal women with iron deficiency anemia, gastrointestinal tract pathology is the likely source of blood loss, and that is where evaluation is generally focused. The diagnosis of iron deficiency anemia should be considered any time that a low serum hemoglobin level or hematocrit is encountered. A reduced mean corpuscular volume supports the diagnosis, but is not definitive. Iron deficiency anemia is best confirmed by documenting a low serum ferritin level. Celiac disease is an important cause of iron deficiency anemia and merits special consideration. It can lead not only to malabsorption of iron, but may also cause occult bleeding and should be ruled out in most patients with iron deficiency anemia. A high index of suspicion is often required to make the diagnosis; therefore, small bowel biopsies should be routinely obtained in patients without another obvious cause of iron deficiency anemia. Gastritis, either of the atrophic variety, or caused by *Helicobacter pylori* may be an important cause of iron deficiency anemia, presumably due to iron malabsorption. Many patients with iron deficiency anemia have no identifiable gastrointestinal tract abnormality after appropriate gastrointestinal evaluation (Figure 1). In this circumstance, explanations for iron deficiency anemia include non-gastrointestinal blood loss, misdiagnosis of the type of anemia, missed lesions, or nutritional deficiency. It is normal to lose 0.5-1.5 mL of blood daily in the gastrointestinal tract, and melena usually is identified when more than 150 mL of blood are lost in the upper gastrointestinal tract. The potential frequency of occult gastrointestinal bleeding is emphasized by the observation that approximately 150-200 mL of blood must be placed in the stomach to consistently produce visible evidence of blood in the stool. Subjects with gastroduodenal bleeding of up to 100 mL per day may have normal appearing stools. Thus, occult bleeding is often only identified by special tests that detect fecal blood, or, if bleeding occurs for a long enough period of time, it may become manifest by iron depletion and anemia[9]. FOBTs have sufficient sensitivity to detect bleeding that is not visible in the stool. There are three classes of FOBTs: guaiac-based tests, heme-porphyrin tests, and immunochemical tests. The standard approach to patients with OGIB is to directly evaluate the gastrointestinal tract. The best approach is to examine the gastrointestinal tract with endoscopy[10,11]. The major advantages of endoscopy versus other diagnostic approaches are that endoscopy is relatively safe and that biopsy and endoscopic therapy can be performed. Esopha gogastroduodenoscopy is the best test in the evaluation of upper gastrointestinal tract while colonoscopy is the best in the examinations of colon. Abdominal computed tomography (CT) can identify lesions that endoscopy has failed to detect, in particular neoplastic mass lesions. However, CT is insensitive for detection of mucosal lesions[12]. Angiography (a technique that uses dye to

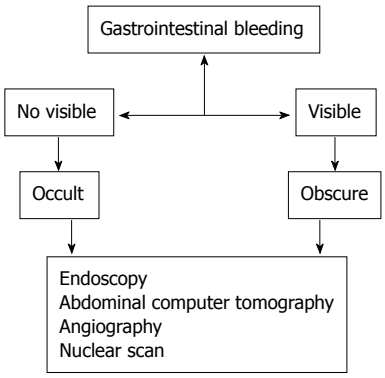

Figure 1 Schema of evaluation occult and obscure gastrointestinal bleeding.

highlight blood vessels) can be useful in situations when the patient is acutely bleeding such that dye leaks out of the blood vessel and identifies the site of bleeding. In selected situations, angiography allows injection of medicine into arteries that may stop the bleeding. Angiography may be useful in patients with active bleeding greater than 0.5 mL per minute and can identify highly vascular non-bleeding lesions such as angiodysplasia and neoplasms. Radionuclide scanning (a non-invasive screening technique) can be used for locating sites but of acute bleeding, especially in the lower GI tract. This technique involves injection of small amounts of radioactive material. Then, a special camera produces pictures of organs, allowing the doctor to detect a bleeding site. Radioisotope bleeding scans may be helpful in identifying the site of bleeding if the volume is greater than 0.1-0.4 mL per minute. However, positive findings in this type of testing must be verified with an alternative test because of a relatively high number of false-positive results. Sometimes, routine radiographic tests can be used (barium enema, upper gastrointestinal series), though these have fallen out of favour[13]. Radiographic studies are effective for detecting masses and large ulcerating lesions, but are not very accurate at detecting mucosal lesions. The small intestine is important to consider as a potential site of bleeding in patients with negative examinations of the colon and upper gastrointestinal tract. A number of approaches can be used to examine the small intestine. Endoscopic evaluation of the small intestine (known as push enteroscopy) has a greater sensitivity for mucosal abnormalities and possibly for mass lesions as well, and therefore has achieved a central position in evaluation of patients who do not present findings in the colon or upper gastrointestinal tract. Push enteroscopy consists of insertion of a long endoscope, usually a specialized enteroscope, and should be the initial approach in most patients[14,15]. Using conscious sedation, the enteroscope can be passed 50-60 cm beyond the ligament of Trietz, allowing examination of the distal duodenum and proximal jejunum. Push enteroscopy has been reported to identify a source of bleeding in approximately 25% of patients. More recently, "balloon" enteroscopy has been developed. This form of enteroscopy allows deeper insertion of the endoscope into the small bowel, and thus a larger portion of the bowel can be examined. However, the pathologies of the small bowel are notoriously difficult to diagnose so these techniques are often unsatisfactory for the identification of small bowel lesions. A new painless technique for endoscopic imagining of the small bowel has been recently suggested: the capsule endoscopy[16-18]. It consists of a swallowable capsule which acquires video images while moving through the gastrointestinal tract propelled by natural peristalsis until it is excreted. The capsule obtains at least 2 images per second, transmitting this data to a recording device worn by the patient. The data are subsequently downloaded to a computer workstation loaded with software that allows images to be analyzed. The video capsule endoscopy is not helpful for the study of some digestive tracts and, in fact it passes too quickly through the esophagus, and the stomach, with its large lumen, and these sites cannot be completely imaged. Moreover sometimes the capsule fails to reach the colon during the acquisition time. Recently, a capsule colonoscopy, in which patients swallow a small video capsule that then examines the colon, was presented[19]. The video capsule is able to evaluate almost all of the small bowel and this is an interesting finding[20-23]. In some trials this wireless endoscope system was found to be much better than radiographs and push endoscopy for evaluation of small bowel disease[24,25]. The propulsion of the capsule depends only on peristalsis, which is variable and sometimes too fast, so an eventual pathology can be seen on a single or few frames only. New methods should be devised to move the capsule, to increase its control, to determine its real location and to do direct biopsy or cauterisation. In our experience[26,27] the video capsule endoscopy, used in patients with intestinal bleeding of obscure etiology but of suspected jejuno-ileal origin, was well tolerated, able to acquire good images and identified lesions particularly if performed early after the bleeding. This new approach to the study of the small bowel is an important innovation for patients with disease of this tract of gut, particularly for those subjects with high surgical risk, however video capsule endoscopy technique should be improved in order to reduce the above said flaws. Intraoperative endoscopy can be used to examine the small bowel when other techniques fail to detect a bleeding source, but surgery itself has attendant increased risk and does not always add to the diagnosis. Surgical manipulation can create artifacts that may be mistaken for bleeding lesions. Intraoperative methods have determined a source of occult bleeding in up to 40% of undiagnosed cases, but they examine only 50%-80% of the small bowel[28-30].

CONCLUSION

The source of OGIB can be identified in 85%-90%, no bleeding sites will be found in about 5%-10% of cases[1,2]. Even if the bleedings originating from the small bowel are not frequent in clinical practice (7.6% of all digestive haemorrhages, in our casuistry), they are notoriously difficult to diagnose. In spite of progress, however, a number of OGIB still remain problematic to deal with at present in the clinical context for both the difficulty in exactly identifying the site and nature of the underlying source and the difficulty in applying affective and durable diagnostic approach so no single technique has emerged as the most efficient way to evaluate OGIB. Most patients will benefit from careful evaluation that includes the evaluation of all gastrointestinal tracts. For some patients, this may mean multiple procedures. Additional studies are needed to clearly identify the most efficient approach to evaluation and definitive diagnosis of OGIB.

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S- Editor Li JL **L- Editor** Alpini GD **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.7

World J Gastrointest Endosc 2009 October 15; 1(1): 7-11
ISSN 1948-5190 (online)

GUIDELINES FOR CLINICAL PRACTICE

Endoscopic clipping in the lower gastrointestinal tract

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Received: March 6, 2009 Revised: August 26, 2009
Accepted: September 2, 2009
Published online: October 15, 2009

Abstract

Endoscopic clipping has been established as a safe and effective method for the treatment of nonvariceal upper gastrointestinal bleeding in numerous randomized studies. Recently, clipping has been applied to various lesions in the lower gastrointestinal tract, including diverticular bleeding, postpolypectomy bleeding, and repair of perforations with successful outcomes. We review the safety and efficacy of this maneuver for the management of diseases in the lower gastrointestinal tract.

Key words: Hemoclip; Clipping; Clips; Hemostasis; Gastrointestinal bleeding; Endoscopy; Diverticular disease; Postpolypectomy bleeding; Acute hemorrhagic rectal ulcer; Colon

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Hokama A, Kishimoto K, Kinjo F, Fujita J. Endoscopic clipping in the lower gastrointestinal tract. *World J Gastrointest Endosc* 2009; 1(1): 7-11 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/7.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.7

INTRODUCTION

Endoscopic clipping devices were developed by Hachisu in cooperation with Olympus Co. Ltd. (Japan) in 1980s[1]. For more than two decades, endoclips have become available worldwide with continuous technical improvements. Numerous trials and a meta-analysis have shown that clipping is an effective hemostatic method for bleeding peptic ulcers, with high rates of primary hemostasis (85%-100%), low rebleeding rates (2%-20%) and an excellent safety record[2-6]. Currently, clipping is an established mandatory technique of endoscopic hemostasis for nonvariceal upper gastrointestinal bleeding, including Mallory-Weiss syndrome[7], duodenal diverticular bleeding, Dieulafoy lesions of the stomach[8] and duodenum[9,10], as well as bleeding peptic ulcers. More recently, clipping has been widely applied to the hemostasis of lower gastrointestinal bleeding and non-hemostatic treatments including closing mucosal defects, leaks and perforations, and marking lesions prior to radiotherapy or surgery. In this review, we discuss the safety and efficacy of endoscopic clipping for the management of colonic diseases.

TECHNOLOGY OF CLIPPING DEVICES

Currently available clipping devices consist of a handle-delivery catheter system that enables development of double-pronged stainless steel clips to mechanically compress the targeted vessels and/or close a mucosal defect by tissue approximation[6]. Clipping avoids chemically or thermally induced ulceration, and thus causes minimal mucosal injury. The spectrum of devices has been expanded by the introduction of ready-to-use (disposable) clip systems and a variety of new clips distributed by several manufacturers. However, an experimental setting

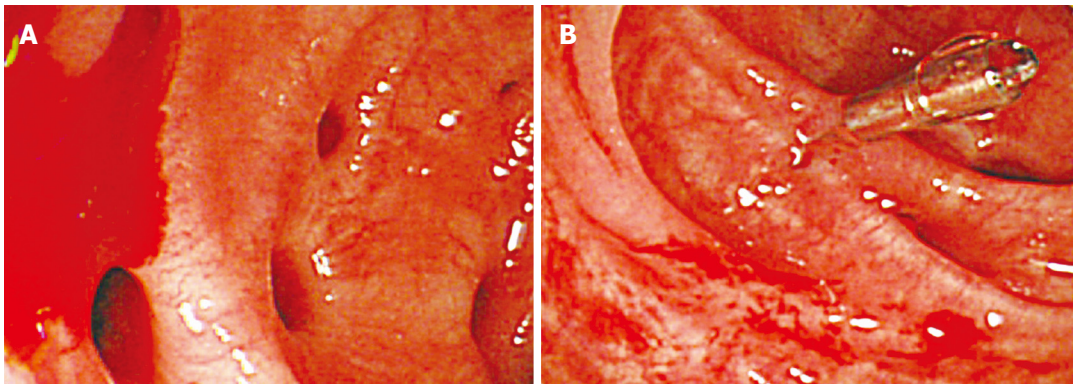

Figure 1 Endoscopic clipping for the treatment of colonic diverticular bleeding. A: An actively bleeding colonic diverticulum of the ascending colon in a 78-year-old man with chronic obstructive pulmonary disease; B: Hemostasis was achieved with a clip.

disclosed that operator familiarity with clipping rather than the particular clip was of relevance for successful hemostasis[11]. Applied clips slough spontaneously at approximately 2-3 wk and pass uneventfully. Clipping-induced complications are extremely rare.

CLIPPING FOR LOWER GASTROINTESTINAL TRACT DISEASES

Clipping has now been applied to various indications in the lower gastrointestinal tract, which include hemostasis for colonic diverticular bleeding, postpolypectomy bleeding, Dieulafoy lesions, acute hemorrhagic rectal ulcer, closure of colonic perforations and leaks, and identifying anatomic landmarks.

DIVERTICULAR BLEEDING

Diverticular bleeding is one of the most common causes of lower gastrointestinal bleeding. Urgent colonoscopy offers not only a diagnostic method but also a therapeutic maneuver for its management[12]. Colonoscopic hemostatic methods including adrenaline injection, thermal and electrical coagulation or combinations of these have been applied, until first reports of the efficacy of endoscopic clipping for colonic diverticular bleeding[13]. In recent times, the impact of clipping for this disorder has been increasing worldwide[14-20]. Although these reports were small case series and there are no data comparing the efficacy and safety of the various endoscopic hemostatic methods available, evidence of the safety and efficacy of clipping for colonic diverticular bleeding has been provided. Mechanical hemostasis by hemoclip application confers a theoretically decreased risk of perforation compared with thermal application in the thin-walled diverticula[21]. The clips have been placed across the margin of the diverticulum (Figure 1) or in a sequential zipper fashion, as well as directly to the vessel. In addition, retained clips may serve as a potential fluoroscopic marker to guide angiographic therapy or surgical intervention, if necessary. It is sometimes difficult to identify the stigmata of bleeding diverticulum because diverticula often are numerous and bleeding may be intermittent. Poor visualization without oral preparation is another difficulty.

POSTPOLYPECTOMY BLEEDING

Postpolypectomy bleeding is the most frequent complication of colonoscopy, which occurs in approximately 1% of the procedures. Most cases can be managed conservatively, however, colonoscopic intervention is often required for continuous bleeding. Endoclips have been used successfully for immediate and delayed postpolypectomy bleeding[1,22]. Clipping is effective in controlling immediate postpolypectomy bleeding as well as resnaring. Despite these excellent results, there are no comparative studies of clipping versus thermal modalities. In immediate postpolypectomy bleeding, there are several possible approaches to apply clips effectively. For bleeding from a pedunculated polyp stalk or its base, the clipping is most effective when deployed across the stalk or the base to ligate the feeding vessels. For bleeding from a sessile polyp removed by endoscopic mucosal resection, the bleeding point should be clipped, followed by closure of the mucosal defect. Delayed postpolypectomy bleeding is usually caused by ulceration at the site of the polypectomy (Figure 2). Clipping is regarded as a more ideal hemostatic maneuver than cautery for this situation, because the postpolypectomy sites usually change to thermal ulcers and thus additional thermal or injection hemostatic methods may cause perforation in thin-walled colon. Although prospective randomized studies are warranted, early clipping certainly provides a safe and effective hemostasis for immediate and delayed postpolypectomy bleeding and reduces the need for transfusion and hospitalization[23].

The effectiveness of prophylactic clipping to prevent delayed postpolypectomy bleeding is controversial. A retrospective study of prophylactic clipping for large polyps (15-40 mm in diameter) indicated a potential for prevention[24]. In comparison, a prospective randomized controlled trial comparing the prophylactic clipping group after endoscopic mucosal resection (n = 205) and the non-clipping group (n = 208) disclosed that clipping did

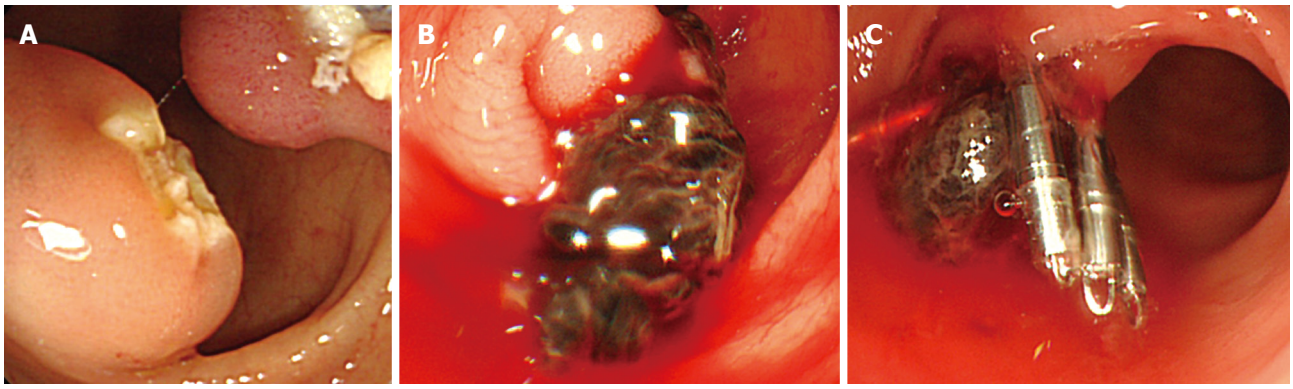

Figure 2 Endoscopic clipping for the treatment of postpolypectomy bleeding. A: A semipedunculated polyp was treated by an endoscopic mucosal resection technique in the sigmoid colon in a 64-year-old man with hypertension; B: Active bleeding occurred at the postpolypectomy ulcer on the next day; C: Hemostasis was achieved with clips.

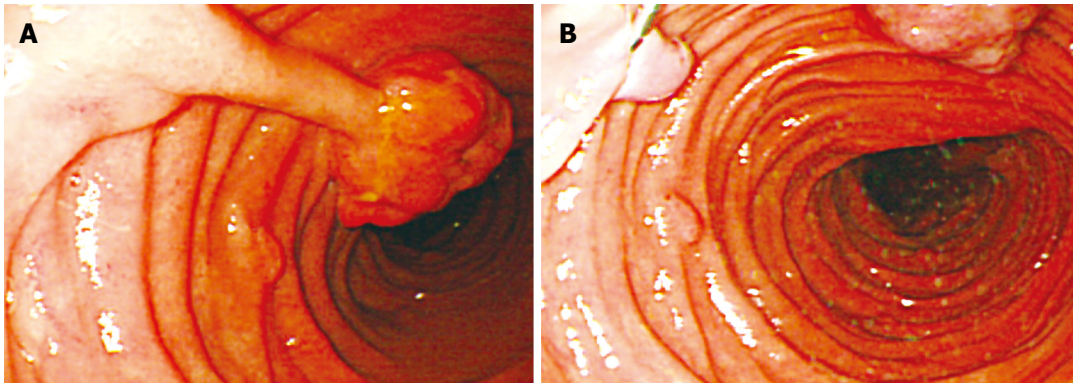

Figure 3 Endoscopic clipping for the prophylactic management to prevent delayed postpolypectomy bleeding. A: A pedunculated polyp of the ileum in a 28-year-old man with Peutz-Jeghers syndrome; B: After application of a clip at the base of the long stalk to prevent delayed bleeding, the polyp was resected by snare.

not decrease the occurrence of delayed bleeding (0.98% versus 0.96%, respectively)[25]. In their study, most polyps were small with a mean diameter of 7.8 mm. Although there is an argument regarding the study's sample size, it is possible that prophylactic clipping might be effective when only larger polyps are included[26]. More recently, a large retrospective cohort study of 6617 polypectomies in 3138 patients clearly showed the risk factors of delayed postpolypectomy bleeding[27]. Hemorrhage occurred in 38 lesions (0.57%) and 37 patients (1.2%). Polyps larger than 10 mm in diameter were at a 4.5 times higher bleeding risk than smaller ones, and hypertension was the strongest patient-related predictive factor with an adjusted odds ratio of 5.6. Twenty-two patients were actively bleeding at the second colonoscopy, all of which were successfully treated with clipping.

The present perspective on colonoscopy is more complicated in older patients. Because colonic polyps are an age-related disease, polypectomies are usually performed in the elderly, who are more likely to be taking anticoagulants as well as antihypertensive medication[28]. Another interesting retrospective study of 41 polypectomies in 21 patients showed that prophylactic clipping immediately after polypectomy prevented bleeding while continuing anticoagulation therapy (international normalized ration, average 2.3, range 1.4-4.9)[29]. Although the average polyp size was 5.0 mm (3-10 mm) and the study sample was small, it has been stressed that prophylactic clipping may be helpful for anticoagulated patients at high risk of thrombosis.

Polypectomy techniques among endoscopists is highly variable. An interesting survey disclosed that 80% of practicing endoscopists had never performed clipping on polypectomy stalks for prevention of bleeding and that academic physicians were more likely to place hemoclips on these stalks than private physicians[30]. Considering that postpolypectomy bleeding occurs in 0.57% of polypectomies[27], and if it is assumed that clipping would reduce this rate to 0%, this would yield 175 polyps needing to be prophylactically clipped to prevent one episode of bleeding[31]. It is reasonable that most physicians think it is neither practical nor cost-effective. Meanwhile, the advanced technique of endoscopic mucosal resection followed by immediate clipping for flat or depressed colonic neoplasms has been increasingly utilized[32]. Therefore, prospective randomized studies are needed to evaluate prophylactic clipping to prevent postpolypectomy bleeding in high-risk patients or with large polyps. Until such evidence is available, we believe that clipping certainly is one of the best strategies to prevent and treat postpolypectomy bleeding in high-risk patients[33] and with large polyps on the basis of our clinical experiences (Figure 3).

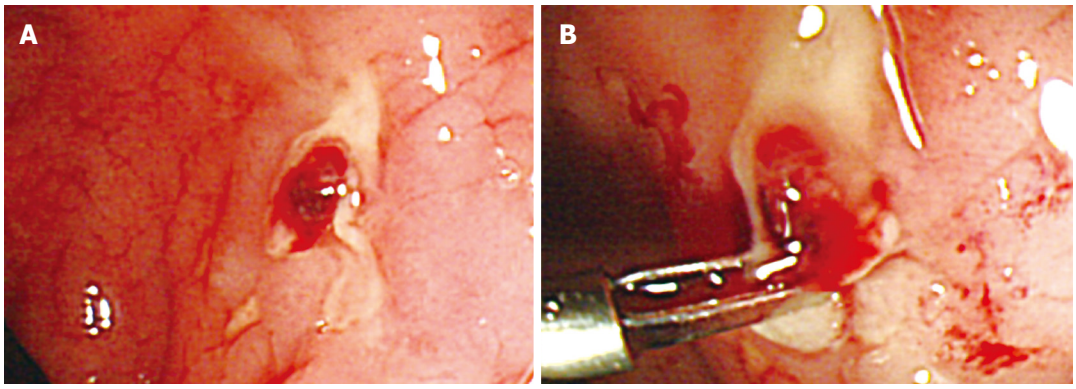

Figure 4 Endoscopic clipping for the treatment of acute hemorrhagic rectal ulcer. A: An exposed vessel of the rectal ulcer in a bed-ridden 70-year-old man with liver cirrhosis and severe burn; B: A clip was directly applied to the vessel.

OTHER DISEASES

Despite the lack of comparative trials, clipping seems to be effective for the treatment of colorectal Dieulafoy lesions[34], acute hemorrhagic rectal ulcer (Figure 4)[35-37], and exposed vessels in inflammatory bowel diseases. In addition to hemostasis, clipping has been applied to endoluminal repair of iatrogenic colonic perforations, which were caused by diagnostic or therapeutic colonoscopy, to avoid surgery with a high successful rate[38].

CONCLUSION

Endoscopic clipping has been shown to be a safe and effective method of hemostasis for lower gastrointestinal bleeding including diverticular bleeding, postpolypectomy bleeding and other hemorrhagic diseases. Further studies are needed to evaluate prophylactic clipping to prevent postpolypectomy bleeding in high-risk patients.

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S- Editor Zhang HN **L- Editor** Lutze M **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.12

World J Gastrointest Endosc 2009 October 15; 1(1): 12-16
ISSN 1948-5190 (online)

GUIDELINES FOR CLINICAL PRACTICE

Perspectives of colorectal cancer screening in Germany 2009

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Received: March 10, 2009 Revised: March 26, 2009
Accepted: April 2, 2009
Published online: October 15, 2009

Abstract

Adequate screening methods can decrease colorectal cancer (CRC) mortality. The guaiac test for fecal occult-blood (FOBT) is part of the German CRC Screening Program since 1970 and has evidence level Ia. In randomized multicenter-studies FOBT has an average sensitivity of 24% and decreases CRC mortality up to 30%. Immunological tests for human haemoglobin (iFOBT) show better performance characteristics than guaiac FOBT, with augmented sensitivity and specificity. However, the single tests show wide differences in diagnostic performance and iFOBT is not yet covered by insurance companies although it should replace the guaiac test for CRC screening. Visual colonoscopy, which was introduced to the German National Cancer Screening Program in 2002, is the gold standard for the diagnosis of colorectal neoplasia. From 2003 to 2007 more than 2.8 million examinations have been documented in Germany. The prevalence of adenomas is around 20% and of CRC about 0.7% to 1.0% of the screenings. Seventy percent of the carcinomas detected during screening are in an early stage (UICC Ⅰ and Ⅱ). Furthermore, screening colonoscopy is a cost saving procedure with a low complication rate (0.25% overall). Insurance companies save 216€ for each screening colonoscopy mainly by prevention of neoplasia due to polypectomy. In Germany, virtual colonography by computed tomography (CT) or magnetic resonance imaging still lacks standardization of the hard and software. In experienced centres the sensitivity for CRC and large polyps of CT colonography is comparable to colonoscopy but in meta-analyses the ranking is lower. New technologies like computer-aided colonoscopies with sheath or double balloon techniques are coming up as well as capsule colonoscopy, which sensitivity for large polyps is about 70%. Advised by his physician, the patient can choose his most acceptable examination method from this whole set of screening tools.

Key words: Screening, colorectal cancer; Prevention; Colonoscopy; Virtual colonoscopy; Fecal occult blood test; Capsule colonoscopy

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Sieg A, Friedrich K. Perspectives of colorectal cancer screening in Germany 2009. *World J Gastrointest Endosc* 2009; 1(1): 12-16 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/12.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.12

INTRODUCTION

With about 71 400 new occurrences, Germany is among the countries with the highest incidence (71/100 000 males and 50/110 0000 females) and mortality rates (30 000 annually) of colorectal carcinoma (CRC). Since the CRC emanates over a time span of 10-15 years from a benign precursor (Adenoma), screening offers an immense opportunity to prevent this malignancy. This review is not about primary prevention like pharmaceuticals or modification of the way of life, but solely about the methods of secondary prevention, excluding DNA testing.

FECAL OCCULT BLOOD TEST

The Guaiac-Test for fecal occult blood test (FOBT) was included to the German CRC Screening Program in the 1970's. If used regularly, FOBT has evidence level Ia for reducing CRC mortality of about 30%[1-4]. FOBT measures peroxidase activity of the haemoglobin. But this reaction is not specific since the peroxidase of herbal or carnal aliments reacts as well. A great disadvantage of FOBT is its low sensitivity for carcinomas or large polyps, which can only be compensated by annual repetition.

IMMUNOLOGICAL FECAL OCCULT BLOOD TEST

Due to the low sensitivity and specificity of the FOBT, immunological tests for human haemoglobin (iFOBT) were developed. Using a monoclonal antibody, iFOBT can specifically identify human haemoglobin without interfering with carnal proteins or herbal peroxidase. Another advantage of iFOBT is the quantitative interpretation of the results, and thus being able to define a cut-off range for standard values depending on the examined population. For CRC iFOBT has a sensitivity of 66%-95%[5-8], however iFOBT was only obtained on one day. On firsthand comparison, iFOBT showed an increased sensitivity and specificity than FOBT[6-20] and higher rates of detection for colorectal neoplasia[9,14,16,20].

Significant differences in the analytical performance among iFOBT methods were found[15,21]. Careful method validation and selection of a method with appropriate sensitivity and specificity is therefore essential in colorectal cancer screening. Attention has to be paid to the sampling of feces, as haemoglobin is progressively degraded over time and undetectable after 10 d. This can only be avoided if feces are immediately deep frozen or collected in iFOBT collection devices[22]. Another way to avoid rapid degradation of hemoglobin is to determine the more stable hemoglobin-haptoglobin complex in stool, which was shown to have a higher sensitivity towards adenomas[23]. Higher costs for immunological tests could be compensated by the increased sensitivity and therefore higher detection rate of colorectal neoplasia[24]. In Japan, iFOBT analyzed on 2 d is used for the National Cancer Screening Program. In a case-control study the odds-ratio (OR) of patients dying from colorectal cancer was 0.2 for those screened with the iFOBT[25]. Even a small percentage of little adenomas in men were detected by iFOBT[26]. Therefore, the immunological test should replace guaiac FOBT.

In two studies tumor pyruvate kinase isoenzyme M2 was shown to have no supplemental value for screening because of a lower sensitivity and specificity[27,28] compared to iFOBT.

SCREENING-COLONOSCOPY

Germany was the first country to introduce preventative colonoscopy to the National Cancer Screening Program in 2002. Until then, no direct evidence for a reduction of mortality existed for this method. Yet, sigmoidoscopy studies[29-31] and case-controlled studies showed indirect evidence for the correctness of this assumption[32,33]. The first analysis of screening colonoscopy in Germany showed a prevalence of 20% for adenomas, 6.1% for advanced adenomas, and 0.7% for CRC[34]. These results are consistent with further studies analyzing screening colonoscopy[8,35-40]; however, one has to account that the study population varies individually. For instance, it is known that the risk for colorectal neoplasia is elevated for men, and it rises with increasing age[34,41]. It is important to note that the majority of carcinomas (70% total) found during screening colonoscopy are detected at an early stage (UICC I and Ⅱ). Thus it is understandable that these carcinomas found during screening accompany a considerably better prognosis than carcinomas found during the clarification of symptoms, as a recent study has proven[42]. An important feature is the safety of a screening method as the examination is performed in healthy adults. Screening colonoscopy in Germany was shown to be a safe method. Perforations occurred in 0.02%-0.03% of the examinations, bleedings in 0.15%-0.17% and cardiovascular events in 0.06%-0.1%[34,43]. Similarly low rates of adverse effects were shown for outpatient colonoscopy in Germany some years ago[44]. A limitation of optical colonoscopy is the miss rate for large adenomas from 2.1% to 6%[45-49]. Poor colonic cleansing[50] or short withdrawal times[51] may contribute to the problem.

By detection and endoscopic resection of early stage adenomas, the successive development of cancer can be prevented. This results in a savings of 216 € in Germany for each screening colonoscopy[52]. One problem of screening colonoscopy in Germany is the low compliance rate. From 2003 to 2007 more than 2.8 million screening colonoscopies were performed. In the age group of 55-74 years, 15.1% of the women and 13.4% of the men were participating within 5 years[43]. This means that after 10 years, nearly 30% of the population will be examined, a number that may improve. However, screening colonoscopies account for only one third of the total rate of colonoscopies in Germany. A chance for compliance improvement may be the system of invitation, which has recently been introduced in the state of Saarland. A study in northern Italy has shown that 26.5% of the patients that received an invitation from their physician for different methods of screening participated in colonoscopy[53].

The common result of all studies is that there are no pathological findings in a majority of screening colonoscopies. The number of patients needed to screen in order to discover an adenoma is 9, for an advanced adenoma 23, and for a CRC 143[41]. Further studies need to define low risk subgroups for colorectal neoplasia, which suit better for a non-invasive method of screening, and high-risk subgroups that necessarily need screening colonoscopy.

VIRTUAL COLONOSCOPY

A meta-analysis[54] of virtual colonoscopy done by computer tomography showed an average sensitivity for large polyps of 85% (range: 48%-100%). In a recently published multicenter trial from the United States, the sensitivity for large adenomas and cancer was 90%[55]. Only the data of a specialized center for radiology in the U.S. showed a comparable sensitivity of CT-Colography and colonoscopy[56].

The dose of radiation of updated equipment is probably too low to cause long-term harm. Yet one has to consider the total dose of radiation to each patient. In Germany, the average dose of radiation is so high that CRC screening is unlikely to be introduced being performed by CT colography. Colography completed by MRI shows a comparable sensitivity than CT colography. In Germany, virtual colonoscopy is only recommended in studies thus far due to the lacking standardization of hardware and software

LATEST DEVELOPMENTS

In the past years, new technologies have been developed intending to abstain from sedation and to allow greater patient comfort. (1) Neo-Guide (Palo Alto, California) is a colonoscope built out of multiple flexible segments that adjust to the intestinal loops, preventing looping of the colonoscope. Biopsies can be taken, and the equipment can be reprocessed[57]; (2) ColonoSight (San Jose, California) has a new infeed system with an inflatable mantle. The parts of the endoscope resting at the colonic walls are disposable, so there is no time-consuming disinfection in between examinations. LED-illumination makes glass-fibre optics and external light sources redundant. Biopsies can be taken[58]; (3) Invendo (Weinheim, Germany) has a remote-controlled infeed with a new mantle technique. It is a disposable and biopsies can be taken[59]; (4) CathCam consists of a disposable catheter with multiple lumina, a 3 mm camera, 6 illuminating diodes, and has a total diameter of 11 mm. CathCam is inserted in the caecum with a lumen detecting guide wire. The guide wire is inserted through a colonoscope that reaches the sigma[60]; (5) Aeroscope (GI View, Israel) is a fully automated infeed system using the double balloon method. It runs with carbon dioxide pressure and reverses on its own once having reached the caecum. The system uses a 360-degree optic camera and a doctor does need to be present during the examination[61]. All new methods of colonoscopy have a high caecum rate of about 90% and sedation is usually not necessary; and (6) Pillcam Colon (Given Imaging, Israel). This newly developed colon capsule has a camera on both sides, taking two pictures per second. The images are recorded on an adaptor attached to the patient's belt and can be viewed *in vivo* on a real-time monitor. After excretion of the capsule, which happens within 10 h, the data can be conveyed on a computer that creates video sequences. The method is completely painless and

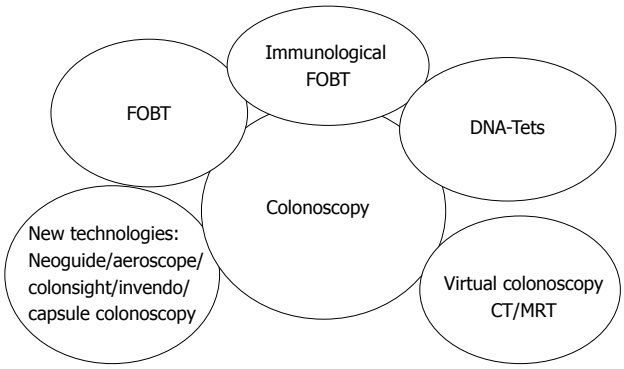

Figure 1 Future strategies of screening.

delivers pictures of the entire colon in good to excellent quality. The sensitivity for large polyps is about 70%[62,63]. The system was approved in Germany in 2008 and may be used for CRC screening in selected persons who are able to drink 4 liters of colon lavage[64].

PERSPECTIVES OF CRC SCREENING

For the foreseeable future, optical colonoscopy with the possibility of biopsy and polypectomy is likely to be the diagnostic test of choice in patients with positive screening tests. Colonoscopy should be the preferred screening method for high-risk groups (familial disposition, diabetes, adipositas, cigarette smoking *etc*). The entire band of possible methods forms a portfolio for screening, so that each patient advised by his family physician can choose his favourite one (Figure 1).

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S- Editor Li JL **L- Editor** Alpini GD **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.17

World J Gastrointest Endosc 2009 October 15; 1(1): 17-20
ISSN 1948-5190 (online)

GUIDELINES FOR CLINICAL PRACTICE

Endoscopic sphincterotomy in acute biliary pancreatitis: A question of anesthesiological risk

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Received: February 1, 2009 Revised: March 16, 2009
Accepted: March 23, 2009
Published online: October 15, 2009

Abstract

Two consecutive surveys of acute pancreatitis in Italy, based on more than 1000 patients with acute pancreatitis, reported that the etiology of the disease indicates biliary origin in about 60% of the cases. The United Kingdom guidelines report that severe gallstone pancreatitis in the presence of increasingly deranged liver function tests and signs of cholangitis (fever, rigors, and positive blood cultures) requires an immediate and therapeutic endoscopic retrograde cholangiopancreatography (ERCP). These guidelines also recommend that patients with gallstone pancreatitis should undergo prompt cholecystectomy, possibly during the same hospitalization. However, a certain percentage of patients are unfit for cholecystectomy because advanced age and presence of comorbidity. We evaluated the early and long-term results of endoscopic intervention in relation to the anesthesiological risk for 87 patients with acute biliary pancreatitis. All patients underwent ERCP and were evaluated according to the American Society of Anesthesiology (ASA) criteria immediately before the operative procedure. The severity of acute pancreatitis was positively related to the anesthesiological grade. There was no significant relationship between the frequency of biliopancreatic complications during the follow-up and the ASA grade. The frequency of cholecystectomy was inversely related to the ASA grade and multivariate analysis showed that the ASA grade and age were significantly related to survival. Finally, endoscopic treatment also appeared to be safe and effective in patients at high anesthesiological risk with acute pancreatitis. These results further support the hypothesis that endoscopic sphincterotomy might be considered a definitive treatment for patients with acute biliary pancreatitis and an elevated ASA grade.

Key words: Acute biliary pancreatitis; Anesthesiological risk; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy

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Pezzilli R. Endoscopic sphincterotomy in acute biliary pancreatitis: A question of anesthesiological risk. *World J Gastrointest Endosc* 2009; 1(1): 17-20 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/17.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.17

INTRODUCTION

Two consecutive surveys of acute pancreatitis in Italy, based on more than 1000 patients with acute pancreatitis, reported that the etiology of the disease indicates biliary origin in about 60% of the cases[1,2].

Why patients with gallstones, especially those with biliary sludge[3], develop acute pancreatitis remains an open issue. Small gallstones, enlarged cystic ducts, impacted stones of normal dimensions, and a functioning

common channel have been demonstrated to be predisposing local etiologic factors in the development of gallstone pancreatitis[4]. McMahon and Shefta have[5] reported that numerous small stones having an irregular shape appeared to be more common in patients who had suffered acute pancreatitis, and might be a factor in the pathogenesis of the attack. Diehl *et al*[6] supported these findings, demonstrating that patients with at least one gallstone smaller than 5 mm in diameter have more than a four-fold increased risk of presenting with acute biliary pancreatitis. Why do patients with small gallstones develop acute pancreatitis? An answer to this question comes from a study carried out in The Netherlands[7]. The authors compared postprandial gallbladder motility using ultrasonography and, after subsequent cholecystectomy, numbers, sizes, and types of gallstones, gallbladder bile composition, and cholesterol crystallization in 21 gallstone patients with previous pancreatitis and 30 patients with uncomplicated symptomatic gallstones. The authors found that gallbladder motility was stronger in patients with pancreatitis than in patients with uncomplicated symptomatic gallstones. Patients with pancreatitis often had significantly more sludge, and a greater number of small gallstones than patients with symptomatic gallstones. Crystallization also occurred significantly faster in the bile of patients with pancreatitis, possibly because of higher mucin concentrations. No significant differences were found in type of gallstones, relative biliary lipid content, cholesterol saturation index, bile salt species composition, phospholipid class, total protein or immunoglobulin, haptoglobin, and α-1 acid glycoprotein concentration. The conclusions drawn from this study are important because they have demonstrated that patients with small gallstones and/or preserved gallbladder motility are at increased risk of pancreatitis because the stones could more easily migrate from the gallbladder to the common bile duct, if gallbladder contraction is preserved.

THERAPEUTIC APPROACH TO ACUTE BILIARY PANCREATITIS

In 1998 the United Kingdom guidelines reported that severe gallstone pancreatitis in the presence of increasingly deranged liver function tests and signs of cholangitis (fever, rigors, positive blood cultures) requires an immediate and therapeutic endoscopic retrograde cholangiopancreatography (ERCP)[8]. The same position was taken by the American Gastroenterological Association[9] and by the Italian Association for the Study of the Pancreas[10]. These societies also recommend that patients with gallstone pancreatitis should undergo prompt cholecystectomy, possibly during the same hospitalization. In fact, a study on the recurrent form of pancreatitis[11] found that of the 1068 patients with acute pancreatitis enrolled in five European countries, gallstones were the cause of recurrent pancreatitis in 25% of the cases. It is also important to emphasize that a substantial number of patients with 'idiopathic' pancreatitis might have small gallstones that were undetected by abdominal ultrasound or computed tomography[12]. However, a certain percentage of patients are unfit for cholecystectomy because advanced age and presence of comorbidity[13,14].

THERAPEUTIC OPTIONS IN PATIENTS UNFIT FOR CHOLECYSTECTOMY

From a practical point of view, therapeutic solutions have been empirically proposed. Even if cholecystectomy is the main therapeutic option in patients with gallstones, some authors have proposed the use of ursodeoxycholic acid in order to prevent further attacks of acute pancreatitis having a biliary origin[15,16]; others have suggested that endoscopic sphincterotomy might be an option, especially in patients considered unfit for surgery[13,14,17]. In fact, it has been suggested that endoscopic sphincterotomy is the method of choice for treatment of lithiasis of the common bile duct, particularly in elderly patients or in patients at poor operative risk[18-20]. This therapeutic approach has also been proposed for the management of severe acute biliary pancreatitis as a definitive procedure to avoid recurrence of the disease in patients unfit for surgery because of age or comorbidities[13,21]. However, there was a lack of follow-up data for these patients after endoscopic procedures. The American Society of Anesthesiology (ASA) grading system[22] has been used for over 50 years as a predictor of risk for perioperative morbidity and mortality. The ASA grade has recently been proposed to stratify the risk of complications in patients who undergo endoscopic procedures[23]. Thus, we undertook a study to evaluate the early and long-term results, i.e., morbidity and mortality, of endoscopic intervention in relation to the anesthesiological risk in patients with mild and severe acute biliary pancreatitis[24].

ERCP AND ANESTHESIOLOGICAL RISK IN PATIENTS WITH MILD AND SEVERE ACUTE BILIARY PANCREATITIS

We studied all patients who underwent ERCP for acute biliary pancreatitis[24]; all the patients were evaluated according to the ASA criteria immediately before the operative procedure. Eighty-seven patients with acute biliary pancreatitis were enrolled (35 males and 52 females; median age, 72 years; range, 34-93). According to the Atlanta classification system, 57 of the 87 patients enrolled (65.5%) had mild acute pancreatitis, whereas 30 (34.5%) had a severe form of the disease (local and systemic complications in these latter 30 patients are reported in Table 1). All patients were treated conservatively.

According to the ASA criteria, the 87 patients' grades were distributed as follows: 49.4% of patients had ASA grade 2; 29.9% ASA grade 3; and 20.7% had ASA grade 4. The major medical diseases in patients having elevated anesthesiological grades are reported in Table 2. None of the patients enrolled in the study were of ASA grade 5.

Table 1 Local and systemic complications in the 30 patients with severe acute pancreatitis

Complication	*n* (%)
Sterile necrosis	9 (63.3)
Infected necrosis	4 (13.3)
Respiratory insufficiency	17 (56.7)
Metabolic alterations	16 (53.3)
Multiorgan failure	3 (10.0)
Renal insufficiency	2 (6.7)
Heart failure	1 (3.3)

More than one complication might occur in the same patient.

Table 2 Major chronic diseases in patients with ASA grade 3 and 4 (44 cases)

Disease	*n* (%)
Chronic myocardial ischemia	34 (77.3)
Arterial hypertension	18 (40.9)
Chronic obstructive pulmonary disease	9 (20.5)
Diabetes mellitus	7 (15.9)
Chronic atrial fibrillation	7 (15.9)
Chronic active hepatitis	2 (4.5)
Chronic renal insufficiency	2 (4.5)
Congestive cardiomyopathy	1 (2.3)
Severe mitral prolapse syndrome	1 (2.3)
Abdominal aortic aneurysm	1 (2.3)
Chronic obliterative arteriopathy	1 (2.3)
Hepatic cirrhosis	1 (2.3)
Active duodenal ulcer	1 (2.3)
Epilepsy	1 (2.3)
Chronic leukemia	1 (2.3)
Systemic lupus erythematosus	1 (2.3)

Nonparametric statistical analyses (Kruskal-Wallis one-way ANOVA, Spearman rank correlation, Fisher exact test, and Mantel- Haenszel test for linear association) and multiple regression analysis were applied to the data. Stepwise multivariate survival analysis was performed by means of the Cox hazard model, and the odds ratios (ORs), with their 95% confidence intervals (95% CIs), were evaluated. The SPSS/PC+ package (SPSS, Chicago, IL, USA) and the BMDP package (University of California, Berkeley, CA, USA) were used to perform the nonparametric tests and survival analysis, respectively. A two-tailed *P* value less than 0.05 was considered statistically significant.

There were no significant differences in gender and frequency of previous cholecystectomy among the three groups of patients, whereas age and the severity of acute pancreatitis were positively related to the anesthesiological grade. Multivariate regression analysis showed that these latter two variables were independently related to the ASA grade. ERCP showed lithiasis of the common bile duct in 55 patients (63.2%) and biliary sludge in the remaining 32 patients (36.8%). Endoscopic sphincterotomy was performed successfully in 86 patients but was unsuccessful in one patient with biliary sludge. All 86 patients in whom endoscopic sphincterotomy was successfully performed had complete stone/sludge clearance of the common bile duct; four patients (4.6%) required two attempts to achieve clearance of the common bile duct, and two (2.3%) of them required extracorporeal shockwave lithotripsy. In 10 patients (six with ASA grade 2, 3 with ASA grade 3, and one with ASA grade 4), deep cannulation of the common bile duct was achieved with precut sphincterotomy. None of the patients had cardiopulmonary complications related to the endoscopic procedure. Six of the 87 patients (6.9%) had complications related to the endoscopic procedure. Two patients (2.3%), one with ASA grade 2 and one with ASA grade 3, had clinically mild hemorrhage, requiring a red blood cell transfusion (2 units) in the former. Three patients (3.4%), one with ASA grade 2 and two with ASA grade 4, had retroperitoneal perforation, which was resolved with nasobiliary drainage and conservative treatment. One patient (1.1%) with ASA grade 3 had mild hemorrhage and a perforation. None of the patients with endoscopy-related complications underwent a surgical procedure, and there were no deaths. The frequencies of the complications related to the endoscopic procedure were equally distributed among the various ASA grades (4.7% in patients having ASA grade 2, 27.7% in those having ASA grade 3, and 11.1% in patients having ASA grade 4).

Three patients (3.4%) died of complications unrelated to the endoscopic procedure: one patient with ASA grade 4 died of irreversible heart failure and two (one with ASA grade 3 and one with ASA grade 4) died of multiorgan failure related to the severity of the acute pancreatitis. Pancreatic surgery was performed on two patients due to infection of the necrosis. All 84 patients discharged from the hospital were followed for a median of 12 mo (range, 1-84). The duration of the follow-up was not significantly different among the three groups of patients studied. Twenty-three patients (27.4%) had biliopancreatic complications: 11 were of ASA grade 2 (25.6%), eight of ASA grade 3 (32.0%), and four of ASA grade 4 (25.0%). There was no significant relationship between the frequency of complication and the ASA grade. Twenty-eight of the 76 patients who had not previously undergone cholecystectomy underwent cholecystectomy during the follow-up period. The frequency of cholecystectomy was inversely related to the ASA grade ($P = 0.003$). Seven patients (8.3%) died during the follow-up period: two with ASA grade 3 (8.0%) and five with ASA grade 4 (31.3%). The causes of death were as follows: heart failure in four, pulmonary embolism in one, chronic leukemia in one, and pulmonary sepsis in one. The death rate significantly increased with the increase in the ASA grade and the multivariate analysis showed that the ASA grade (OR = 10.9; 95% CI: 1.2-96.6) and age (OR = 1.1; 95% CI: 1.0-1.3) were significantly related to survival, whereas gender and the severity of pancreatitis had no bearing on survival.

CONCLUSION

The data reported in this study indicated that patients at

elevated anesthesiological risk had a significantly higher rate of severe acute pancreatitis. Early complications after endoscopy were unrelated to age or comorbidities, even if the deaths occurred only among severely ill patients. Finally, endoscopic treatment also appeared to be safe and effective in patients at high anesthesiological risk with acute pancreatitis. After exclusion of age as a confounding factor, survival remained significantly related to ASA grade.

These results further support the hypothesis that endoscopic sphincterotomy might be considered a definitive treatment for patients with acute biliary pancreatitis and an elevated ASA grade. This finding might also reflect the reluctance on behalf of the surgeon to operate on patients at high anesthesiological risk.

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S- Editor Li JL **L- Editor** Stewart GJ **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.21

World J Gastrointest Endosc 2009 October 15; 1(1): 21-31
ISSN 1948-5190 (online)

REVIEW

Endoscopic mucosal resection and endoscopic submucosal dissection for early gastric cancer: Current and original devices

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Received: June 16, 2009 Revised: September 5, 2009
Accepted: September 12, 2009
Published online: October 15, 2009

Abstract

Compared with endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR) is easier to perform and requires less time for treatment. However, EMR has been replaced by ESD, because achieving en bloc resection of specimens > 20 mm in diameter is difficult with EMR. The technique of ESD was introduced to resect large specimens of early gastric cancer in a single piece. ESD can provide precise histological diagnosis and can also reduce the rate of recurrence, but has a high level of technical difficulty, and is consequently associated with a high rate of complications, a need for advanced endoscopic techniques, and a lengthy procedure time. To overcome disadvantages in both EMR and ESD, various advances have been made in submucosal injections, knives, other accessories, and in electrocoagulation systems.

Key words: Endoscopic mucosal resection; Endoscopic submucosal dissection; Endoscopic device; Endoscopic mucosal resection device; Endoscopic submucosal dissection device

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Kume K. Endoscopic mucosal resection and endoscopic submucosal dissection for early gastric cancer: Current and original devices. *World J Gastrointest Endosc* 2009; 1(1): 21-31 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/21.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.21

INTRODUCTION

Early gastric cancer confined to the mucosa can be treated successfully with endoscopic resection alone. Endoscopic resection of early gastric cancer originated with the development of a polypectomy technique using high-frequency current for gastric polyps in 1968[1], and has become popular as endoscopic mucosal resection (EMR) since the birth of the strip biopsy method in 1984[2]. Endoscopic submucosal dissection (ESD) is a new endoscopic technique using cutting devices that developed from one of the EMR techniques, namely endoscopic resection after local injection of a solution of hypertonic saline-epinephrine[3]. EMR has recently been replaced by ESD, because en bloc resection of specimens > 20 mm in diameter is difficult to achieve with EMR, and piecemeal resection is associated with increased rates of local recurrence to about 15%[4,5]. The technique of ESD was introduced to resect large specimens of early gastric cancer in a single piece. However, the question remains as to whether ESD is superior to EMR in all regards.

This review provides an overview of the techniques and devices of EMR and ESD.

EMR

Various devices and techniques of EMR have been

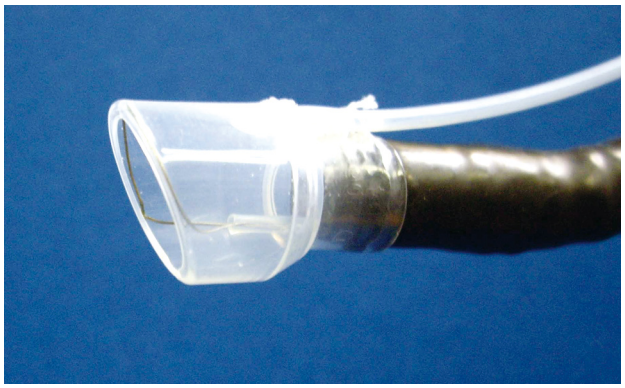

Figure 1 Irrigation prelooped cap.

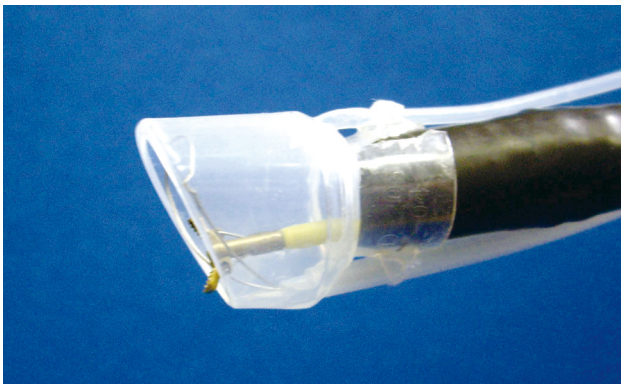

Figure 2 The 2-channel soft prelooped hood.

described. EMR is divided into techniques without an aspiration cap and techniques with an aspiration cap. Strip biopsy methods using a single-channel scope or double-channel scope are regarded as techniques without an aspiration cap. Cap-assisted endoscopic mucosal resection (EMRC), endoscopic aspiration mucosectomy (EAM), endoscopic mucosal resection with ligation (EMRL), and others are regarded as techniques with an aspiration cap.

Strip biopsy method using a single-channel scope

The lesion is raised off the muscularis propia by the creation of a submucosal bleb, strangulated by a snare, and resected using an electrosurgical snare[2,6].

Strip biopsy method using a double-channel scope

Submucosal injection is performed in standard fashion. Both the snare and grasping forceps are advanced through the channels. In preparation for EMR, the snare is opened to capture the forceps, then closed snugly. The lesion is grasped by the forceps and pulled gently into the now-opened snare. The snare is then closed and the lesion is resected[6-8].

EMRC

EMRC (standard): EMRC is a simpler and easier refinement of EMR methods[9]. The technique requires a specialized transparent plastic cap that is fitted to the tip of the endoscope. Different-sized caps are available, according to the diameter of the endoscope (Olympus, Japan). In addition, a soft 18-mm diameter cap designed for en bloc resection of larger lesions is available. Matsuzaki *et al*[10] used this soft cap for resection of gastric lesions 1.4-times larger than specimens that could be removed by the conventional cap.

After marking the periphery of the lesion, submucosal solution (saline, glucose, Glycerol®, *etc.*) is injected into the submucosa. The crescent-shaped snare (SD-221L-25 or SD-7P-1; Olympus) is then prelooped into the groove of the rim of the cap. The endoscopist performs this pre-looping by lightly pressing against and suctioning normal mucosa to seal the cap outlet. The snare is opened and forced to rest along the inside groove of the rim of the cap to form the loop. Suction is released and the cap is then used to suck the lesion with medium to high vacuum into the cap. The endoscopist then strangulates the lesion by closing the snare and the suction is again released. Once the lesion looks similar to a snared polypoid lesion, blend electrosurgical current is typically used to resect the lesion.

EMRC-UI (EMRC under irrigation): One problem with the EMRC method is that the lesion cannot always be kept in the center of the cap, because the procedure is performed in a blind manner after aspiration. The usefulness of a novel end-hood that facilitates endoscopic hemostatic procedures while simultaneously allowing irrigation of the bleeding site was improved by the author, who developed a soft, prelooped cap with attached irrigation tube (Figure 1)[11-14].

The aspiration method of EMRC-UI method is similar to EMRC. Aspiration is applied repeatedly until the lesion is stabilized in the center of the hood. If the field of view is compromised because of the presence of mucus and/or blood, the site is irrigated. After strangulating the lesion by closing the snare, the negative aspiration pressure is released.

EMR-UI was performed in 15 patients with a median time required of 19 min. Mean diameter of specimens was 24.5 mm (interquartile range, 15-35 mm). The proportion of en bloc-resected lesions was 86.7% (13/15).

Grasping forceps-assisted EMRC using a 2-channel prelooped cap: The author has also improved the EMRC-UI cap. Two side holes were fabricated by drilling in the hood portion of a conventional soft prelooped cap, and then the irrigation tube and the accessory channel tube were glued to the exterior surface of the holes. The author developed a 2-channel prelooped cap that facilitates EMRC while simultaneously allowing both grip of the central position of the lesion and irrigation of the aspiration site (Figure 2)[15].

The aspiration method of grasping forceps-assisted EMRC using a 2-channel prelooped cap method is similar to EMRC. The endoscopist releases the negative aspiration pressure while slowly pulling the regular biopsy forceps gripping the center of the lesion. Until

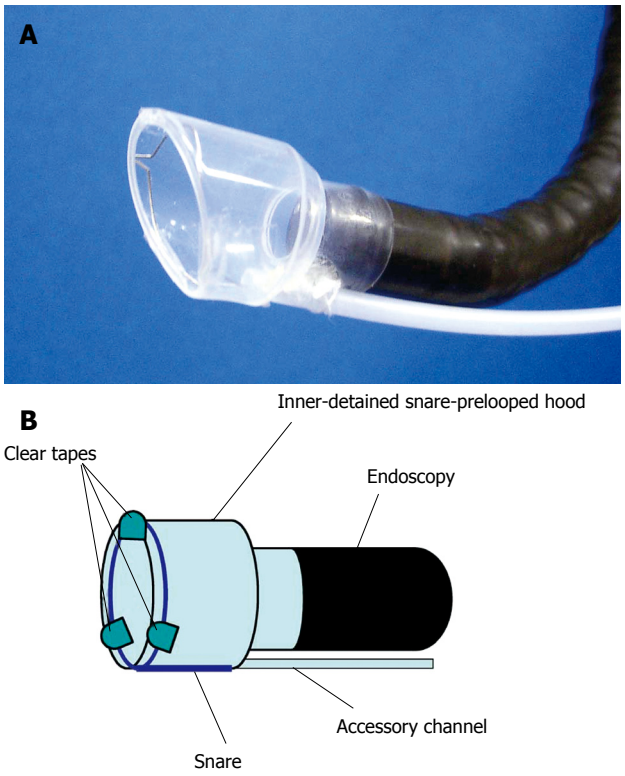

Figure 3 The internally retained snare (IRS) cap. A: Photograph; B: Schema.

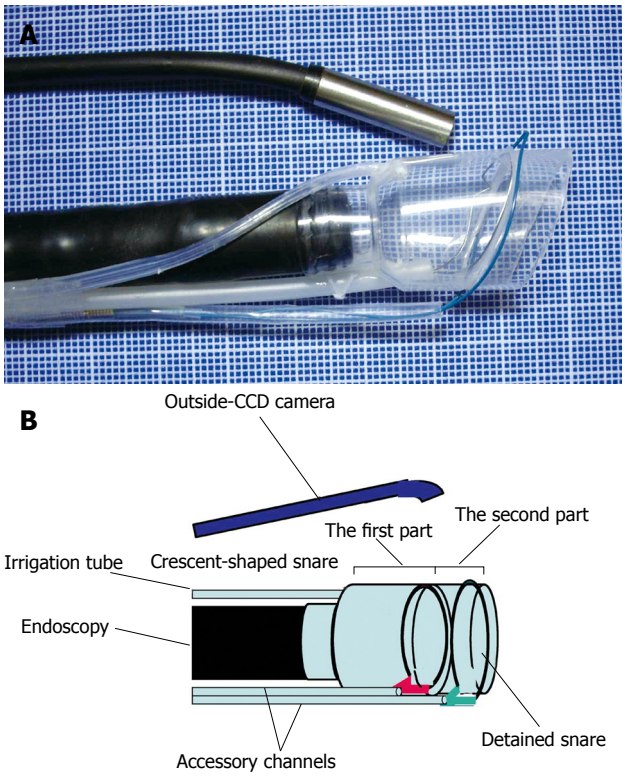

Figure 4 EAMC hood. A: Placed at the tip of the endoscope and outside-CCD camera; B: Schema of endoscope with EAMC hood. EAMC: endoscopic aspiration mucosectomy and closure.

the lesion is stabilized in the center of the hood, the endoscopist repeatedly performs grasp and aspiration of the lesion. If the field of view at the aspiration site is poor as a result of contamination by mucus and blood, the endoscopist repeatedly performs irrigation of the site. After strangulating the lesion by closing the snare, the endoscopist again releases the aspiration.

Grasping forceps-assisted EMRC using a 2-channel prelooped cap was performed in 12 patients with a median time required of 19 min. Mean diameter of specimens was 22.3 mm (interquartile range, 15-31 mm). The rate of en bloc resection was 91.7% (11/12).

EMRC using IRS (internally retained snare) cap: In EMRC, the crescent-shaped snare needs to be prelooped into the groove on the rim of the cap during the procedure itself. As this pre-looping can be initially difficult, the author has avoided this step by developing a new type of prelooped cap, the "internally retained snare" (IRS) cap that makes pre-looping unnecessary (Figure 3)[16].

After fitting the IRS cap to the tip of the endoscope, EMRC using the IRS cap method is similar to EMRC. The endoscopist releases the negative aspiration pressure and the cap is then positioned to aspirate the lesion with medium to high vacuum into the hood. The endoscopist again releases the aspiration, after strangulating the lesion by closing the snare.

EMRC using an IRS cap was performed in 27 patients with a median time required of 16 min. Mean diameter of specimens was 27.6 mm (interquartile range, 15-38 mm). The rate of en bloc resection was 88.9% (24/27).

EMRC-C (EMRC and closure): Delayed bleeding may occur from a gastric ulcer after EMRC. Solving this problem may allow surgery on an outpatient basis. The author therefore developed a novel EMRC and closure (EMRC-C) cap that facilitates the EAM procedure whilst simultaneously allowing endoscopic closure (Figure 4)[17]. The EMRC-C hood was produced by attaching an additional hood of short length and another accessory channel to the top of the 2-channel prelooped cap. Two types of snares are then set. The crescent-shaped snare (SD-221L-25; Olympus) is inserted through the accessory channel tube of the first part of the hood, and prelooped into the groove of the rim of the hood. The detained snare (HX-20L-1; Olympus) is passed through and tightened around the outer circumference of the second part of the hood.

The endoscopist places the EMRC-C hood at the tip of the endoscope. Aspiration is released and the hood is then used to aspirate the lesion by high-power vacuum into the hood. The endoscopist confirms aspiration of the lesion with the outside CCD camera then snares the lesion using the detained and crescent-shaped snares. The endoscopist uses the former to tightly strangle the lesion, and resected the lesion using blend electrosurgical current and closing the latter snare.

Two specimens were resected in an animal model (pigs). Mean diameter of the resected specimens was 15 mm. This device has not yet been used in human patients.

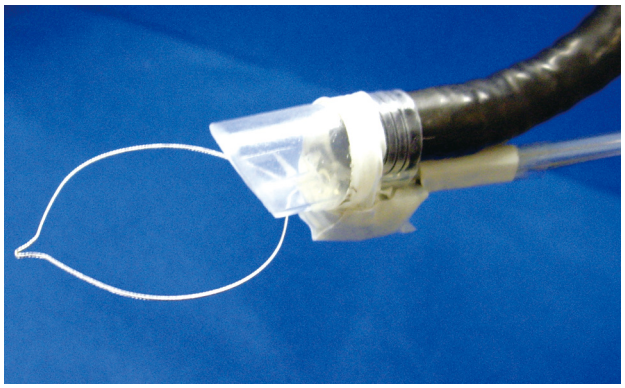

Figure 5 Vibration hood at the tip of the endoscope.

EAM

EAM (standard): EAM uses a conventional hood (Create Medic, Yokohama, Japan, and TOP, Tokyo, Japan). In this device, a snare is passed through an outside channel and tightened around the outer circumference of the hood[16,18-20]. Pre-looping during the EAM procedure is thus unnecessary.

In an adaptation of EAM with a snare on the tip of the endoscope, the EAM hood method is similar to EMRC. The endoscopist releases the negative aspiration pressure and the hood is then placed to aspirate the lesion with medium to high vacuum into the hood. The snare is pushed over the tumor while the lesion is aspirated. In addition, the loop is pulled tightly around the specimen. The endoscopist again releases the aspiration, after strangulating the lesion by closing the snare.

EAM hood was performed in 27 patients. Mean diameter of specimens was 27.1 mm (interquartile range, 20-43 mm). The rate of en bloc resection was 85.2% (23/27).

EAM-V (EAM with vibration): EAM carries a risk of aspirating and perforating the full thickness of the gastric wall. A novel vibration hood to reduce such risks was therefore developed (Figure 5)[21]. This novel hood enables strangulation and resection of only the mucosal and submucosal layers by vibrating the snare during strangulation to shake off the muscle layer and serous membrane.

Investigations were conducted separately with and without vibration at 10000 rpm applied at the time of strangulation and resection. Eighteen specimens were resected in an animal model (pigs). Perforation rates were lower in the vibration group (0/9: 0%) than in the group without vibration (2/9: 22.2%). This device has not yet been used in human patients.

EMRL (EMR with ligation)

The technique of EMR with ligation (EMRL) uses a standard endoscopic variceal ligation device fitted to a single-channel endoscope[22]. The maximum lesion size for en bloc resection is 1.5 cm. Larger lesions may require piecemeal resection. This technique has been reported with or without prior submucosal injection. The lesion is snared by standard snare polypectomy after it has been ligated at its base with an endoscopic variceal ligation device.

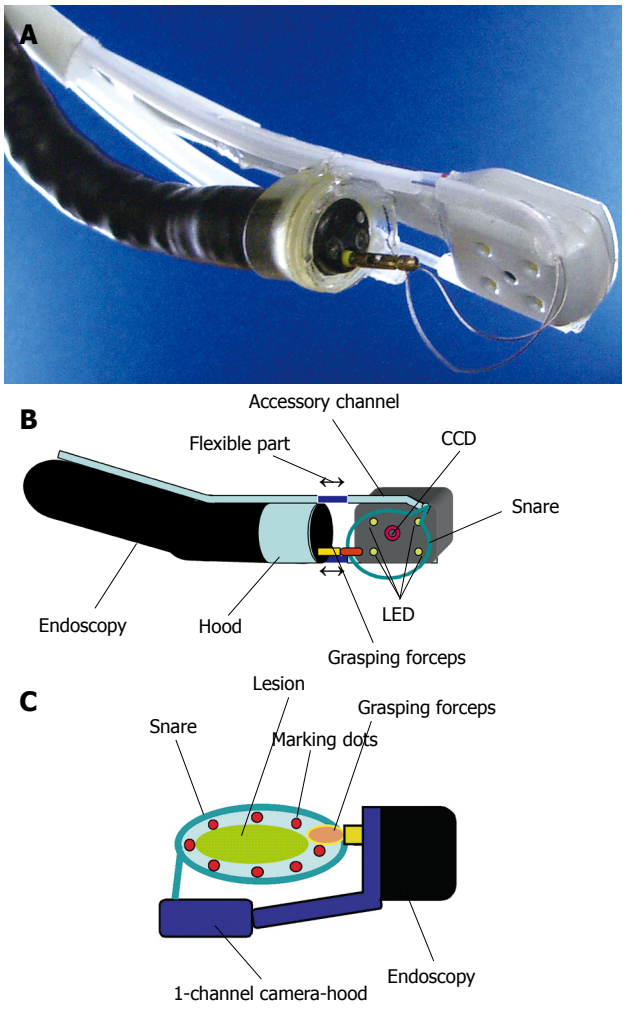

Figure 6 The 1-channel camera-hood. A: Placed at the tip of the endoscope; B: Schema of the 1-channel camera-hood (B); C: Schematic representation of endoscopic mucosal resection (EMR) using the 1-channel camera-hood.

Multi-camera system using a novel 1-channel camera-hood

Precise snaring during EMR is important to achieve en bloc resection. However, this can be difficult to achieve in practice, because snaring cannot be performed under complete observation. Although we can easily observe the proximal side of the lifting lesion, the distal side is hard to see after injection of saline solution into the submucosa. The author therefore developed a novel 1-channel camera-hood that allows observation of the distal side of the lesion during snaring in the EMR procedure (Figure 6)[23]. The 1-channel camera-hood was fabricated by cutting a "U-shape" in the cap portion of the hood and then attaching a machined camera, originally developed for dental use, that consisted of a charge-coupled device (CCD) camera and 4 light-emitting diodes (LEDs) ("Miharu-kun"; RF System Lab, Japan) through

two tubes. The length of the two tubes is variable and one is an accessory channel (Figure 6A and B).

EMR using the 1-channel camera-hood was performed as follows (Figure 6C). After injection of saline solution into the submucosa, the endoscope was removed and the 1-channel camera-hood was placed on the tip and fixed with tape. A snare was passed through the accessory channel of the hood, and grasping forceps were passed through the accessory channel of the endoscope. The grasping forceps were used to catch hold of the snare. The lesion was then strangulated by precisely closing the snare under adequate observation by both the CCD camera of the 1-channel camera-hood and the endoscope. Blend electrosurgical current was used to resect the lesion. This device has not yet been used in human patients.

ESD

The technique of ESD was introduced to resect large specimens of early gastric cancer in a single piece. ESD can provide precise histological diagnosis and can also reduce the recurrence rate[4]. The drawback of ESD lies in the technical difficulty, and this technique is therefore associated with a high rate of complications, the need for advanced endoscopic techniques, and a lengthy procedure time[5,24].

Standard ESD

Standard ESD requires special cutting knives, such as a needle knife[3], an insulation-tipped electrosurgical (IT) knife[4,5,24-28], a hook knife[29,30], a flex knife[31], a flush knife[32], a triangle-tip (TT) knife[33], a Fork knife[34], or a mucosectomy[35].

Standard ESD is performed with a standard single accessory-channel endoscope. Typical sequences are the following: marking; incision; submucosal dissection with simultaneous hemostasis. After marking with several dots outside the lesion, various submucosal solutions are injected, including the normal saline solution and epinephrine mixture, glycerol mixture, and hyaluronic acid. A circumferential incision into the mucosa is made using one of the special cutting knives. Direct dissection of the submucosal layer is performed with one of the specified knives until complete removal is achieved. During ESD, the endoscopist performs endoscopic hemostasis with either the knife itself or hemostatic forceps whenever active bleeding is noticed. After ESD, the endoscopist performs preventive endoscopic hemostasis for any oozing or exposed vessels. High-frequency generators (Erbotom ICC200 or VIO 300D; ERBE, Tübingen, Germany) were used for marking, incision of the gastric mucosa, gastric submucosal dissection, and endoscopic hemostasis.

Special cutting knives

IT knife: The IT knife consists of a small ceramic ball attached to the tip of a high-frequency needle knife[4,5,24-28]. The ceramic ball functions as an insulator for the tip of the needle knife, so that incision and dissection of the mucosa and submucosa can be performed safely. The insulator helps to prevent perforation due to accidental cutting of the muscularis propria. A specialized feature of the IT knife is that the portion between the insulator tip and sheath is used for incision, sweeping off the tissue with the blade portion of the knife instead of the tip. This feature makes a pull-cut, whereas the direction of incision is limited, and straight-forward incision is difficult while looking directly at the incision line or submucosa.

Hook knife: The top of the hook-type knife is right-angled, 1 mm in size[29,30]. Compared to the use of a needle knife, safety is improved because the submucosal tissue is hooked and pulled before incision. This knife has a rotating function so that the operator can select the optimal direction of the hook.

Flex knife: The point of the flex knife is rounded with a twisted wire, like a snare[31]. The sheath is soft and flexible. This knife is less likely to cause perforation when reaching the muscular layer, as the tip is round and the entire knife is soft and flexible. As the tip of the sheath is thick and functions as a stopper, operators can easily control the depth of incision.

Flush knife (Water jet short needle knife): The Flush knife is a characteristic knife with a needle 0.4 mm in a diameter and five projecting parts of 1, 1.5, 2, 2.5, and 3 mm in length[32]. A knife clamp at the tip of the sheath is ceramic for heat insulation. The outer sheath is 2.6 mm in diameter and water emission is possible through the lumen of the sheath by connecting a water pump. The water jet is swiftly activated by pressing a foot pedal on the conduction pump. The conductor of the sheath lumen is insulated to prevent electric current dispersion.

TT knife: The TT knife evolved from the process of ESD, which began with the IT knife[33]. The triangular tip of the knife can be used for either cutting or coagulating, and has been designed to operate in any direction.

Fork knife: The Fork knife has two interchangeable knives; a fixed flexible snare and a forked knife, all of which form a single working unit. The Fork knife also has an inlet for material injection or saline irrigation during the procedure[34]. Such knives can be changed during a procedure by using two switches, the fork knob and core knob, located on the center of the body.

The first of the two knives that constitute the Fork knife is the fixed flexible snare, which is operated by sliding the core knob switch forward. The blade is shaped into an elongated loop much like the Flex knife. Endoscopists mainly use the fixed flexible snare for marking and making incisions around lesions.

The second knife is a forked knife, which has a

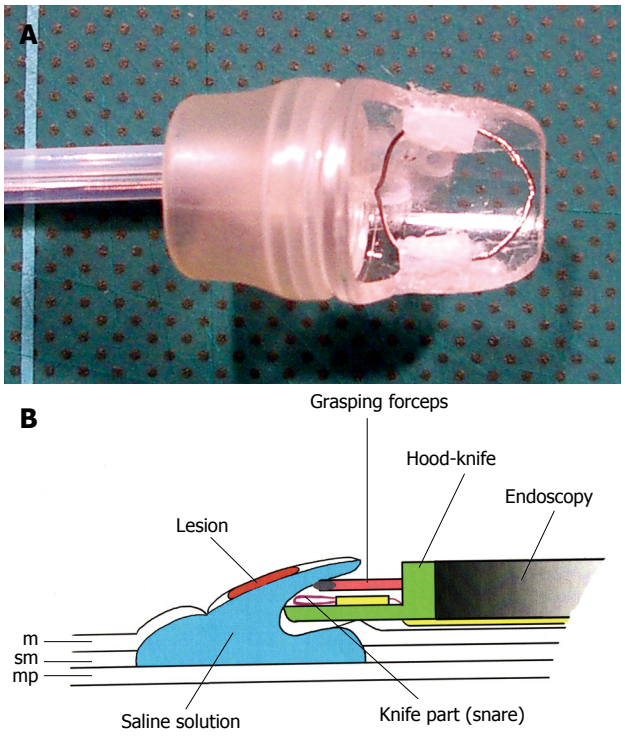

Figure 7 Irrigation hood knife. A: Photo; B: Schematic representation of endoscopic submucosal dissection (ESD) using the hood-knife.

double-tipped blade (longer tip length, 2 mm; shorter tip length, 1.5 mm) with a forked shape. The fork knife is located on the opposite side from the fixed snare knife and is operated by sliding the fork knob switch forward. This form of needle knife has an M-shape that maximizes the power applied to contacted surfaces and is advantageous for dissection and coagulation. The longer tip of the forked knife can be used as an injection needle for making a submucosal cushion, or for injecting agents. The opening of the needle is located in the center of the knife, between both tips, so that the mucosa must be injected deeply and at an oblique angle for maximum injection into the submucosa. Endoscopists use the forked knife mainly for submucosal dissection performed in the proximal to distal direction of the endoscope, under direct visualization of the dissection area.

Mucosectome: The mucosectome is composed of a flexible plastic shaft and cutting wire[35]. The handle-operated top of this device turns freely, assisting the cutting wire to face the proper direction. The plastic shaft moves the muscular layer aside. The cutting wire moves the mucosal layer aside from the submucosa during ESD, and then the procedure itself can be performed safely.

Transparent hood

A transparent hood is helpful for better visualization of the operating field. In particular, good visualization of the submucosal tissue with the aid of a small-caliber-tip transparent hood makes cutting procedures easy and safe[36]. EMR using a small-caliber-tip transparent hood is a peeling-off method using a needle-knife for mucosal and submucosal incisions.

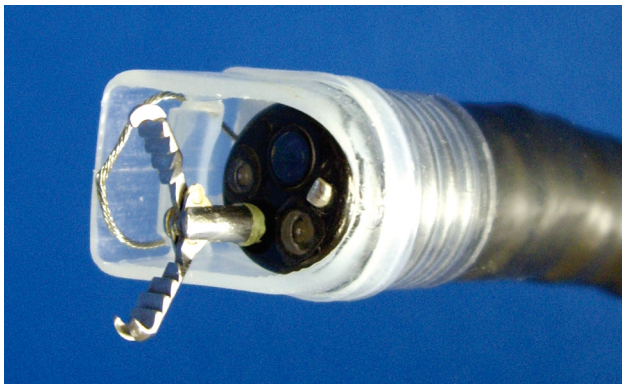

Figure 8 Cap-knife attachment (Type KUME) with a fixed snare placed on the tip of the endoscope through grasping forceps.

Tip hood

Cap knife: The author developed a novel one-third partially transparent hood that facilitates endoscopic hemostatic procedures while simultaneously allowing the irrigation of bleeding (Figure 7)[12]. The one-third partial hood is easily placed on the tip of the endoscope, although it must be fitted to the right side of the endoscope. The hood-knife was fabricated by drilling another side hole in addition to the hole for the irrigation tube in the cap portion of a transparent end hood[37]. A snare forceps was glued to the exterior surface over the hole and attached using short tubes on the inside of the cap. Based on this prototype, the irrigation cap-knife (cap-knife attachment (Type KUME) with a fixed snare) was developed as shown in Figure 8 (Create Medic, Yokohama, Japan)[38].

The ESD procedure using the cap-knife is performed as follows. After the tumor is separated from surrounding normal mucosa by complete incision around the lesion using the IT knife, the endoscope is then removed, and the cap-knife is placed on the tip and fixed with tape. Grasping forceps are passed through the accessory channel and push the lesion away from the muscle layer. Submucosal exfoliation was achieved simply by sliding the cap-knife onto the muscle layer and applying a coagulation current.

Wiper-knife: The wiper-knife was fabricated by installing a needle-knife in exchange for a snare forceps (Figure 9A and B)[39]. A handling wire intersects the needle-knife and fixes it. The handling wire is passed through a hole opening at either end of the hood. A novel wiper-knife was fabricated such that ESD could be performed by movements similar to a windshield wiper.

ESD using the wiper-knife was performed as follows (Figure 9C). A grasping forceps was passed through accessory channel and pushed the lesion away from the

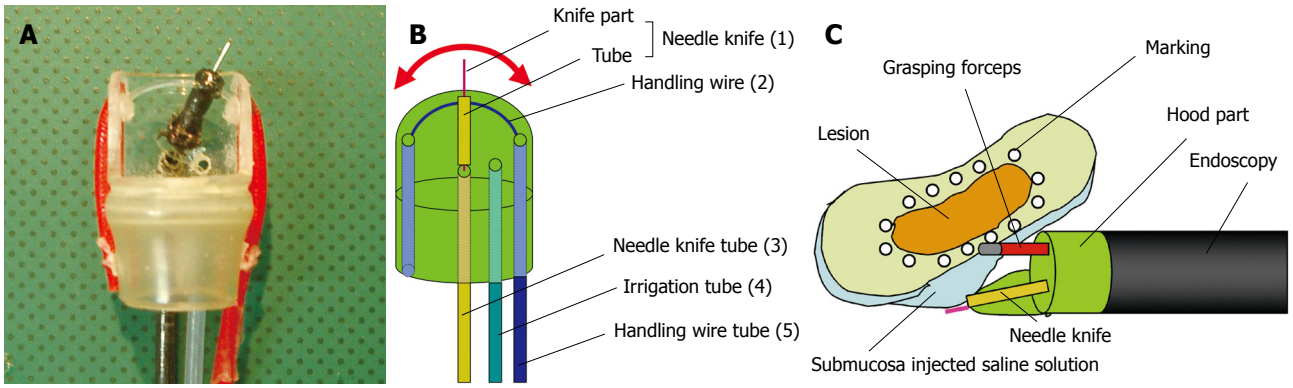

Figure 9 The irrigation wiper-knife. A: Photo; B: Schema of a needle-knife moving like a windshield wiper (both ends red arrow); C: Schematic representation of the ESD using the wiper-knife.

muscle layer. The wiper-knife moved like a windshield wiper, applying a coagulation current on the muscle layer to separate submucosal exfoliation from the muscle layer. This device has not yet been used in human patients.

B-cap: B-cap is a device in which the snare of the cap knife has been replaced with a bipolar knife[40]. The direction for use of the B-knife is the same as the cap knife.

Therapeutic endoscope

Multi-bending scope: Some tumor locations make it difficult to carry out EMR using a conventional scope. There include the lesser curvature or posterior wall of the gastric body, and the cardia. To facilitate EMR of tumors at these locations, a two-channel scope with two independently curving segments, that is, a Multi-bending scope (the 'M-scope') was developed[41]. The M-scope consists of a distal flexible segment that can bend in any of the four major directions and a proximal flexible segment that can bend in two directions. Combined operation of the segments allows the operator to obtain a variety of visual fields, to randomly approach or recede from the lesions, and to obtain an en face view.

Multi-bending double-channel therapeutic endoscope: The multi-bending double-channel therapeutic endoscope (the 'R-scope') has been designed for lifting lesions and for improved dissection by the incorporation of two movable channels[42,43]. The R-scope has two movable instrument channels; one moving vertically and the other horizontally. The two instruments can be manipulated during the operation with a knob and a lever that surrounds the angulation control knobs of the R-scope.

Vibration endoscope: The author attempted to increase the efficiency of endoscopic treatment techniques by vibrating the endoscope itself. The vibration used must be at a frequency that ensures safety when applied to the body. Examples of inventions that are made effective by adding safe vibration to the body are vibrating oral care devices developed to clean between the teeth and

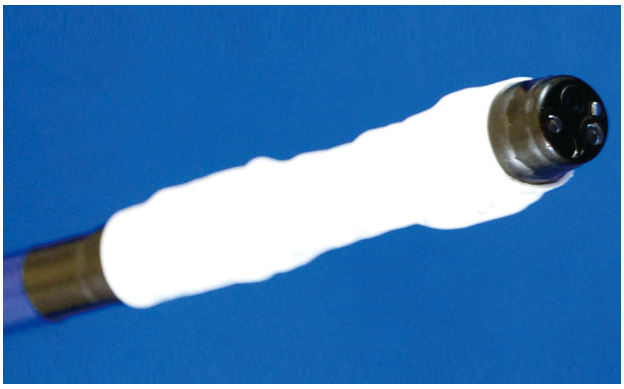

Figure 10 Vibration endoscope.

manual multiple-blade shavers with vibration added to increase cutting efficiency. The latter is a commercial product in which vibration successfully raises cutting efficiency without harming the skin, even though the blades cut whiskers in direct contact with the face (M3 Power; Gillette, Japan; Figure 1). An endoscope with an incorporated eccentric motor was therefore developed and used in conducting ESD. The vibration endoscope comprised a modified commercial endoscope (GIF-Q200; Olympus). First, the covering plastic of the tip and the metal mesh were stripped off. After exposing the interior, a vibration motor (J71; Shicoh, Japan) fitted within a cylinder was attached and this section was covered using heat-shrinkable tubing (Figure 10)[44].

Mean procedure durations for circumferential incisions, submucosal dissection or a combination of both were significantly shorter when vibration at 10 000 rpm was applied, compared to procedures without vibration. When performing peripheral incisions and submucosal dissection with a knife in ESD, the time for the procedure can also be reduced by adding vibration. This device has not yet been used in human patients.

Traction methods

Magnetic anchor system: The magnetic anchor (Pentax, Tokyo, Japan) consists of 3 parts: a hand-made magnetic weight, made of magnetic stainless steel; microforceps; a

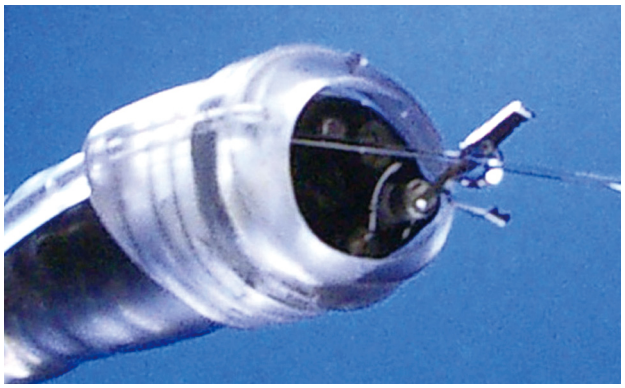

Figure 11 Irrigation cap (Type KUME) placed on the tip of the endoscope through clipping device.

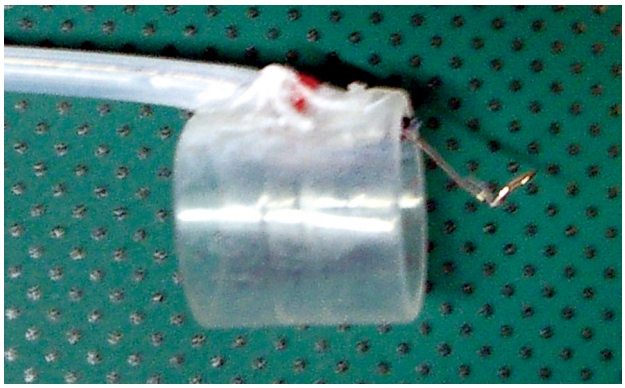

Figure 12 Coagula-irrigation hood (CI hood).

connecting thread. A weight is designed to facilitate gastric ESD by use of an extracorporeal hands-free electromagnet, whereby magnetic forces allow a suitable counter-traction for submucosal dissection[45].

Percutaneous traction: A small snare is introduced into the gastric lumen through a percutaneous gastric port (2-mm diameter) to grasp and pull the lesion away from the muscularis propria to facilitate resection[46].

External grasping forceps: In ESD using an external grasping forceps, oral traction applied with the external forceps can elevate the lesion and make the submucosal layer on the aboral side wider and more visible, thereby facilitating submucosal dissection under direct vision[47].

Water jet

Water jet endoscope: By washing the bleeding field with the water jet, the bleeding source can be immediately identified and coagulated, although in a small number of cases of erupting venous bleeding, identifying the bleeding source can be difficult.

Irrigation hood: The author developed an end hood that facilitates endoscopic hemostatic procedures while simultaneously allowing irrigation of the hemorrhage site. The end hood piece was fabricated by drilling a side hole in the cap portion of a conventional transparent hood, then the irrigation tube was glued to the exterior surface of the hole[11,12]. The fabricated transparent hood was placed at the tip of the endoscope. Based on this prototype, the irrigation hood (irrigation cap; Type KUME) was developed as shown in Figure 11 (Create Medic, Yokohama, Japan).

Hemostatic device

Coagula-irrigation hood (CI hood): The author developed a new type of hood, the "coagula-irrigation hood" (CI hood), which could simultaneously perform both coagulation and irrigation[48]. The CI hood was fabricated by installing a machined papillotomy knife in exchange for an irrigation tube on the irrigation hood (Figure 12)[11,12]. The tip of papillotomy knife was cut off and the tip of a wire was bent into a hoop. A CI hood was fabricated such that ESD and endoscopic hemostasis could be performed while simultaneously applying adequate coagulation and irrigation.

Fan devices

During resection, incision, and detachment using an endoscope, smoke is produced due to electrocautery. Accumulation of this smoke in the gastrointestinal (GI) tract impairs the visual field and makes continuation of the procedure difficult. The author therefore developed two types of new fan device that improve the visual field by circulating air without changing the air volume[49]. Both devices were created using a super-micro fan motor (Shiko, Japan). The first works by blowing air (Figure 13A), while the second uses ventilation (Figure 13B). This device has not yet been used in human patients.

Injection solutions

Injection solutions for elevation: Two types of solution are used for submucosal injection: isotonic solution (normal saline, hyaluronic acid); and hypertonic solution (hypertonic saline, glucose, Glycerol®)[36,50-53]. The advantages of hypertonic solution are better mucosal elevation and better hemostatic effect than normal saline. However, hypertonic solution is more likely to damage tissue in a resection sample, post-resection ulcer, or the surrounding mucosa compared with isotonic solution..

Hyaluronic acid solution makes a better long-lasting submucosal cushion than other available solutions without causing tissue damage[36,50].

Injection solution for submucosal dissection: The author reported a new method of ESD by submucosal injection of a jelly, which obviates the need for submucosal incision with a knife[54]. As the jelly is thick and viscous, the mucosal layer can be dissected from the muscular layer when it is injected into the submucosal layer.

Sodium carboxymethylcellulose (SCMC) is a water-soluble polymer derived from cellulose. When dissolved in water, it becomes very viscous, like a jelly. We used

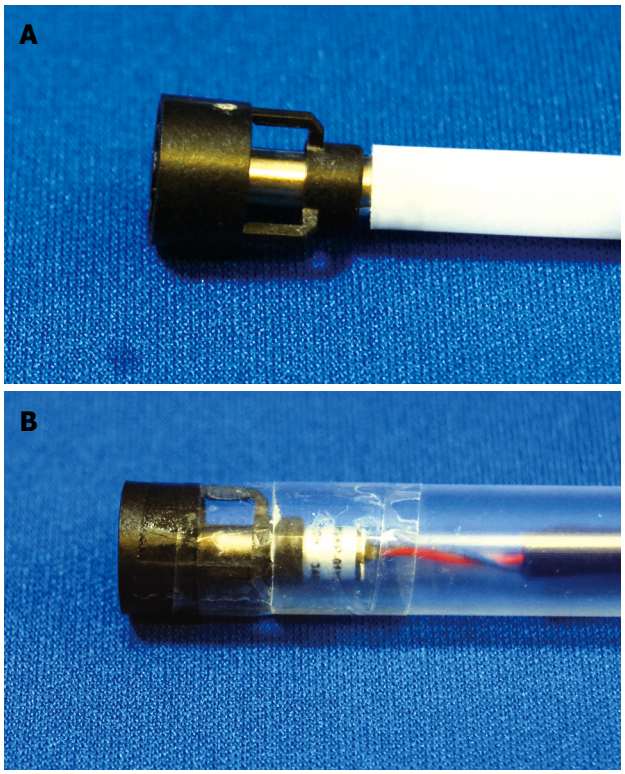

Figure 13 Endoscopic fan device. A: Blowing type; B: Ventilation type.

SCMC for ESD in porcine stomachs[55]. The mucosal layer was dissected from the muscular layer with submucosal injection of 2.5% SCMC.

EMR *VS* ESD

Advantages and disadvantages of EMR

A Japanese multicentre collaborative prospective study of endoscopic treatment for early gastric cancer found that if the diagnosis of intramucosal cancer [≤ 20 mm, UL (-)] from the specimen resected at initial EMR was histologically correct, then local cure could be achieved with EMR, including cases of recurrence, with appropriate follow-up and use of concomitant techniques such as piecemeal resection and coagulation therapy[56].

EMRC and EAM represent simpler and easier refinements of EMR methods[9]. The main advantage of these techniques is that a standard endoscope can be used and only one endoscopy assistant is required to close the snare. However, two potential disadvantages of the EMR technique have been identified[57-59]. First, aspiration of the centre of the lesion into the cap may be difficult to ensure as it is often tethered down by a submucosal desmoplastic reaction. The mucosa which readily moves into the cap on aspiration may represent normal surrounding mucosa, while the centre of the lesion can be more difficult to aspirate. Second, ensuring that the lesion has been completely removed with an adequate clear margin of 1 cm remains the responsibility of the endoscopist. Reconstituting lesions removed piecemeal by this approach may be impossible.

On the other hand, the author reduced the disadvantages of both EMRC and EAM[13-17,21,23]. In fact, a high rate of en bloc resections of lesions < 20 mm in diameter has been achieved with the EMRC and EAM[13-16].

Compared with ESD, EMR is easier to perform and requires less time for treatment. For example, mean procedure time using the author's device is < 20 min[13-16]. The longer the procedure time, the greater the potential disadvantages for high-risk patients (greater age or poor cardiopulmonary status). Moreover, the feasibility and safety of ESD by less-experienced endoscopists have not been evaluated. Under these conditions, a good alternative method to ESD is needed.

In conclusion, intramucosal cancer less than 20 mm in size and with no ulceration is considered appropriate for EMR.

Advantages and disadvantages of ESD

ESD enables the treatment of even large ulcerative lesions and lesions with scarring, and a high en bloc resection rate (> 90%) has been reported in several Japanese studies[5,28,60-62]. A recent trend has been seen with the selection of ESD as an effective and safe endoscopic treatment method for all GI neoplasms. With accurate pathological evaluation by en bloc resection through ESD, the endoscopist can reach a decision about complete resection or curative resection as a complete therapeutic option for early gastric neoplasms. However, this highly technical procedure needs a high level of expertise and experience to correctly perform the submucosal dissection and to promptly control any procedure-related complications.

ESD procedure time is one important drawback. A long procedure can be followed by unwanted clinical complications related to premedication or heavy stress for patients. To reduce this time, various advances have been made in submucosal injections, knives, other accessories, and well-equipped electrocoagulation systems[24-55]. ESD procedure time is increased in cases with ulceration, scarring, a large lesion, or location in the upper portion of the stomach[63]. The large upper portion of the stomach region has a large vascular network, resulting in technical difficulty in the approach to dissection or control of bleeding, all of which increases the procedure time. Multi-bending endoscopy can be used to minimize technical difficulty[41]. In cases of recurrent lesion or a lesion with an accompanying scar, the endoscopist needs to dissect very carefully, as a thin submucosal cushion and hard fibrotic tissue both make dissection difficult to perform without perforation.

The comparison of outcomes between conventional EMR and ESD would obviously be better evaluated in a prospective randomized trial. Such a study, however, is difficult to conduct outside of Japan, as the incidence of early gastric cancer is extremely low in other parts of the world.

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S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.32

World J Gastrointest Endosc 2009 October 15; 1(1): 32-38
ISSN 1948-5190 (online)

REVIEW

Endoscopic submucosal dissection for colorectal neoplasms

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Received: March 3, 2009 Revised: March 31, 2009
Accepted: April 7, 2009
Published online: October 15, 2009

Key words: Colorectal neoplasm; Early colorectal cancer; Endoscopic submucosal dissection; Endoscopic mucosal resection; Endoluminal surgery

Peer reviewers: Zvi Fireman, MD, Associate Professor of Medicine, Head, Gastroenterology Department, Hillel Yaffe Medical Center, Hadea 38100, Israel; G Payeras Llodrá, MD, Department of Digestive Diseases, Division of Endoscopy, Hospital Infanta Elena, Madrid 28340, Spain

Fujishiro M. Endoscopic submucosal dissection for colorectal neoplasms. *World J Gastrointest Endosc* 2009; 1(1): 32-38 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/32.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.32

Abstract

Although endoscopic submucosal dissection (ESD) gains acceptance as one of the standard treatments for esophageal and stomach neoplasms in Japan, it is still in the developing stage for colorectal neoplasms. In terms of indications, little likelihood of nodal metastasis and technical resectability are principally considered. Some of intramucosal neoplasms, carcinomas with minute submucosal invasion, and carcinoid tumors, which are technically unresectable by conventional endoscopic treatments, may become good candidates for ESD, considering substantial risks and obtained benefits. ESD as a staging measure to obtain histological information of the invasion depth and lymphovascular infiltration is acceptable because preoperative prediction is difficult in some cases. In terms of techniques, advantages of ESD in comparison with other endoscopic treatments are to be controllable in size and shape, and to be resectable even in large and fibrotic neoplasms. The disadvantages may be longer procedure time, heavier bleeding, and higher possibility of perforation. However, owing to refinement of the techniques, invention of devices, and the learning curve, acceptable technical safety has been achieved. Colorectal ESD is very promising and become one of the standard treatments for colorectal neoplasms in the near future.

INTRODUCTION

Endoscopic submucosal dissection (ESD), which first developed in the stomach, is a new endoluminal therapeutic technique involving the use of cutting devices to permit a larger resection of the tissue over the muscularis propria[1]. The technique has also spread to other organs in the gastrointestinal tract[2].

In comparison with endoscopic mucosal resection (EMR), ESD needs very experienced hands because of its far more complex procedural sequence. However, the obtained outcomes seem to be more advantageous especially for early-stage neoplasms with a large size or submucosal fibrosis, although long-term data are still lacking. Additionally, by using ESD technique, the resected area can be precisely controlled by the operators, which may not only lead to complete removal of even large lesions, but also to the least non-neoplastic mucosal resection. In this review, the present indications, techniques, and outcomes of colorectal ESD were described including our experiences for further development of this wonderful technique.

INDICATIONS

Two aspects are considered to determine the application

of ESD for each lesion by each operator. The first is a little likelihood of lymph node metastasis and the second is the technical resectability. The former has been determined by the large numbers of surgically resected cases in each organ before establishment of ESD and the latter may be determined by the applied technique, the expertise of the operators, the location of the lesions or their characteristics[3].

Aspects of nodal metastasis

From the large numbers of surgically resected colorectal cases, intramucosal carcinomas and those with slight submucosal invasion (< 1000 micrometers below the muscularis mucosa; sm1) without lymphovascular infiltration have little risk of nodal metastasis[4].

Tumor morphology and surface pit pattern are good endoscopic indicators for submucosal invasion. From this aspect, depressed lesions, laterally spreading tumors of non-granular type (LST-NG) and large protruding tumors are considered as good candidates for ESD because these lesions have a high risk of submucosal invasion, which may be difficult to diagnose preoperatively, and a thorough histopathological assessment of the resected specimen is essential. It is controversial whether one should perform ESD or piecemeal EMR for laterally spreading tumors of granular type (LST-G), because most lesions are intramucosal and the endoscopic prediction of invasiveness is highly feasible[5]. To obtain the above information, magnification chromoendoscopy or narrow band imaging endoscopy is very useful.

Technical aspects

In terms of technical resectability, *en bloc* resection is more desirable than piecemeal resection for accurate assessment of the appropriateness of the therapy, because the depth of invasion and lymphovascular infiltration of cancer cells (that are considerable risk factors for nodal metastasis) are not accurately assessed by piecemeal resection. Almost all possible node-negative lesions can be resected *en bloc* by ESD, when very experienced hands treat them. This does not mean that all endoscopic resection should be performed as ESD. Polypectomy or EMR is beneficial for patients with pedunculated neoplasms or small neoplasms because of the little invasiveness. If the lesions are apparently premalignant neoplasms, piecemeal resection by using EMR may be permissible with the best balance of risks and benefits[6]. Surgical organ resection with lymphadenectomy should be applied to those neoplasms with high probability of positive lymph nodes or failure in complete removal by ESD. Recurrent lesions can be also indicated for ESD, if they fulfill the criteria of no nodal metastasis, but indication should be carefully determined considering the risks of accompanying complications[7].

Even for lesions that meet the node-negative criteria, laparoscopic or open surgery may be selected in some institutions considering the location and size of the lesion. The rectum is fixed to the pelvis, therefore the endoscope is more easily maneuvered than in other locations of colorectum. Furthermore, panperitonitis may be less likely, even if the muscularis propria is torn, although penetration leads to air accumulation in the retroperitoneal space, which may then spread to a wider area[8,9]. On the other hand, there are several tortuous folds in the colon. Peristalsis and residual feces may sometimes disturb ESD procedure. So it is commonly believed that the technical difficulty of colon ESD exceeds those of the stomach, the esophagus, and the rectum, although there are many differences.

Carcinoid

Carcinoids are classified based on organ site and cell of origin and occur most frequently in the gastrointestinal tract (67%) where they are most common in small intestine (25%), appendix (12%), and rectum (14%)[10]. In the colorectum, those in the appendix should be treated by laparotomy considering risks and benefits. Rectal carcinoids < 2 cm in size may become candidates of ESD, because those rarely metastasize[11], although another group revealed that colorectal carcinoids < 1 cm without lymphovascular infiltration could be curatively treated by local resection, but others would need radical nodal dissection[12].

However, almost all lesions less than 1 cm in size are treatable by using band ligation resection[13] or cap-technique[14] and the application of ESD for carcinoids may be limited. When the lesions are in intermediate size, such as 1-2 cm, or invade massively the submucosal layer, which may result in tumor-positive margin resection, ESD should be applied[15,16].

TECHNIQUES

The operation is performed in in-patients setting. The day before ESD, the patients eat only low fiber diet and 10 mL of 0.75% sodium picosulfate solution is prescribed before bed. In the early morning of the operation, 10 mg of mosapride citrate and 2 L of an isotonic polyethylene glycol electrolyte solution are used for bowel preparation.

The techniques of ESD are slightly different according to the individual operators at different hospitals, although main procedural sequence is quite similar. In our hospital, the ESD is recently carried out using a slim, single-channel, and high-definition endoscope with the water-jet system (e.g. GIF-Q260J, PCF-Q260J, Olympus; EG-2990i, EC-3890i, HOYA Pentax) and a high-frequency generator with special cutting (ENDOCUT mode) and coagulation (swift coagulation mode) current (VIO 300D, ERBE Elektromedizin GmbH, Tübingen, Germany). If the lesion is located within the distance where upper gastrointestinal (GI) endoscopes can reach, application of these upper-GI endoscopes is also preferable to using a slim colonoscope, because they have greater maneuverability. The transparent attachment is fitted on the tip of the endoscope mainly to obtain a constant

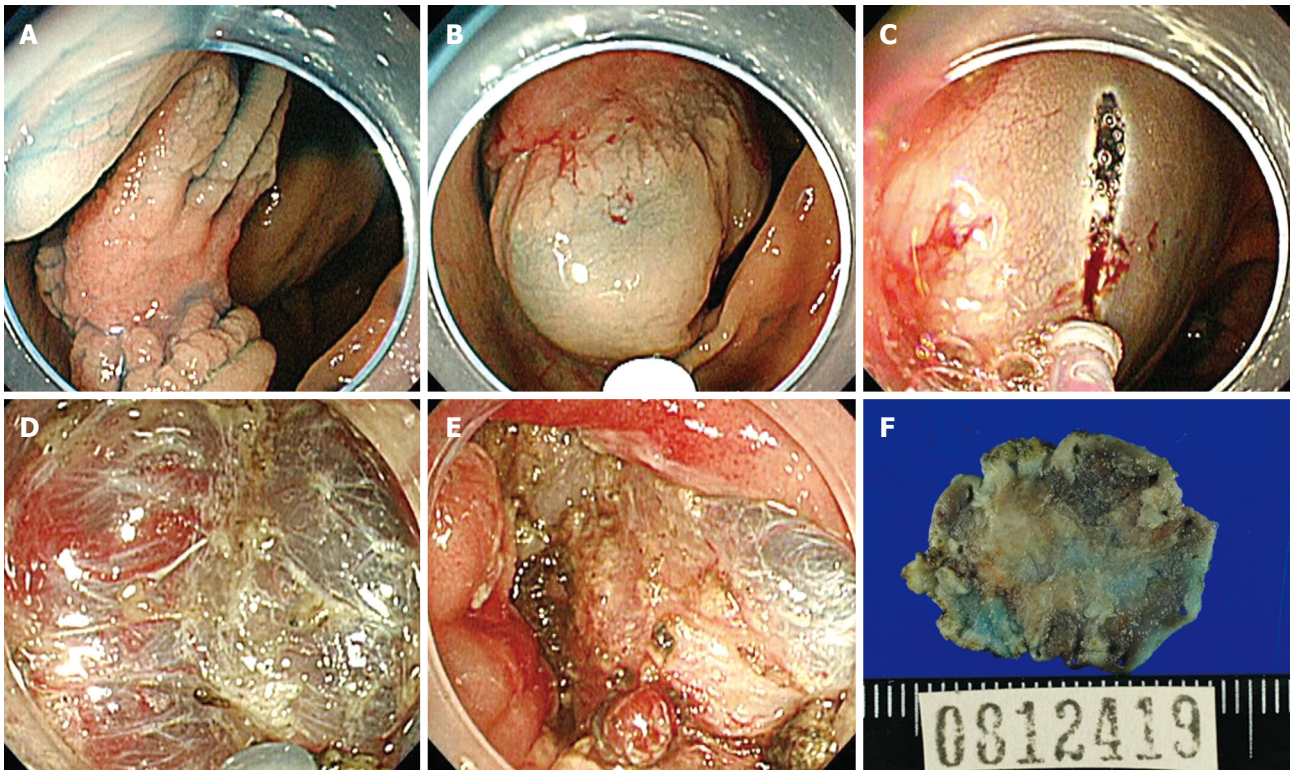

Figure 1 Colorectal endoscopic submucosal dissection. A: Chromoendoscopy; B: Submucosal injection; C: Mucosal incision; D: Submucosal dissection; E: Mucosal defect; F: Resected specimen.

endoscopic view and to create tension on the connective tissue for the submucosal dissection. The representative procedural sequence is shown in the Figure 1.

Marking around the lesions

Markings are not made because the margins of the lesions are clearly identified and the colorectal wall is thin enough to perforate only by marking.

Creating a submucosal fluid cushion

The solution is colored in slight blue with mixture of a small amount of indigocarmine. The first injection, about 1 mL in volume, to create an initial bulge where the first mucosal incision should be made should be done with normal saline in order to place hyaluronic acid in the appropriate submucosal layer. After confirming the right needle depth, additional injection by using hyaluronic acid is followed[16-19]. The volume of injection is about 2 mL at one time, and injection is repeated several times before starting mucosal incision, until the targeted area is lifted enough. It is important to count the volume of injection loudly every 0.2 mL so that the operator can determine whether the injection is working effectively. Complete marginal cutting of the mucosa before submucosal dissection is not necessary; mucosal incision and submucosal dissection are repeated several times before marginal cutting is complete. After exposure of the submucosal layer, additional submucosal injection is needed to lift up the layer you intend to cut. The total injection volume to complete ESD is from 20 mL to 60 mL according to the lesion size.

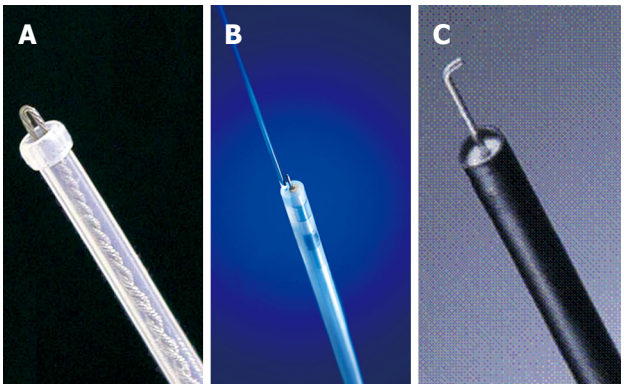

Figure 2 Electrosurgical knife. A: Flex-knife; B: Splash-needle; C: Hook-knife.

Incising the mucosa outside the lesion

After the lesions are lifted, a mucosal incision is made with a flex-knife[20] or a splash-needle[21] (Figure 2). The knife is fixed at a length of 2 mm and gently pressed onto the mucosa to produce a cutting effect using the ENDOCUT I mode (effect 1 duration 3 interval 3) for a flex-knife or the ENDOCUT Q mode (effect 3 duration 1 interval 3) for a splash-needle. The distal half of the mucosal incision is completed first, followed by the proximal half. If the mucosal incision reaches below the muscularis mucosa, the submucosal layer dyed blue by the injected

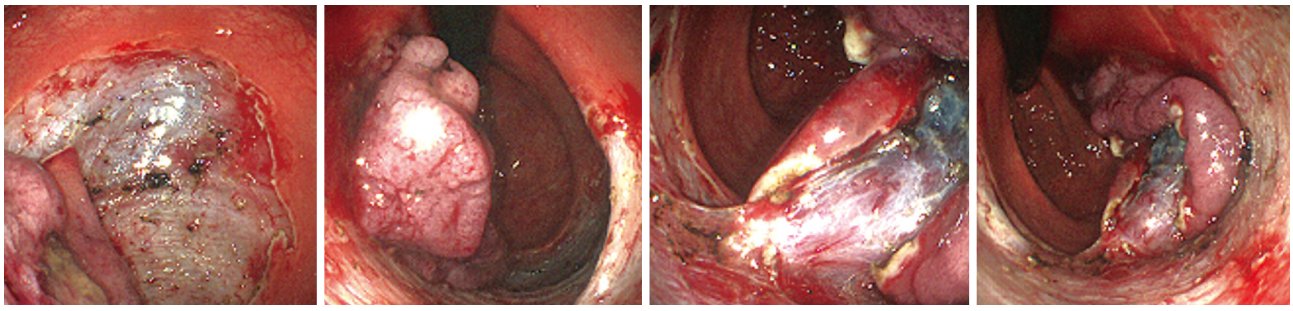

Figure 3 Use of gravity by changing patient's position.

fluid comes into sight. If the blue submucosal layer does not appear, it means that the muscularis mucosa has been cut incompletely. In this situation, the incising line is traced again until the blue submucosal layer comes out. The starting point for cutting depends on the location of the lesions. Principally, it is recommended to start cutting distally from the endoscope. Retroflex positioning of the endoscope is usually used, if possible, in the cutting of a distal part, but cutting is also done in the straight position when retroflex positioning being impossible. As the submucosal injection solution retained in the submucosa comes down toward the ground, it is better to start cutting from an opposite part of the ground as well as a distal part or put the lesion on an opposite part of the ground if the patient's body positions are changeable.

Dissecting the submucosal layer beneath the lesion

Small lesions can be resected with an electrosurgical snare only after circumferential mucosal incision without submucosal dissection. However, large lesions, lesions with submucosal fibrosis, or lesions located in a tortuous area cannot be resected by an electrosurgical snare, which means dissecting the submucosa completely. Dissection of the submucosa is begun from the proximal area to the distal end. The principle knife used for the submucosal dissection is the same length as that used for the mucosal incision using swift coagulation mode (effect 4, output 40W) for a flex-knife or forced coagulation mode (effect 3 output 30W) for a splash-needle, and in difficult dissections the hook-knife in swift coagulation mode (effect 4, output 40W) is also used in combination with the principle knife[22]. To control bleeding, a pair of hemostatic forceps (SDB2422, HOYA Pentax) is used in soft coagulation mode (effect 5, output 50W)[23]. The device has a narrow opening angle, a small cup, and a blunt edge, which looks similar to a pair of small-sized hot-biopsy forceps. After pinpoint holding and mechanical compression, electrocoagulation is easily performed to obtain hemostasis. The water-jet system supplies a continuous jet of water at high pressure, which easily and swiftly washes away any blood obstructing the visual field, allowing identification of the vessel that is bleeding. Gravity is used for submucosal dissection by changing the patient's body positions (Figure 3). The lesions should be positioned opposite to the ground because the detached parts of the specimen come down and the connective tissue in the submucosa to be dissected is stretched enough to enable an easy and safe dissection. The injected solution in the submucosa leaks out gradually after mucosal incision, and the submucosal cushion flattens down with time. Thus, it is important to start dissecting the submucosa immediately from the incising part of the mucosa before marginal mucosal cutting.

Management after endoscopic submucosal dissection

After resection of the lesion, visible vessels of the resulting artificial ulcer are also treated with the hemostatic forceps to prevent delayed bleeding, but it is also kept in mind that the intensive coagulation of visible vessels on the exposed muscle layer may cause delayed perforation. So it is advisable to use hemoclips to treat these vessels.

Three hours after the ESD, patients are permitted to drink a small amount of water with bed rest. The next day, if the patient's symptoms, laboratory findings, and chest X-ray are unremarkable, a light meal and walking is permitted and the patients are discharged within 1 wk. If complications occur, the schedules are changed according to the individual patient's conditions.

OUTCOMES

In comparison with outcomes of other endoscopic treatments, those of ESD are extremely good and promising as shown in the Table 1[15,20,24-31]. The *en bloc* resection rate is around 90% even if the mean tumor size is more than 20 mm. Although the *en bloc* + R0 (tumor free margins) resection rate is lower, the marginal cutting around the lesions before submucosal dissection results in extremely lower rates of local recurrence. Longer operation time (mean 61-110 min) and complications may become disadvantages. Perforation is a major complication related to ESD, which is experienced in around 5% of cases. Immediately recognized perforation can be successfully sealed with endoclips and conservatively observed without emergency laparotomy by antibiotics and no feeding for a few days in almost all cases[32]. However, in some cases of perforation, especially delayed perforation, emergency laparotomy is necessary. Bleeding is the most common complication in the stomach, but in case of colorectum, the complication occurs less frequently and is typically minor and treatable with colonoscopy.

Table 1 Outcomes of colorectal endoscopic submucosal dissection

Authors	Year	Organ	Total cases	Mean size (mm)	Operation time (min)	*En bloc* resection (%)	En bloc + R0 resection (%)	Local recurrence (%)	Bleeding (%)	Perforation (%)	emergency surgery (%)
Yahagi *et al*[20]	2004	Colorectum	146	35.8	-	91.1	-	-	-	-	-
Fujishiro *et al*[24]	2006	Rectum	35	32.8	-	88.6	62.9	3.1	0.0	5.7	0.0
Onozato *et al*[15]	2007	Rectum	35	26.2	Median, 70	73.3	70.0	0.0	0.0	2.9	0.0
Fujishiro *et al*[25]	2007	Colorectum	200	29.9	-	91.5	70.5	1.8	1.0	6.0	0.5
Tamegai *et al*[26]	2007	Colorectum	71	32.7	Mean, 61	98.6	95.6	0.0	0.0	1.4	0.0
Saito *et al*[27]	2007	Colorectum	200	35.0	Median, 90, Mean, 110	84.0	70.0	0.6	2.0	5.0	0.5
Tanaka *et al*[28]	2007	Colorectum	70	28.0	Mean, 71	-	80.0	0.0	1.4	10.0	2.9
Hurlstone *et al*[29]	2007	Colorectum	42	30.7	Median, 48	78.6	73.8	11.0	12.0	2.4	0.0
Toyonaga *et al*[30]	2008	Colorectum	361	-	-	-	98.3	-	0.8	2.2	0.6
Zhou *et al*[31]	2009	Colorectum	74	32.6	Mean, 110	93.2	89.2	0.0	1.4	8.1	1.4

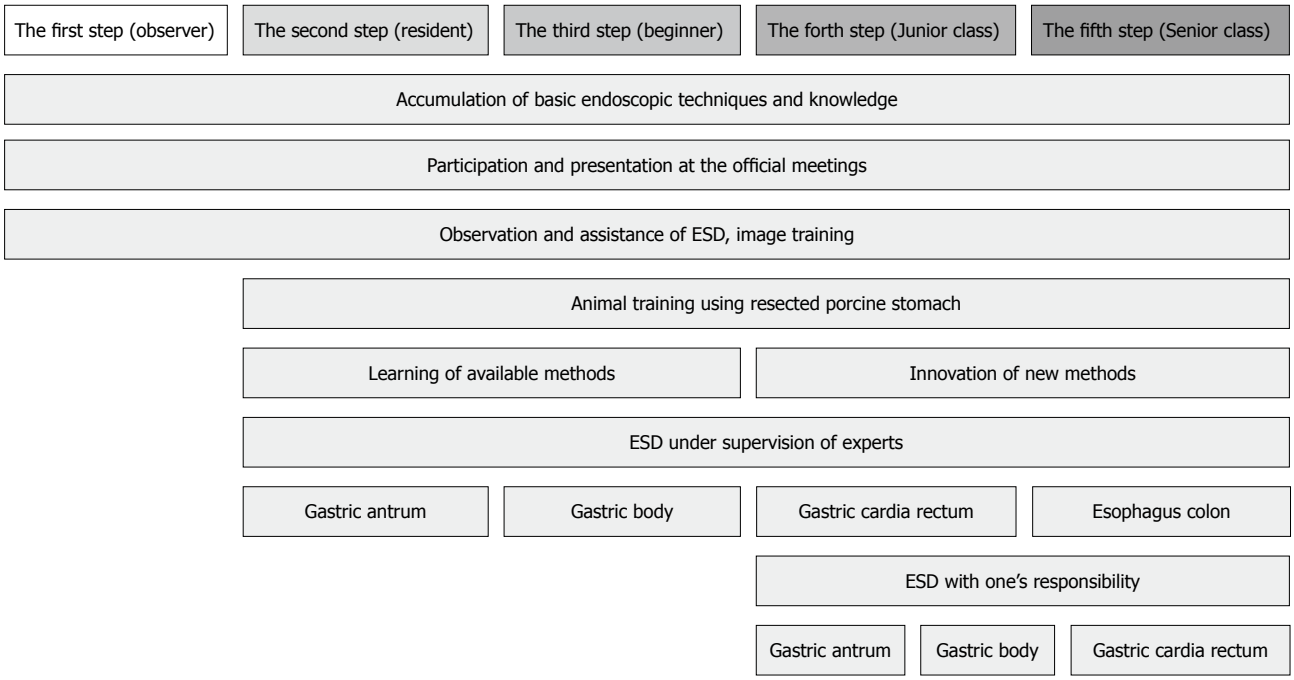

Figure 4 Proposal of training for endoscopic submucosal dissection.

FUTURE PERSPECTIVES

Because of the remarkable progress in the endoscopic technologies, ESD is applicable in the colorectum with promising results as well as the stomach[33] and the esophagus[34]. However, there is still a room for innovation. Our major concerns are (i) expansion of indications owing to novel knowledge for node-negative cancer, (ii) technical innovation for quicker and safer techniques, and (iii) training system to spread the technique.

In terms of indications, the criteria of node-negative cancer are only obtained by histological evaluation with hematoxylin & eosin staining of surgically-resected materials so far, which revealed that depth of cancer invasion and lymphovascular infiltration of cancer cells are major determinants of nodal metastasis. However, we have to notice that the incidence of nodal metastasis from submucosal invasive cancers is at most 10%[35], which means that the rest of cases might be cured by local treatment including ESD. In the near future, we expect that unnecessary laparotomy will be avoidable, by using novel predictive markers of nodal metastasis, for example, using gene analysis of biopsy samples or resected specimens by ESD. Furthermore, combination with chemo-/radio- therapy may achieve less invasive treatments instead of colectomy or rectal resection with lymph node dissection.

In terms of technical aspects, major drawbacks of ESD may be the long procedure time and its complexness, and then, that the obtained results are highly operator-dependent so far. Except for the rectum, tortuous structure and the peristalsis prevent from constant endoscopic view field and stability of the endoscope. So, the innovation regarding electrosurgical knives and submucosal fluid cushion is insufficient

to achieve the goal and we look forward to a big breakthrough regarding novel instruments or endoscopes, which enable us to perform precise cutting easily and quickly without complications.

Until the above dream comes true, it is absolutely necessary to establish the training system to spread the present technique. Because ESD in the colon is far more difficult than that in the stomach, step-by-step approach, e.g. as shown in the Figure 4, which is performed in our university, is recommended. Among locations in the colorectum, it is preferable to start ESD from the rectum. The endoscopists who graduate from the fifth step can become experts and trainers for the next generation in our university.

In summary, colorectal ESD has already been established with favorable outcomes in the advanced institutions. We are convinced that colorectal ESD will become one of the standard treatments for early-stage colorectal neoplasms not only in Japan but also all over the world in the near future.

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S- Editor Li JL **L- Editor** Alpini GD **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.39

World J Gastrointest Endosc 2009 October 15; 1(1): 39-44
ISSN 1948-5190 (online)

REVIEW

Interventional endoscopic ultrasound: Therapeutic capability and potential

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Received: January 16, 2009 Revised: March 9, 2009
Accepted: March 16, 2009
Published online: October 15, 2009

Abstract

The linear echoendoscope, introduced in the 1990s, opened the era of interventional endoscopic ultrasound (IEUS). The linear echoendoscope enabled EUS guided Fine Needle Aspiration (EUS-FNA) allowing the path of the needle to be traced during the puncture process. After EUS-FNA, other interventional procedures were introduced in clinical practice. Tissue acquisition was the first EUS-guided interventional procedure and its higher diagnostic quality has undoubtedly been established. After EUS-FNA, Celiac plexus neurolysis (CPN) and block (CPB), pancreatic pseudocyst drainage, abdominal and mediastinal collections/abscesses drainage, and in selected cases, pancreatic and biliary ductal system drainage, were introduced in clinical practice. EUS-guided fine needle injection with local delivery of antitumor agents is considered a promising modality. We have reviewed published data on EUS guided interventional procedures with the object of summarizing the diagnostic capability of endoscopic ultrasound and elaborates in detail its therapeutic capability and potential.

Key words: Endoscopic ultrasound; Interventional endoscopic ultrasound; Endoscopic ultrasound guided fine needle aspiration; Endoscopic ultrasound-guided drainage; Endoscopic ultrasound-fine need injection

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Tarantino I, Barresi L. Interventional endoscopic ultrasound: Therapeutic capability and potential. *World J Gastrointest Endosc* 2009; 1(1): 39-44 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/39.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.39

INTRODUCTION

Linear echoendoscope, introduced in the 1990s, opened the era of interventional endoscopic ultrasound (IEUS). The linear echoendoscope enabled EUS guided Fine Needle Aspiration (EUS-FNA) allowing the path of the needle to be traced during the puncture process. Tissue acquisition was the first EUS-guided interventional procedure and the higher diagnostic quality of EUS-FNA has undoubtedly been established for other tissue acquisition modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) guided biopsy. After EUS-FNA, other procedures, including celiac plexus neurolysis (CPN) and block (CPB), pancreatic pseudocyst drainage, abdominal and mediastinal collections/abscesses drainage, and, in selected cases, pancreatic and biliary ductal system drainage, were introduced in clinical practice. Recently, EUS-guided fine needle injection with local delivery of antitumor agents (cellular therapy, gene therapy, alcohol injection, and radiofrequency ablation) has been considered a promising modality to treat solid and cystic tumors of the pancreas or other abdominal or mediastinal malignancies.

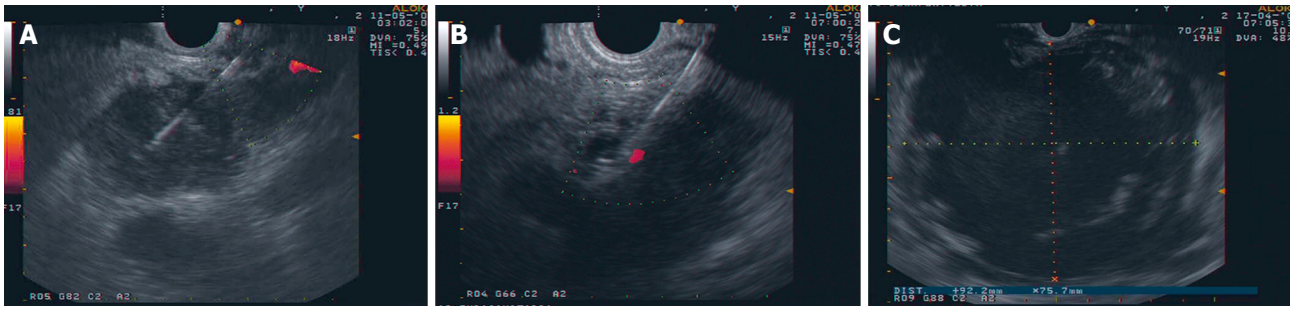

Figure 1 Images of interventional EUS. A: EUS FNA with a 22G needle on a solid pancreatic mass; B: CPN: the needle (19G) is inserted immediately adjacent to the lateral aspect of the aorta at the level of the celiac trunk; C: Large pancreatic collection seen from the posterior gastric wall.

This review summarizes the diagnostic capabilities of endoscopic ultrasound and elaborates in detail its therapeutic capability and potential.

EUS-FNA

The diagnostic utility of EUS-FNA has been clearly established. EUS-FNA is a simple, cost-effective, and versatile technique that has been adapted for the diagnosis of gastrointestinal tract lesions as well as other organ sites[1]. Compared to other techniques, EUS-FNA has the advantage of being able to detect lesions not clearly visualized by other imaging tests[2]. Indications for EUS-FNA are numerous: intra-abdominal and mediastinal lymph nodes[3], pancreatic masses[4], pancreatic cysts[5,6], and gastrointestinal sub-mucosal masses[7]. The major advantage is documented in case of failure of other biopsy techniques[1]: EUS-FNA performed after other unsuccessful diagnostic attempts can provide a diagnosis in 85%-95% of cases[4,7,8]. Today, EUS-FNA is recommended as the primary modality in diagnosis of pancreatic masses, pancreatic cysts, and posterior mediastinal lymph nodes. As mentioned above, FNA performed under EUS requires a linear array echoendoscope, because the full length of the needle can be tracked in real time into the lesion. The use of color-Doppler avoids the accidental puncture of intervening vessels. Needles are designed to have a tip visualized by ultrasound. The needle comprises a protective plastic cover of the working channel, a handle at the proximal end allowing the needle to move out from the cover into the lesion, and a needle with a stylet that prevents contaminations with gut cells. Their are available in arrange of sizes (e.g. 19G, 22G and 25G). Trucut needles (19G) are also available and used for gastric sub-mucosal tumors and solid and cystic lesion of the pancreas[9]. The use of trucut needles is limited in the stomach due its stiffness. The real value of trucut needles is not well established, although in cases of insufficient sample with the EUS-FNA alone, the use of sequential trucut biopsy seems to improve the diagnostic power[10]. More recently, the echo-brush, a device that allows brushing on the EUS guide, has become available, although evidence of its effectiveness has not been published.

EUS-FNA is performed by positioning the target lesion on top of the ultrasound image. The correct positioning of the needle in the lesion is monitored in real time, intervening vessels are also visualized to avoid accidental puncture. The stylet is withdrawn, aspiration with a 10 mL syringe applied, and the needle moved back and forward several times (Figure 1A). Many centers offer on-site cytopathological adequacy evaluation; the main reason being the reduction of non-diagnostic specimens. Apparently, on-site evaluation increases the diagnostic yield by 10%-15%[11]. In a recent comparison between trained endosonographers in sample adequacy assessment and cytotechnologists, there was a significant difference in favor of cytotechnologists for adequacy assessment (P = 0.004) and preliminary diagnosis of benign vs. malignant (P = 0.001)[12]. The endosonographer's and pathologist's expertise, the type of lesion, the vascularization, and needle size all represent factors that impact on the diagnostic yield. However, the continuous feedback between the endosonographer and dedicated cytopathologist is mandatory to obtain diagnostic FNAs. Information on clinical condition and lesion characteristics are necessary for subsequent processing of the specimen, as are performance of ancillary studies to reach the definitive diagnosis, such as immunochemical staining, molecular analysis or genetic evaluation by PCR.

EUS-GUIDED CELIAC PLEXUS NEUROLYSIS AND CELIAC PLEXUS BLOCK

In the same way as FNA, the close proximity between the tip of the echoendoscope and the target organ allows therapeutic procedures, such as injection therapies, to be performed safely and effectively, when compared with radiologic or surgical procedures. The term CPN refers to the injection of alcohol in the celiac ganglion to induce neurolysis in patients with pancreatic cancer or other malignancies. The term CPB refers to the injection of steroids to inhibit celiac ganglion function in benign conditions, such as the chronic pancreatitis. However, many use the term without distinction. CPN has been established as an effective technique to improve pain control in patients with pancreatic carcinoma. The effectiveness of surgical CPN with injection of absolute

alcohol in the celiac plexus was confirmed by prospective randomized trials[13]. Similar results were demonstrated for percutaneous injection guided by CT[14,15]. There are several advantages of using EUS *vs* a CT-guided percutaneous approach: the proximity of the posterior lesser curve of the stomach to the celiac plexus, the use of continuous real time visualization of the target area, and the color-Doppler to avoid accidental puncture of vascular structures. The needle (19G or 20G) is inserted under EUS guidance immediately adjacent to the lateral aspect of the aorta at the level of the celiac trunk. For CPN, 10 mL of bupivacaine (0.25%) followed by 10 mL of alcohol (98%) are injected. The process can be repeated in the other side of the aorta. For CPB, a steroid (triamcinolone suspension 40 mL bilateral or 80ml unilateral) is used in place of alcohol (Figure 1B). Evidence suggest EUS-guided CPN is a safe and effective procedure with a significant response in term of reduction of pain and opioid intake[16]. The efficacy data for CPB in treating pain for chronic pancreatitis are less well established, with a transient response in about 50% of patients[17]. However, recent recognition that celiac ganglia can be visualized by EUS in almost 81%[18] of patients, allows the performance of direct CPN and CPB on the ganglia thus significantly improving results for both CPN and CPB[19]. Further studies are needed to establish the real efficacy of CPB in chronic pancreatitis with this direct injection.

EUS-GUIDED PANCREATIC COLLECTIONS DRAINAGE

The therapeutic options for treating pancreatic pseudocysts, abscesses and necrosis, include surgery, percutaneous drainage, and trans-mural non-EUS-guided or EUS-guided drainage. The success rates and complications of these different approaches were analyzed in a review: the success rate for surgical, percutaneous, non EUS-guided and EUS-guided trans-mural drainage were 100%, 84%, 90%, and 94%, respectively. The rate of complications were 28%-34% with 1%-8.5% mortality for surgery, 18% with 2% mortality for percutaneous drainage, 15% with 0% mortality for trans-mural non EUS-guided drainage, and 1.5% with 0% mortality for EUS-guided trans-mural drainage[20]. In the 1980s, reports by Sahel *et al*[21] and Cremer *et al*[22] showed the feasibility and efficacy of trans-mural drainage for treating pancreatic fluid collection. The limitation of trans-mural non-EUS-guided drainage is its relatively blind approach: in this way, no bulging collection can be drained due to the risk of perforation, and hemorrhages take place in about 6% of cases[23]. EUS-guided trans-mural drainage improves both the safety of the trans-mural procedure and the number of candidates for this treatment. Real time EUS visualization with Doppler allows the puncture of collection in patients without bulging and in patients with portal hypertension with multiple collateral vessels[24-28]. The positioning is also selected based on EUS evaluation of the distance between the gastrointestinal wall and cyst wall that should be less of one cm. EUS-guided drainages are performed with a linear array echoendoscope, the color Doppler used to identify regional vessels, the puncture is performed with a 19G needle and a guide-wire introduced through the needle and coiled within the collection under fluoroscopic guidance. The tract is sequentially dilated and finally the stents are placed (double pigtail, nose-cystic tube, plastic stents) (Figure 1C). The higher technical quality of EUS-guided over non-EUS-guided trans-mural drainage of pancreatic collections has been clearly demonstrated by two reports[28,29]. More recently, a randomized trial comparing EUS and EGD for trans-mural drainage showed a higher technical success rate of EUS than EGD and a superior safety profile of EUS-guided drainage, although it was not statistically significant. Finally, major complications were observed in the group who underwent non-EUS-guided drainage[30].

With the same technique, other EUS-guided procedures, such as the trans-rectal drainage of pelvic abscess, are considered useful and safe[31].

EUS-GUIDED BILIARY/PANCREATIC DRAINAGE

Endoscopic Retrograde Cholangiopancreatography (ERCP) is the most appropriate technique for treating common bile duct and pancreatic duct stenosis secondary to benign and malignant diseases. Biliary and/or pancreatic duct cannulation and visualization are successful with ERCP in a high percentage of cases managed by experienced hands. Common causes of failure include complex peripapillary diverticula, prior surgery procedures (such as gastrectomy with Billroth Ⅱ anastomosis), tumor involvement of the papilla, biliary sphincter stenosis, and impacted stones[32]. Percutaneous transhepatic cholangiography (PTC) and surgery are alternative approaches to access and drain obstructed ducts. Since 1996, when Wiersema *et al*[33] first described EUS-guided bile duct puncture, several case reports have been published on EUS-guided biliary and pancreatic duct puncture and drainage[34-42]. These case reports illustrate different techniques to approach bile and pancreatic ducts: transgastric or transduodenal puncture, rendezvous after positioning a guide wire through the papilla, or creating a new papilla by fistula formation.

The puncture is performed with 19G or 22G needles and the positioning is selected based on EUS evaluation of the distance between the gastrointestinal wall and the bile or pancreatic duct over the stricture (Figure 2). After puncture, bile or pancreatic juice is aspirated and iodine contrast injected to obtain a cholangiogram/pancreatogram; a 0.018-inch guide wire is positioned in the duct and the rendezvous procedure is attempted. The wire is captured with a snare and pulled out of the EUS-scope, which is replaced with a standard duodenoscope. When the wire fails to pass through the papilla in the duodenal lumen, a new papilla can be created by precut,

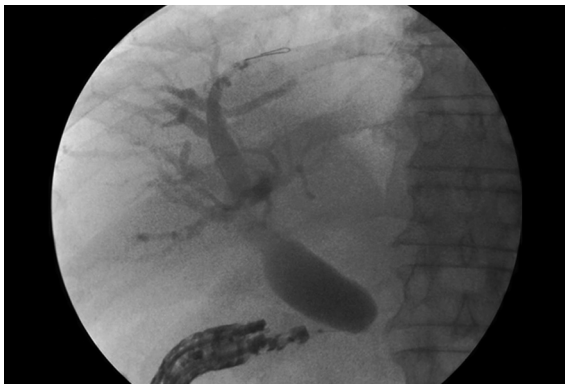

Figure 2 EUS-guided cholangiography through the duodenal wall.

and pneumatic dilatation is performed with a biliary balloon dilatation catheter. Finally, a plastic stent is placed. In all these reports, interventional EUS proved feasible and safe with a low complications rate; however, only few series have been published. Kahaleh *et al*[43] recently described a series of 23 patients treated with interventional endoscopic ultrasound cholangiography (IEUC). Biliary decompression was accomplished in over 90% of the cases that had previously received ERCP without success. In one of such case, bile leakage occurred using the extrahepatic approach. We describe a series of consecutive patients in whom ERCP failed for different reasons and IEUC was applied instead of the traditional percutaneous approach. Our series of nine patients confirmed the feasibility and safety of EUS-assisted procedures[44]. In our opinion, in the extrahepatic approach, the stent placement prevents the bile leakage.

Recently, EUS-guided transmural cholecystostomy was described in nine high-risk patients with severe acute cholecystitis at high operative risk for immediate cholecystectomy. The report showed that the procedure was feasible and safe as an initial, interim, or even definitive treatment of patients[45].

These techniques however, are currently restricted to expertise centers dedicated to biliopancreatic therapy.

EUS-GUIDED ANTI-TUMORAL THERAPY

EUS-guided FNI is emerging as an attractive delivery method for antitumor agents. This technique is the latest development in interventional ultrasound and seems particularly promising in the treatment of cystic and solid pancreatic lesion. Two reports described this EUS-guided treatment by alcohol injection on adrenal gland metastasis[46] and by TNFerade injection on metastatic lymph nodes[47]. The first study on the treatment of solid pancreatic lesions assessed the feasibility and safety of EUS-direct injection of allogenic mixed lymphocyte culture (cytoimplant) in locally advanced pancreatic adenocarcinoma[48]. The technique of EUS-guided FNI was also applied to the delivery of antitumor viral therapy using ONYX-015, a replication selective adenovirus, with a deletion in the E1B-55kDa gene, which preferentially replicates in and kills malignant cells[49]. These experimental studies showed the feasibility and safety of these therapeutic procedures. More recent studies on TNFerade, used in combination with chemo-radiation in the treatment of locally advanced pancreatic cancer[50] and in patients with locally advanced esophageal cancer[47], showed good tolerability and seem to optimize long-term outcomes.

The ablation of pancreatic tissue by EUS-guided ethanol injection was recently proposed as an effective therapy for cystic pancreatic lesions. Despite recent advances in diagnostic modalities and molecular studies, substantial morphological overlap restricts the accuracy of differentiation of each cystic lesion, and consequently drafting a management plan. To date, surgical resection is recommended for malignant and potentially malignant lesions. Surgical resection carries significant morbidity. A pilot study showed that the ethanol lavage on cystic lesions of the pancreas allowed complete resolution in one third of patients, but with complete epithelial lining ablation in all resected specimen[51]. In an experimental study on a porcine model, Matthes *et al*[52] showed how the efficacy of the ethanol lavage is concentration-dependent. Recently, a prospective study on EUS-guided ethanol lavage with paclitaxel injection indicated that this method is safe, feasible and effective to treat pancreatic cystic tumors of the pancreas. This study found that 11 of 14 patients showed complete resolution and highlighted no significant complications[53]. These promising results indicate further studies are warranted involving larger populations and longer follow up. Ablative modalities such as radiofrequency (RF), cryotechnology and brachytherapy are widely used in oncology and an EUS-guided approach has been proposed. Goldberg *et al*[54] investigated the feasibility and safety of performing radiofrequency ablation in the normal pancreas of pigs. The results were positive in term of necrosis, and the authors concluded that management of small neuroendocrine tumors and unresectable solid tumors might be potential indications of this technique. More recently, Carrara *et al*[55,56] investigated the ability of a new flexible ablation device that combines bipolar radiofrequency with cryotechnology, into the porcine pancreas, liver and spleen. These studies demonstrated the feasibility, efficacy, and safety of EUS-guided transgastric application of the hybrid cryotherm probe in the porcine models.

However, these positive results need further systematic studies investigating the effect of EUS-guided RF in tumor tissues. Jin *et al*[57] evaluated the clinical efficacy and safety of EUS-guided interstitial implantation of radioactive iodine 125 seeds in twenty patients with advanced pancreatic cancer. There were no obvious complications following therapy, however, their preliminary data suggested improvement in pain, but no long-term survival benefit.

CONCLUSION

The role of EUS in therapeutic procedures continues to expand. The principles behind endoscopic ultrasound-

guided fine needle aspiration paved the way for the development of therapeutic endoscopic ultrasound. The endoscopic ultrasound-guided puncture of fluid collections, abscesses and obstructed biliary and pancreatic ductal systems facilitated the passage of guidewires, thus allowing therapeutic drainage procedures to be performed. Substances can be delivered by endoscopic ultrasound into targeted areas; an example where the EUS has a clear and define role is the celiac plexus block and neurolysis. There is also a potentially important role for EUS FNI therapies as part of the management strategy for unresectable cancer and for pancreatic cystic lesions.

Finally, EUS-guided techniques, such as the radiofrequency ablation, might evolve into routine procedures as soon as the necessary basic tools become commercially available.

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S- Editor Li JL **L- Editor** Stewart GJ **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.45

World J Gastrointest Endosc 2009 October 15; 1(1): 45-50
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

White light endoscopy, narrow band imaging and chromoendoscopy with magnification in diagnosing colorectal neoplasia

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Received: January 13, 2009 Revised: March 20, 2009
Accepted: March 30, 2009
Published online: October 15, 2009

Abstract

AIM: To evaluate the sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of 3 different techniques: high resolution white light endoscopy (WLE), Narrow Band Imaging (NBI) and Chromoendoscopy (CHR), all with magnification in differentiating adenocarcinomas, adenomatous and hyperplastic colorectal polyps.

METHODS: Each polyp was sequentially assessed first by WLE, followed by NBI and finally by CHR. Digital images of each polyp with each modality were taken and stored. Biopsies or polypectomies were then performed followed by blinded histopathological analysis. Each image was blindly graded based on the Kudo's pit pattern (KPP). In the assessment with NBI, the mesh brown capillary network pattern (MBCN) of each polyp was also described. The Sn, Sp, PPV and NPV of differentiating hyperplastic (Type Ⅰ & Ⅱ-KPP, Type Ⅰ-MBCN) adenomatous (Types Ⅲ, Ⅳ-KPP, Type Ⅱ-MBCN) and carcinomatous polyps (Type Ⅴ-KPP, Type Ⅲ-MCBN) was then compared with reference to the final histopathological diagnosis.

RESULTS: A total of 50 colorectal polyps (5 adenocarcinomas, 38 adenomas, 7 hyperplastic) were assessed. CHR and NBI [KPP, MBCN or the combined classification (KPP & MBCN)] were superior to WLE in the prediction of polyp histology ($P < 0.001$, $P = 0.002$, $P = 0.001$ and $P < 0.001$, respectively). NBI, using the MBCN pattern or the combined classification showed higher numerical accuracies compared to CHR, but this was not statistically significant ($P = 0.625$, 0.250).

CONCLUSION: This feasibility study demonstrated that this combined classification with NBI could potentially be useful in routine clinical practice, allowing the endoscopist to predict histology with higher accuracies using a less cumbersome and technically less challenging method.

Key words: High-resolution magnification endoscopy; Narrow band imaging with magnification; Chromoendoscopy with magnification; Colorectal polyp; Colorectal neoplasia

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Singh R, Owen V, Shonde A, Kaye P, Hawkey C, Ragunath K. White light endoscopy, narrow band imaging and chromoendoscopy with magnification in diagnosing colorectal neoplasia. *World J Gastrointest Endosc* 2009; 1(1): 45-50 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/45.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.45

INTRODUCTION

Improvements in the resolution of imaging in video endoscopy over the years have resulted in a tremendous increase in the polyp detection rate in the colon. Although encouraging, this phenomenon has unfortunately provided additional burden to the pathologist, as most polyps, which are either biopsied or removed, are non-neoplastic in nature[1]. The distinction therefore between non-neoplastic and neoplastic colorectal polyps *in vivo* and a suitable technique, which allows this differentiation, could increase the efficiency of treatment by eliminating the cost associated with unnecessary biopsies and the risk with polypectomies. Chromoendoscopy (CHR) has long been propagated as a technique that improves prediction of polyp histology. However, due to failure of standardisation and the very nature of CHR being labour intensive, the technique has not had widespread acceptance in routine colonoscopy practice especially in the West. Narrow Band Imaging (NBI) is a novel endoscopic imaging technique that has recently come to the forefront[2]. It relies on altering the normal red, green and blue optical filters in the light source of the video endoscopy system that are used to make up sequential coloured frames of an endoscopic image. The relative contribution of the longer wavelength and deeper penetrating red light is negated and the superficial penetrating narrowed spectral blue and green wavelengths are used instead. This results in enhancement of the surface mucosal morphology whereby the microvascular and microstructural pit patterns are visualised in greater detail. Incorporated into the endoscope, NBI is relatively simple to use, involving the activation of a switch thus enabling the endoscopist to obtain images, which simulate chromoendoscopy almost instantaneously during the procedure. We embarked on this study to evaluate 3 different techniques which could potentially be used in colorectal cancer (CRC) screening: conventional high resolution white light endoscopy (WLE), NBI and CHR, all with magnification in predicting hyperplastic, adenomatous and carcinomatous colorectal polyps.

MATERIAL AND METHODS

Patients

The study was approved by the Nottingham Research and Ethics Committee, UK. Patients undergoing colonoscopy for bowel symptoms, polyp surveillance and family history screening for bowel cancer were invited to participate in the study. All patients gave written informed consent.

Endoscopy equipment

All examinations were performed with the prototype NBI system (Olympus, Japan). This system is equipped with a red, green and blue (RGB) sequential illumination xenon light source (XCLV-260HP), a high resolution zoom colonoscope (CF-H260AZL/I), a video processor (XCV-260HP3P) and a high definition television monitor (Olympus OEV181H). The light source contains one rotating RGB filter and one NBI filter. The NBI filter can be placed between the RGB filter and the light source. It splits white light into two specific lights with narrowed bandwidths; blue (400-430 nm) and green (530-550 nm) while the contribution of the red light is taken out of the equation. This allows the blue and green lights, which have more superficial penetration to penetrate the superficial mucosal architecture leading to enhancement of both the pit patterns and vasculature. The insertion of the NBI filter between the RGB filter and the xenon lamp is achieved by activating a switch on the scope. The endoscopist can then alternate freely between WLE and NBI at any time. The magnification function is activated by depression of a lever on the colonoscope which activates a motorised zoom lens at the distal tip of the scope. The lever's location on the endoscope simulates the "raiser bridge" on duodenoscopes and is relatively easy to use. By altering the focal distance of the lens, a maximal magnification of up to 115X can be achieved. Prior to endoscopy, a black rubber cap/hood (MB-046 Olympus, Japan) was fitted and adjusted to a distance of 2 mm from the tip of the endoscope. This was performed by visualising a thin rim of the cap on endoscopic views once it had been snugly fitted to the tip. This made it possible for the endoscopist to fix the mucosa to the endoscope before applying the zoom mode. Optimal focus of the area of interest was thus easily obtainable using this technique and the endoscopist was able to focus in or hone out effortlessly.

Endoscopic examination

All patients were offered conscious sedation with intravenous Midazolam (2.5-5 mg) and/or Pethidine (25-50 mg). Bowel preparation was done with Senna tablets (80 mg) followed by Polyethylene Glycol (4 litres) the day prior to the procedure. All endoscopies were recorded using a Digital Video Cassette Recorder (Sony Mini DV GV-D1000E PAL). With such high magnification, it is imperative to visualise the mucosa clearly, hence liberal flushing was done with water mixed with a mucolytic agent, n-Acetylcysteine and a defoaming agent, Simethicone, during the procedure. If the colon exhibited excessive peristaltic activity, which interfered with the examination, an antispasmodic agent, Hyoscine butyl bromide (10-20 mg), was administered intravenously. Once a polyp was detected, it was examined in greater detail. Any overlying mucous or faeces was flushed with water until the mucosal surface of the polyp was clearly visualised. Each lesion was then evaluated sequentially first by WLE, then NBI and finally by CHR using 0.4% indigo carmine spray. All polyps were assessed in the magnification mode. This was done by gently applying the zoom function during the assessment. If the image was out of focus, the non-zoom mode could be applied to obtain an overview of the colon and re-identify the polyp before application of the zoom mode again. Digital images of each polyp with each modality were taken and stored as high quality

Table 1 Accuracy of various imaging modalities in the prediction of polyp histology

	WLE	NBI (KPP)	NBI (MBCN)	NBI (COMB)	CHR
Hyperplastic (7)	1	2	7	7	5
Adenomatous (38)	28	36	36	36	35
Carcinoma (5)	4	5	4	5	5
Total (50)	33	43	47	48	45

JPEG files (200-300 kb, 1280 × 1024 pixel array and 32 bit colour). This was followed by either taking biopsies or performing polypectomy.

Post procedural assessment

All images were subsequently transferred using a movie making software (U Lead Video Studio 7SE DVD, U Lead Systems Inc., USA) to another programme (Powerpoint; Microsoft; Redmond, Redmond, WA, USA). Each image was then blindly graded based on the standard Kudo's pit pattern (KPP)[3] for assessment of colorectal polyps. In the assessment with NBI, the mesh brown capillary network pattern (MBCN) of each polyp was also described (Type Ⅰ-absent pattern, Type Ⅱ-regular capillary network, Type Ⅲ-irregular capillary network)[4,5].

Histology

Biopsy or polypectomy specimens were processed with HE stains. These were reviewed by an expert gastrointestinal pathologist (PK) who was blinded to the endoscopic findings.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 14, SPSS Inc, Chicago, Ill). The sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and Negative Predictive Value (NPV) of differentiating hyperplastic (Type Ⅰ & Ⅱ-KPP, Type Ⅰ-MBCN) (Figure 1A-C) from adenomatous (Types Ⅲ, Ⅳ-KPP, Type Ⅱ-MBCN) (Figure 2A-C) and carcinomatous (Type Ⅴ-KPP, Type Ⅲ-MCBN) (Figure 3A-C) polyps was then compared with reference to the final histopathological diagnosis.

RESULTS

A total of 50 colorectal polyps in 37 patients with a mean size of 15.2 mm (range 3-50) were assessed. Seventeen lesions were located in the proximal colon (Caecum 5, Ascending Colon 7, Transverse Colon 5), 15 in the distal (Descending Colon 2, Sigmoid Colon 13) and 18 in the rectum. Morphologically, according to the updated Paris classification of superficial neoplastic lesions[6], 19 were classified as Type 0-Ⅰs, 6 Type 0-Ⅰp, 24-Type 0-Ⅱa after that 1 Type 0-Ⅱa-c. On final histopathological assessment, 7 polyps were hyperplastic, 38 adenomatous and 5 carcinomatous.

The performances of various modalities in the assessment of the polyps are depicted in Table 1. WLE, as expected was only modestly accurate in the prediction of polyp histology. NBI, using the KPP only correctly predicted 2 of 7 hyperplastic polyps, although it performed relatively well in the prediction of neoplastic polyps (adenomatous and carcinomatous polyps) (95%). In the assessment of the polyps using the combination of KPP and MBCN, the performance of NBI was numerically better than CHR. This combined approach correctly predicted all the hyperplastic and carcinomatous polyps although it failed to accurately predict 2 of the 38 adenomatous polyps. It was interesting to note that NBI using the MBCN pattern only performed better in the assessment of hyperplastic and adenomatous polyps compared to CHR although it did miss 1 out of the 5 carcinomatous polyps.

Table 2 The Sn, Sp, PPV and NPV looking individually at the performances of each modality compared to the final histopathological diagnosis (95% CI)

	Sn	Sp	PPV	NPV
WLE				
HP	14.3 (2.6, 51.3)	97.7 (87.9, 99.6)	50 (9.5, 90.5)	87.5 (75.3, 94.1)
A	73.7 (58.0, 85.0)	91.7 (64.6, 98.5)	96.6 (82.8, 99.4)	52.4 (32.4, 71.7)
C	80.0 (37.6, 96.4)	97.8 (88.4, 99.6)	80 (37.6, 96.4)	97.8 (88.4, 99.6)
Overall	94.1 (80.9, 98.4)	6.3 (1.1, 28.3)	68.1 (53.8, 79.6)	33.3 (6.1, 79.2)
NBI (KPP)				
HP	28.6 (8.2, 64.1)	100 (91.8, 100)	100 (34.2, 100)	89.6 (77.8, 95.5)
A	94.7 (82.7, 98.6)	100 (75.8, 100)	100 (90.4, 100)	85.7 (60.1, 96.0)
C	100 (56.6, 100)	97.8 (88.4, 99.6)	83.3 (43.6, 97.0)	100 (92.0, 100)
Overall	100 (91.4, 100)	22.2 (6.3, 54.7)	85.4 (72.8, 92.8)	100 (34.2, 100)
NBI (MCBN)				
HP	100 (64.6, 100)	97.7 (87.9, 99.6)	87.5 (52.9, 97.8)	100 (91.6, 100)
A	94.7 (82.7, 98.6)	91.7 (64.6, 98.5)	97.3 (86.2, 99.5)	84.6 (57.8, 95.7)
C	80.0 (37.6, 96.4)	97.8 (88.4, 99.6)	80.0 (37.6, 96.4)	97.8 (88.4, 99.6)
Overall	95.2 (84.2, 98.7)	87.5 (52.9, 97.8)	97.6 (87.4, 99.6)	77.8 (45.3, 93.7)
NBI (COMBINED)				
HP	100 (64.6, 100)	97.7 (87.9, 99.6)	87.5 (52.9, 97.8)	100 (91.6, 100)
A	94.7 (82.7, 98.6)	100 (75.8, 100)	100 (90.4, 100)	85.7 (60.1, 96.0)
C	100 (56.6, 100)	97.8 (88.4, 99.6)	83.3 (43.6, 97.0)	100 (92, 100)
Overall	97.6 (87.7, 99.6)	87.5 (52.9, 97.8)	97.6 (87.7, 99.6)	87.5 (52.9, 97.8)
CHR				
HP	71.4 (35.9, 91.8)	97.7 (87.9, 99.6)	83.3 (43.6, 97.0)	95.5 (84.9, 98.7)
A	92.1 (79.2, 97.3)	100 (75.8, 100)	100 (90.1, 100)	80.0 (54.8, 93.0)
C	100 (56.6, 100)	97.8 (88.4, 99.6)	83.3 (43.6, 97.0)	100 (92.0, 100)
Overall	97.6 (87.4, 99.6)	55.6 (26.7, 81.1)	90.9 (78.8, 96.4)	83.3 (43.6, 97.0)

Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; HP: Hyperplastic polyp; A: Adenomatous polyp; C: Carcinoma.

The Sn, Sp, PPV and NPV looking individually at the performances of each modality compared with the prediction of histology are depicted in Table 2. As expected, CHR was clearly superior to WLE in the prediction of polyp histology ($P < 0.001$). NBI, using either the KPP, MBCN or the combined classification, performed similarly to CHR in the prediction of polyp histology compared to WLE ($P = 0.002$, $P = 0.001$ and $P < 0.001$, respectively). NBI, using only the MBCN or the combined classification showed higher accuracies compared to CHR; although this proved to be statistically not significant ($P = 0.625$, $P = 0.250$).

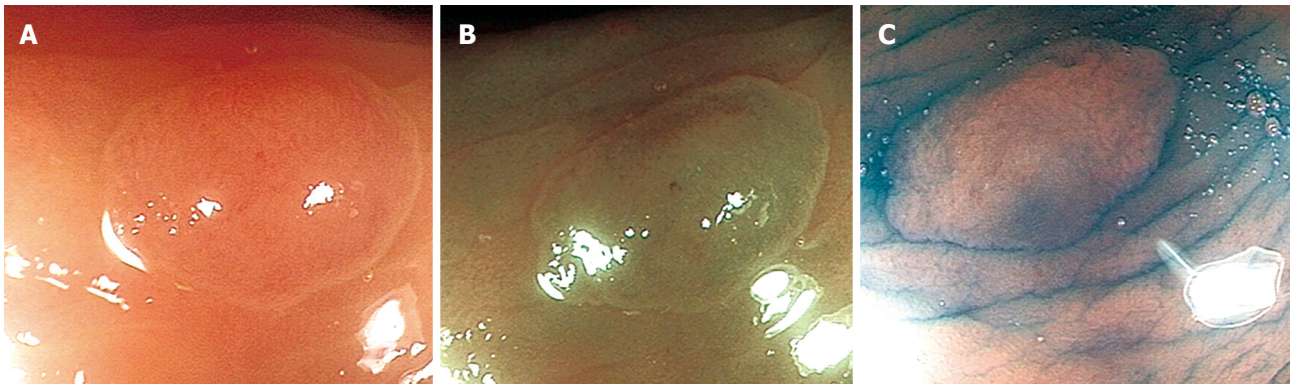

Figure 1 Hyperplastic polyp. A: High resolution white light magnified image: the pit pattern cannot be clearly discerned; B: Narrow band imaging with magnification where the Mesh Brown Capillary pattern is not visualised (Type Ⅰ MBCN); C: Chromoendoscopy with magnification depicting a Kudo's Type Ⅱ pit pattern.

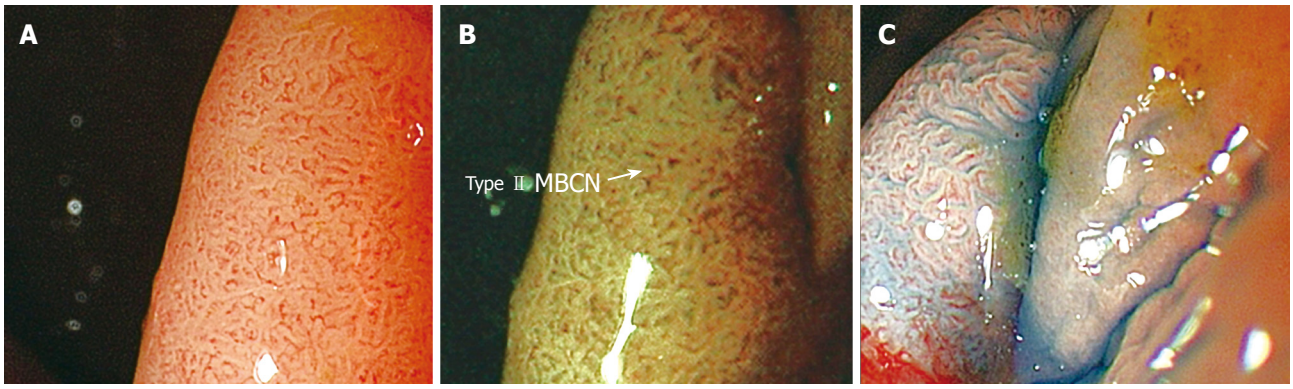

Figure 2 Adenomatous polyp. A: High resolution white light magnified image: Kudo's Type Ⅳ pit pattern can be visualised; B: Narrow band imaging with magnification demonstrating Kudo's Type Ⅳ pit pattern and regular capillary network surrounding the pits (Type Ⅱ MBCN); C: Chromoendoscopy with magnification depicting a Kudo's Type Ⅳ pit pattern.

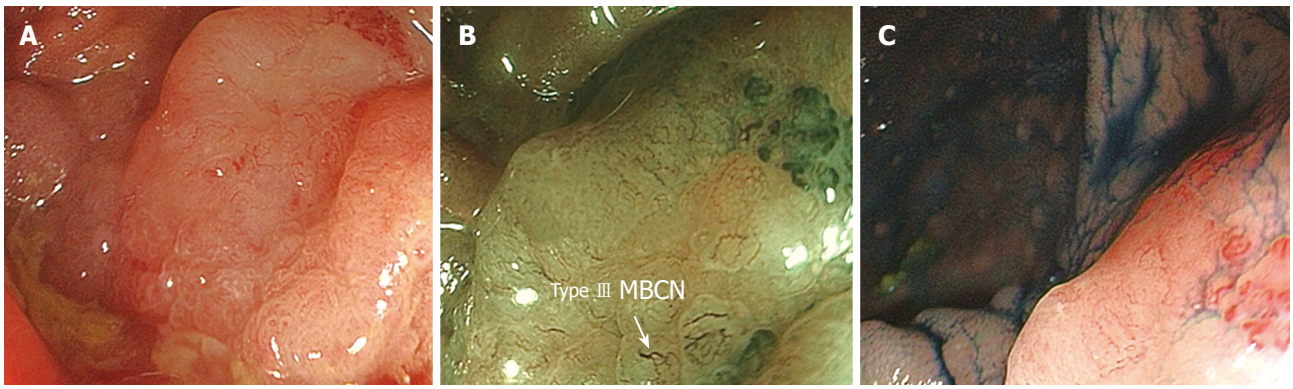

Figure 3 Carcinoma. A: High resolution white light magnified image where the Type Ⅳ/Ⅴ Kudo's pit pattern can be made out but with difficulty; B: Narrow band imaging with magnification demonstrating where the Kudo's pit pattern is not visualised but irregular and tortuous Mesh Brown Capillary Network is clearly seen (Type Ⅲ MBCN); C: Chromoendoscopy with magnification depicting a Kudo's Type Ⅴ pit pattern.

DISCUSSION

It is important to realise that in order for bowel cancer screening and surveillance to be optimised, a two pronged strategy which involves detection of polyps followed by an accurate assessment of its nature would be a logical if not ideal approach. There have been numerous studies looking at the ability of NBI in the detection of colonic polyps[7-9]. This study however was designed to answer the latter question i.e. predicting the histology of a polyp once it has been detected. The ability to discriminate neoplastic from non-neoplastic polyps could potentially result in a "one stop" approach[10] where hyperplastic polyps are ignored; adenomatous polyps are resected and carcinomatous polyps are biopsied for confirmation of histology and further management. NBI with magnification, a novel modality that is relatively easy to use could potentially

be incorporated into standard practice given that the technology is now commercially available. A single push of a button enables the endoscopist to visualise the mucosa quickly and then decide which of the 3 approaches should be used.

The utility of this novel modality has been studied in two previous studies[11,12], which showed similar diagnostic accuracy compared to CHR in the prediction of polyp histology in the diagnosis of colorectal neoplasia. However, in a study performed by East *et al*[10] comparing the magnified pit pattern with NBI versus CHR for diminutive colonic polyps, the pit pattern classification on NBI was found to be not always identical with CHR. Vascular pattern intensity and a simple colour change on NBI were deemed to be as accurate as the KPP classification with CHR. The authors went on to suggest that assessing polyps with NBI using the KPP classification may need to be modified before it can be used.

Sano *et al*[4] elegantly proposed the MBCN pattern classification in their benchmark study describing the microvasculature surrounding the mucosal pits in colonic polyps. We hence attempted to gauge this classification in our cohort of patients. The results of our feasibility study suggest that NBI with the combination of the KPP and the MBCN network performed on par if not better than CHR in predicting the histology of colorectal polyps. It is interesting to note that NBI using the MBCN pattern alone proved to be more accurate than CHR in the assessment of hyperplastic and adenomatous polyps albeit reduced accuracies in prediction of carcinomatous polyps.

There were however some limitations in the study which needs to be addressed. The interpretation of the data could have been skewed by the small sample size especially in the hyperplasic and carcinomatous polyp arms. However, as this was a preliminary feasibility study, sample size calculations were not performed. Single photographs representing each polyp with each modality were evaluated. This methodology is certainly less accurate than real time endoscopy. To minimize this bias, we selectively chose the best image representing each modality. The polyps were also assessed by a single assessor and it would have been useful to perform inter/intraobserver assessments to demonstrate its reproducibility.

In conclusion, although numerically superior but not statistically, NBI with magnification performed similarly to CHR with magnification if both the KPP and MBCN criteria were combined and applied in the prediction of histology of non neoplastic and neoplastic colorectal polyps. This feasibility study demonstrated that, perhaps the combined classification could potentially be useful in routine clinical practice, allowing the endoscopist to predict histology with higher accuracies using a less cumbersome method.

ACKNOWLEDGEMENTS

Dr. Singh received a grant from the Lancet to pursue an Advanced Endoscopy Fellowship at the Queens Medical Centre, Nottingham, UK. The endoscopy equipment used in this study was provided by Olympus-Keymed, UK.

COMMENTS

Background

The distinction between non neoplastic from neoplastic colorectal polyps during colonoscopy is paramount. This study evaluated the sensitivity, specificity, positive predictive value and negative predictive value of 3 different techniques: high resolution white light endoscopy, narrow band imaging (NBI) and chromoendoscopy (CHR), all with magnification in differentiating adenocarcinomas, adenomatous and hyperplastic colorectal polyps.

Research frontiers

To date there have been a paucity of studies looking at the diagnostic capability of NBI with magnification in real time in assessing colorectal polyps. This study combined the novel concept of both the Kudo's Pit Pattern (KPP) and the Mesh Brown Capillary Network (MBCN) classifications in predicting polyp histology.

Innovations and breakthroughs

NBI, using the MBCN pattern or the combined classification (KPP and MBCN together) showed higher numerical accuracies compared to CHR, but this was not statistically significant ($P = 0.625$, $P = 0.250$).

Applications

It may lead to significant implications to the practising gastroenterologist if narrow band imaging with magnification is readily available in future. Further larger scale, multi-center, randomized controlled trials would be of value to determine if this novel technology has a role in colorectal cancer screening and diagnosis.

Terminology

Narrow band imaging: Altered and narrowed spectrum light used to accentuate the surface morphology accentuating the microvascular and microstructural appearance of the mucosa. Magnification: Optical technique used to magnify a given area by 125X.

Peer review

Although primarily a feasibility study, this study is limited by its small sample size.

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S- Editor Li JL **L- Editor** Alpini GD **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.51

World J Gastrointest Endosc 2009 October 15; 1(1): 51-55
ISSN 1948-5190 (online)

BRIEF ARTICLE

CT colonography: Friend or foe of practicing endoscopists

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Received: April 28, 2009 Revised: August 31, 2009
Accepted: September 7, 2009
Published online: October 15, 2009

Abstract

AIM: To investigate the perceived impact of computed tomographic colonography (CTC) on endoscopists' current and future practice.

METHODS: A 21-question survey was mailed to 1570 randomly chosen American Society for Gastrointestinal Endoscopy (ASGE) members. Participants reported socio-demographics, colonoscopy volume, percentage of colonoscopies performed for screening, and likelihood of integration of CTC into their practice.

RESULTS: A total of 367 ASGE members (23%) returned the questionnaire. Respondents were predominantly male (> 90%) and white (83%) with an average age of 49 years. Most respondents (58%) had no plans to incorporate CTC into daily practice and only 7% had already incorporated CTC into daily practice. Private practice respondents were the least likely to incorporate this modality into their daily practice (P = 0.047). Forty-three percent of participants were willing to take courses on CTC reading, particularly those with the highest volume of colonoscopy (P = 0.049). Forty percent of participants were unsure of CTC's impact on future colonoscopy volume while 21% and 18% projected a decreased and increased volume, respectively. The estimated impact of CTC volume varied significantly by age (P = 0.002). Respondents > 60 years felt that CTC would increase colonoscopy, whereas those < 40 years thought CTC would ultimately decrease colonoscopy.

CONCLUSION: Practicing endoscopists are not enthusiastic about the incorporation of CTC into their daily practice and are unsure of its future impact on their practice.

Key words: Computed tomographic colonography; Virtual colonoscopy; Endoscopy; Colonoscopy; Screening; Colorectal cancer

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Menees SB, Carlos R, Scheiman J, Elta GH, Fendrick AM. CT colonography: Friend or foe of practicing endoscopists. *World J Gastrointest Endosc* 2009; 1(1): 51-55 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/51.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.51

INTRODUCTION

Colorectal cancer (CRC) screening compliance remains suboptimal for all accepted modalities. In 2004, the Behavioral Risk Factor Surveillance System demonstrated that 57% of the US population adheres to current CRC guidelines[1]. A follow-up CDC report further demonstrated that approximately 41 million people over the age of 50 were noncompliant with CRC screening[2]. Computed tomographic colonography (CTC), is a non-invasive technology used for CRC screening which may improve compliance. Data supporting the use of CTC

as a primary screening modality stems primarily from a multi-center trial of 1233 average risk patients by Pickhardt *et al*[3] This study demonstrated a sensitivity of 96% for adenomas at least 10 mm in diameter, 92.2% for adenomas at least 8 mm in diameter and 79.6% for polyps at least 6 mm in diameter. Three other large CTC studies have been less convincing, reporting a sensitivity for 10 mm polyps ranging from 55%-64%[4-6]. Regardless, in the most recent published CRC screening guidelines, computed tomographic colonography (CTC) has been identified as one of the recommended modalities to be offered first to patients for CRC prevention along with colonoscopy, barium enema and flexible sigmoidoscopy[7].

At this time, there are no published data regarding the opinions of endoscopists on this technology. Given their central role in CRC screening, their views have enormous implications on the efforts of policymakers and payers. The objectives of our study were to survey endoscopists regarding varying aspects on the use of CTC, and to assess predictors regarding its use.

MATERIALS AND METHODS

This study was undertaken with the approval of the Institutional Review Board of the University of Michigan. The American Society for Gastrointestinal Endoscopy (ASGE) membership directory was utilized to obtain potential participants. The eligible population consisted of physicians aged 75 and younger with an active license of which 6213 individuals met these eligibility criteria. The eligible population was selected using a systematic, stratified random sampling approach, yielding 1570 potential respondents.

Survey methods

The survey was mailed to all 1570 potential respondents in the spring and summer of 2006. To enhance participation, a personalized cover letter, close-ended questions and first class stamps on the mailing and return envelopes were used. The survey instrument was composed of 21 questions based on an extensive literature review using the following search terms: colonography, colography, CT colonoscopy, CT pneumocolon, virtual colonoscopy, virtual endoscopy, and virtual colonoscopy. In order to establish content validity, the results of this literature search were used to develop a draft questionnaire which was then reviewed by the gastroenterology clinical research group at the University of Michigan, followed by a revision of the survey instrument. The survey instrument was composed of questions created in a close-ended fashion to maximize response rates and avoid ambiguity. Data regarding personal and practice demographics were ascertained, including gender, race/ethnicity, practice type, community size, years in practice, percentage of practice devoted to screening colonoscopies and monthly colonoscopy volume. Present use of CTC was assessed by its availability and insurance coverage and recent use by practitioners. Inquiry into the future use of CTC included assessing active plans to incorporate CTC into daily practice or taking a CTC reading course as well as assessing the perceived impact of CTC on their practice volume and the amenability of their practice to allow same day colonoscopy after a positive CTC. Other solicited questions addressed the perceived value of CTC, the size of polyp that should be reported, and patient characteristics that would make participants more likely to order CTC.

Statistical analysis

All returned surveys were included in the analysis, regardless of the completeness of the survey. Descriptive statistics and multivariate analysis were used to demonstrate the survey findings. Demographic data were collected to discern any predictors of the likelihood for future CTC use. Age was analyzed as a continuous variable. Race/ethnicity was ascertained as: Caucasian, African-American, Asian, Hispanic, or American Indian. Practice type was categorized as: private practice, multispecialty group, health maintenance organization (HMO), academic or other. The number of years in practice was categorized as: less than 5 years, 5-10 years, and greater than 10 years. The number of colonoscopies per month, and the percentage of screening colonoscopies performed were also collected as continuous variables.

Each potential predictor variable was first examined in relation to likelihood of future CTC use; bivariate analyses were performed using chi-square tests for categorical variables and Student's t-tests for continuous variables. Multivariable logistic regression analysis was subsequently performed to determine the adjusted odds ratios of variables that achieved bivariate statistical significance. All statistical analyses were done using Microsoft Excel® and STATA® version 9.0.

RESULTS

The response rate for our mailings was 23%. A total of 279 ASGE members responded to our first mailing, with an additional 89 responses after the second mailing. The characteristics of the respondents are noted in Table 1.

Colonoscopy/CTC use

Respondents performed a mean of 87 colonoscopies monthly with 48% devoted solely for CRC screening. Screening colonoscopy was covered by insurance for ninety-six percent of respondents. Seventy-five percent of respondents had CTC available to them, although only 12% of participants had CTC covered by insurance. Fifty-eight percent of participants had utilized CTC prior to our survey.

Future use of CTC

Close to sixty percent (58%) had no intention of integrating CTC into daily practice. Only 7% had already incorporated this modality into their practice and the

Table 1 Study population characteristics

Characteristic	*n* (%)
Sex	
Male	335 (91)
Age (yr)	
mean (SD)	48.7 (11.2)
Race	
Caucasian	303 (83)
Asian	41 (11)
Other	25 (6)
Practice type	
Private	219 (60)
Multi-specialty	56 (15)
Academic	80 (22)
HMO	18 (4)
Other	16 (4)
MD type	
GI	337 (92)
Surgeon	30 (8)
Community size	
< 50 000	29 (8)
51 000-100 000	46 (12)
> 100 000	115 (31)
> 500 000	63 (17)
> 1 000 000	122 (33)
Years practicing	
< 5 yr	60 (16)
5-10 yr	68 (19)
> 10 yr	237 (65)
Colonoscopies per month, mean number (SD)	86.8 (71.0)
Percentage of screening colonoscopies, mean, (SD)	48 (23.3)

remaining 28% were unsure of their future plans. Private practice respondents were the least likely to incorporate this modality into their daily practice ($P = 0.047$). Forty-three percent of participants were willing to take courses on CTC reading, particularly those practitioners with the highest volume of colonoscopy ($P = 0.049$). Thirty nine percent of participants had no intention of learning to read CTC. Practitioners were split regarding the impact of CTC on future colonoscopy volume: 19% projected an increase in volume, 21% projected a decrease in volume, 21% projected no change and 39% were unsure of its impact on colonoscopy volume. The estimated impact of CTC volume did not vary by practice type or colonoscopy volume; however age was a significant correlate ($P = 0.002$). Respondents > 60 years felt that CTC would increase colonoscopy, whereas gastroenterologists < 40 years thought CTC would ultimately decrease colonoscopy volume. Thirty one percent of respondents estimated that their endoscopy practice could accommodate colonoscopy on the same day following a positive CTC, while 39% felt they could not. Only 4% of practitioners already performed colonoscopy on the same day as a positive CTC and 25% were unsure if their practice could accommodate this request.

Other pertinent CTC issues

Practitioners would be more inclined to order CTC in patients with previously failed colonoscopy (86%), had multiple co-morbidities (63%), had a previous painful/unpleasant colonoscopy experience, and those who had with a very large or very small body habitus (14%). When respondents were asked what polyp size should be reported for CTC, 66% of practitioners felt that all polyps, regardless of size, should be documented. The remaining respondents felt that polyps > 5 mm need to be reported on CTC, however, none of our respondents felt that only polyps > 10 mm should be reported. Seventy two percent of respondents felt that CTC was valuable in patients not willing to undergo colonoscopy for screening.

Thirty-four percent felt that CTC was valuable to identify patients without polyps (in average risk populations), whereas 17% felt it was valuable in identifying patients with polyps (in high-risk populations). However, more than one-fifth of respondents did not see any value in CTC, as colonoscopy is the gold standard. Finally, we asked participants to respond to the clinical scenario where a patient had a positive CTC for an 8 mm polyp, and the follow-up colonoscopy was negative, what follow-up test would they recommend and at what interval. The majority of respondents (71%) would have repeated a colonoscopy either at one year (31%), 5 years (40%) or 10 years (17%). Few would have repeated the CTC at one year (10%) or 5 years (1%).

DISCUSSION

This research offers a cross section of opinions from endoscopists regarding CTC, a colon cancer screening modality that is likely to be more widely reimbursed within a few years. Unpublished data from an online survey conducted by the American Gastrointestinal Association (AGA) (AGA websource: www.gastro.org) demonstrated a comparable response rate to our survey (23%), however the AGA online survey results varied from our mailed survey significantly. The majority of our respondents (58%) were not planning on incorporating CTC into their practice and only 7% already had incorporated CTC. In contrast, one-third of the respondents from the AGA on-line survey were already performing or in the planning stages of utilizing CTC for their practice. The reasons for these different outcomes may reflect real opinion differences between the membership of the two societies (ASGE, AGA), or may reflect the different type of respondents to an online versus mailed survey.

The uneasiness of our respondents to embrace this technology may be secondary to the discordant results of CTC studies. Data from the previous largest four clinical trials prior to the American College of Radiobiology Imaging Network (ACRIN) trial for screening in asymptomatic individuals demonstrate a sensitivity rate varying from a low of 48% to a high of 94% for polyps > 1 cm[3-6]. The marked variations in sensitivity may be secondary on technical differences between the studies. Particularly, the Pickhardt study utilized solid stool tagging with barium and luminal opacification with gastrografin along with software that electronically re-

moved the opacified residual colonic fluid from the CT images[3]. Data from the ACRIN trial in 2531 patients who underwent both CTC and optical colonoscopic examinations demonstrated that CTC failed to detect a lesion measuring 10 mm or more in diameter in 10% of patients. For adenomas 6 mm or more in diameter, the sensitivity was 0.78[8].

Pending further studies, endoscopists may embrace CTC in the future. In our survey, 43% of respondents were willing to take courses on CTC reading, particularly those with the highest colonoscopy volumes, and 7% had already incorporated CTC into their daily practice. An argument for gastroenterologists to start reading CTC is that the 3D endoluminal "fly-through" portion is similar to the views encountered in optical colonoscopy. Therefore, gastroenterologists should be able to read this portion of CTC accurately[9]. In taking the lead on CTC, the AGA has published standards for gastroenterologists in performing and interpreting diagnostic CTC[10].

Respondents were split on their opinions regarding the impact of CTC as a screening tool on colonoscopy volumes and the ability for their practice to accommodate colonoscopy for a positive CTC. The estimated impact of CTC volume varied significantly by practitioner age ($P = 0.002$). Respondents > 60 years felt that CTC would increase colonoscopy, whereas those < 40 years thought CTC would ultimately decrease colonoscopy. If CTC were to increase adherence rate for CRC screening, this may easily increase colonoscopy volumes, as greater than 40% of the population has not undergone CRC screening. However, available data from the literature are diametrically opposed on this issue. Ladabaum *et al*[11] projected that colonoscopy demand would increase if screening uptake reached 75% with various mixes of strategies, including a substantial increase in the use of CTC, whereas, Ladabaum *et al*[11] and Hur *et al*[12] concluded that widespread use of CTC would decrease colonoscopy demand by assuming a relatively small increase in overall screening uptake (to 53%) and significant replacement of current strategies by CTC (two thirds of screening with CTC). There are no data to support the suggestion that the availability of CTC will increase adherence rate. Patients offered CTC as a primary screening modality in two different studies failed to showed an increase in CRC screening[13,14]. In Madison, Wisconsin, where CTC is reimbursed by the majority of payers, almost 50% of the patients and/or primary care physicians have chosen CTC as their first-line screening tool. Authors from that same area reported no change in colonoscopy volumes although this may reflect a relative decrease since their colonoscopy numbers have not increased as they have continued to do elsewhere in the country[15]. How many patients and primary care physicians will choose CTC if it becomes widely reimbursable remains uncertain. Ultimately, the true impact of CTC on colonoscopy volume may be difficult to measure since the percentage of patients screened by colonoscopy continues to increase due to public and primary care physician awareness.

Lastly, our respondents felt CTC may have a role in patients with a previously failed colonoscopy, in patients with multiple co-morbidities and in those not willing to undergo colonoscopy for CRC screening. Incomplete examinations occur in 2%-5% of cases and traditionally, double contrast barium enema (DCBE) is ordered to evaluate the remaining colon[16]. Studies have shown comparable results between DCBE and CTC after a failed colonoscopy[17,18]. DCBE generally can be performed immediately after colonoscopy, although institutions may differ on the policy of performing the examination after endoscopic biopsy and polypectomy of small polyps[19]. However, more recently, a large retrospective study of 546 patients suggests that CTC can also be performed safely on the same day as an incomplete colonoscopy[20]. Participants also recognized the utility of CTC in patients that are unwilling to undergo colonoscopy for CRC screening. Since national CRC screening rates are still suboptimal, CTC may appeal to certain individuals and increase CRC screening compliance.

Our study has several potential limitations. First, the low response rate (23%) may limit the generalizability of our findings. However, our response rate is similar to the unpublished data from the AGA online survey on this topic. Demographic data on those who did not participate in our study were not available, so we can not ensure that those who responded did not differ significantly from non-responders. It is possible that our participants were more interested in the subject of the survey than those who did not participate. However, if this is the case, then our results should represent the views of well-informed endoscopists. Additionally, reporting bias may be present in these data since we are relying on self-reported data. Finally, despite the age of the data, given the delay in approval of CTC as a primary screening tool by Medicare, the results remain relevant

In conclusion, practicing endoscopists are not enthusiastic about the incorporation of CTC into their daily practice. However, some endoscopists may be willing to take CTC reading courses and did value CTC in patients with previous failed colonoscopy or in those unwilling to undergo colonoscopy for CRC screening. Only time will tell, how this modality will affect the livelihood of practicing gastroenterologists.

COMMENTS

Background

Computed tomographic colonography (CTC) is a radiological exam for colorectal cancer screening that has been identified as one of the recommended modalities to be offered to patients for CRC prevention along with colonoscopy, barium enema and flexible sigmoidoscopy. CTC will likely impact endoscopists' practice patterns.

Research frontiers

At this time, there are no published data regarding the opinions of endoscopists on this technology. Given their role in CRC screening, the views of endoscopists may have enormous implications on the efforts of policymakers and payers. The objectives of our study were to survey endoscopists regarding varying aspects on the use of CTC, and to assess predictors regarding its use.

Applications

This survey study demonstrated that almost 60% of practicing endoscopists do not plan to incorporate CTC into their daily practice. However, some endoscopists may be willing to take CTC reading courses in the future. Additionally, endoscopists value CTC in patients with previous failed colonoscopy or in those unwilling to undergo colonoscopy for CRC screening.

Terminology

Computed tomographic colonography is a radiological exam utilizing CT scan to view the entire colon

Peer review

Overall this paper is interesting,and has clearly stated aims and reasonably valid conclusions. It is well organized with a good presentation and readability.

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S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.56

World J Gastrointest Endosc 2009 October 15; 1(1): 56-60
ISSN 1948-5190 (online)

BRIEF ARTICLE

A comparison of transanal excision and endoscopic resection for early rectal cancer

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Received: March 12, 2009 Revised: August 26, 2009
Accepted: September 15, 2009
Published online: October 15, 2009

Abstract

AIM: To compare the outcomes of endoscopic resection with transanal excision in patients with early rectal cancer.

METHODS: Thirty-two patients with early rectal cancer were treated by transanal excision or endoscopic resection between May 1999 and December 2007. The patients were regularly re-examined by means of colonoscopy and abdominal computed tomography after resection of the early rectal cancer. Complications, length of hospital-stay, disease recurrence and follow up outcomes were assessed.

RESULTS: Sixteen patients were treated by endoscopic resection and 16 patients were treated by transanal excision. No significant differences were present in the baseline characteristics. The rate of complete resection in the endoscopic resection group was 93.8%, compared to 87.5% in the transanal excision group (P = 0.544). The mean length of hospital-stay in the endoscopic resection group was 2.7 ± 1.1 d, compared to 8.9 ± 2.7 d in the transanal excision group (P = 0.001). The median follow up was 15.0 mo (range 6-99). During the follow up period, there was no case of recurrent disease in either group.

CONCLUSION: Endoscopic resection was a safe and effective method for the treatment of early rectal cancers and its outcomes were comparable to those of transanal excision procedures.

Key words: Endoscopic resection; Rectal cancer; Transanal excision

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Lee SH, Jeon SW, Jung MK, Kim SK, Choi GS. A comparison of transanal excision and endoscopic resection for early rectal cancer. *World J Gastrointest Endosc* 2009; 1(1): 56-60 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/56.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.56

INTRODUCTION

Rectal cancer is one of the commonest gastrointestinal cancers worldwide[1]. Low anterior resection and abdomino-perineal resection with total mesorectal excision are the standard treatment methods used for patients with low rectal cancer. However, rectal resection requires surgical intervention with considerable morbidity[2].

Low rectal cancer presents a challenge to surgeons with regard to local disease control and sphincter preservation[3-8]. With conventional abdomino-perineal resection, an acceptable local control rate can be achieved; however,

the permanent stoma is associated with an increased risk of sexual and/or urinary dysfunction[9].

Endoscopic resection and transanal excision are regarded as alternative procedures to radical surgery in patients with early rectal cancer[2]. However, until now, no comparisons between transanal excision and endoscopic resection in patients with early rectal cancer have been made.

The aim of the present study was to compare complete resection and recurrence of early rectal cancer after transanal excision to endoscopic resection, and to investigate the safety and efficacy of transanal excision compared to endoscopic resection for early rectal cancer.

MATERIALS AND METHODS

Patients

Between May 1999 and December 2007, 32 patients were selected for the study. Candidates for transanal excision were chosen according to the following criteria: the mobility, size (< 3.5 cm), and accessibility (usually within 10 cm of the anal verge) of the tumor. Criteria for endoscopic resection of early rectal cancer at our institution included the following: (1) well or moderately differentiated adenocarcinoma on the forceps biopsy; (2) the mucosal or minute submucosal (sm1 < 1000 μm) type; (3) no lymphatic or vascular invasion. Whether these criteria were satisfied or not was not known before endoscopic resection. The decision to treat patients with endoscopic resection was therefore based on our own close observation and confirmation of the lesion.

After the transanal excision or endoscopic resection procedures, the patients were regularly re-examined by means of colonoscopy and/or abdominal computed tomography.

Methods

A data collection sheet was designed to obtain the relevant clinical information including baseline characteristics, tumor size, pathology of the tumor specimen, resection method used, margin involvement of specimens and any complications; this information was retrospectively reviewed. The recurrence of early rectal cancer and other associated factors were also analyzed. The study was approved by the Institutional Review Board of our institute.

Endoscopic resection: Endoscopic resection was performed after close observation and confirmation of the lesion. In cases of semi-pedunculated or pedunculated types, the mass was resected by polypectomy method with snaring. If the mass was a flat or excavated type, submucosal hypertonic saline mixed with epinephrine (1:10 000) was injected to make a mucosal bleb. The lesion was incised and dissected if larger than 3 cm (Endoscopic submucosal dissection, ESD) or snared and cut out if smaller than 3 cm (Endoscopic mucosal resection, EMR). The resected specimens were washed in normal saline, fixed in 8% formaldehyde solution, and embedded in paraffin. Complete resection was defined as free of marginal invasion by cancer cells.

Transanal excision: Transanal endoscopic microsurgery (TEM) as the treatment option seems to be superior to transanal excision in someways. However, we had no TEM instruments at our institution. Therefore, transanal excision as the treatment option was always chosen. The procedure was performed under local anesthetic. Prone jack-knife or lithotomy position were the preferred positions. A Parks three-bladed anal retractor was inserted through the anus. After confirmation of the tumor, full-thickness excision with Metzenbaum scissors and electrocautery was performed. The defect was repaired with synthetic absorbable sutures.

Statistical analysis

All analyses were performed using the statistical package for the social sciences program (SPSS, version 14.0, Chicago, IL, USA). The differences between the two groups were compared using the *t*-test or χ^2 test. A $P < 0.05$ was considered statistically significant.

RESULTS

Complete resection rate

Thirty-two patients were included in the study. One was found to have positive resection margins on the endoscopic resection specimen, and two were found to have positive resection margins on the transanal excision specimen. Therefore, the number of complete resections carried out on the 16 endoscopic resection patients was 15 (93.8%) and the number of complete resections carried out on the 16 transanal excision patients was 14 (87.5%). No significant difference was found between the two groups with regard to complete resection ($P = 0.544$, Figure 1). The three patients with positive resection margins were excluded from further analysis.

The endoscopic resection methods used were ESD in 1, EMR in 9, and polypectomy in 5 patients.

Tumor and patient characteristics

There were 7 males and 7 females in the transanal excision group. The mean age was 57.0 ± 12.7 years in the transanal excision group. There were 7 males and 8 females in the endoscopic resection group. The mean age was 59.8 ± 8.9 years in the endoscopic resection group. No significant difference was found between the two groups with regard to age and gender ($P = 0.419$ and $P = 0.858$, respectively).

In the transanal excision group, the mean tumor size was 2.0 ± 1.0 cm and the mean tumor location from the anal verge was 5.2 ± 2.2 cm. In the endoscopic resection group, the mean tumor size was 1.8 ± 1.0 cm and the mean tumor location from the anal verge was 9.6 ± 6.5 cm. No significant difference with regard to tumor size and location was observed in either of the two groups.

Table 1 Characteristics of patient and rectal cancer

	Transanal excision group (n = 14)	Endoscopic resection group (n = 15)	P value
Patient characteristics			
Age (yr)	57.0 ± 12.7	59.4 ± 8.9	0.419
Sex (male/female)	7/7	7/8	0.858
Rectal tumor characteristics			
Location from AV (cm)	5.2 ± 2.2	9.6 ± 6.5	0.188
Size (cm)	2.0 ± 1.0	1.8 ± 1.0	0.728
Tumor depth			
Mucosa	14	14	
Submucosa	0	1	
Tumor histology			
Well differentiation	13	15	
Moderate	1	0	

AV: Anal verge.

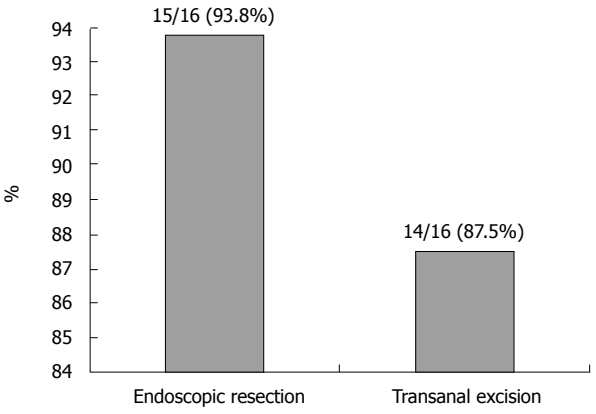

Figure 1 Complete resection rates for early rectal cancer. No significant difference was found between the two groups (P = 0.544).

The histological diagnosis of the tumors in the transanal excision group was that of well differentiated adenocarcinoma in 13 and moderately differentiated adenocarcinoma in 1 patient. All tumors in the transanal excision group were confined to the rectal mucosa. The histological diagnosis of the tumors in the endoscopic resection group was that of well differentiated adenocarcinoma in all 15 patients. The tumor invasion depth in the endoscopic resection group was mucosa in 14 and sm1 (< 1000 μm) in 1 patient (Table 1).

Clinical outcomes

The median follow up period was 21.5 mo (6-99 mo) for the transanal excision group and 12.0 mo (6-70 mo) for the endoscopic resection group. These differences were not significant.

There was one episode of delayed bleeding after the endoscopic resection which was managed successfully by endoscopic hemoclipping. This episode of delayed bleeding did not need a transfusion and the patient was hospitalized and treated for 2 d. There were no other serious complications in the two groups.

The mean hospital-stay was 8.9 ± 2.7 d for the patients in the transanal excision group and 2.7 ± 1.1 d for the patients in the endoscopic resection group. The patients in the endoscopic resection group had a shorter hospital-stay duration compared to those in the transanal excision group (P = 0.001, Table 2).

Table 2 Follow-up and results after transanal excision and endoscopic resection of rectal cancer

	Transanal excision group (n = 14)	Endoscopic resection group (n = 15)	P value
Median follow up period (mo)	21.5	12.0	0.605
Mean hospital-stay (d)	8.9 ± 2.7	2.7 ± 1.1	0.001
Severe complications			
Severe bleeding	0	1	
Recurrence	0	0	

During a median follow-up period of 21.5 mo, all 14 patients in the transanal local excision group were free of disease recurrence. In addition, during a median follow-up period 12.0 mo, all 15 patients in the endoscopic resection group were free of disease recurrence (Table 2).

DISCUSSION

Colorectal cancer is the second most common cause of cancer death in the Western world. More than 35 000 new rectal cancers are diagnosed every year in the USA, and of these, 25% are stage I disease. Fewer than half of these cases are lesions confined to the mucosa and submucosa[10]. Increasing concerns regarding the burden of rectal cancer have led to growing efforts to achieve early endoscopic detection and treatment of cancer in the rectal mucosa. Secondary prevention of rectal cancer depends on simultaneous detection of early rectal cancers and their premalignant precursors. Early rectal cancers have a better prognosis than advanced rectal cancer.

Local excision of early rectal cancer has potential benefits for patients in terms of sphincter preservation, with low mortality and fast recovery. There are several methods of local excision; transanal excision, transanal endoscopic microsurgery (TEM), and endsocopic resection[11].

Low associated morbidity and semicolon mortality makes the treatment of early rectal cancer by transanal excision an appealing alternative to radical resection[11]. The Association of Coloproctology of Great Britain and Ireland recommends that transanal excision to cure early rectal cancer should be restricted to pT1 cancers with well or moderate differentiation and < 3 cm in diameter[12].

Transanal excision was the most commonly performed procedure for local excision of rectal masses. TEM has long been utilized in Europe but has been adopted much more slowly in the United States[13]. Recent resurgence in local excision of rectal masses has stimulated renewed interest in the procedure. TEM has been advocated by some as a superior technique to transanal excision, offering lower recurrence rates without increas-

es in morbidity[14-16].

On the other hand, the treatment of early rectal cancer by means of endoscopic resection might well be a safe and effective alternative. Endoscopic resection can be used as curative treatment in selected patients with early rectal cancer. It has been accepted not only in Japan but also in Western countries. However, prospective studies are still needed to compare the outcomes of endoscopic resection techniques with laparoscopic surgery for patients with early rectal cancer[17-19]. The criteria for endoscopic resection of early rectal cancer are controversial, but generally include the following: (1) well or moderately differentiated adenocarcinoma; (2) the mucosal or minute submucosal (sm1 < 1000 μm) type; (3) no lymphatic or vascular invasion[20].

No large studies have compared the effectiveness of endoscopic resection with transanal excision.

In this study, the number of complete resections in the 16 endoscopic cases was 15 (93.8%) and in the 16 transanal local excisions it was 14 (87.5%). Moore *et al*[21] reported a 78% rate of complete resection after transanal excision. Bergmann *et al*[22] reported a 97% rate of complete resection after endoscopic resection. In our study, no significant difference was found for complete excision between the two groups, consistent with the reports of the previous two studies.

The mean hospital-stay was 8.9 ± 2.7 d for the patients in the transanal excision group and 2.7 ± 1.1 d in the endoscopic resection group. The patients in the endoscopic resection group had a shorter hospital stay, compared to the transanal excision group ($P = 0.001$). This might be explained by the fact that transanal excision required full-thickness excision, and needed longer observation times.

There were no significant differences between the two study groups with regard to rectal cancer size, location from the anal verge and histological differentiation. All of the patients in both groups were free of recurrence during the follow-up period. For early rectal cancer, transanal excision has a 0%-32% recurrence rate[23-25], whereas TEM has yielded recurrence rates of 5 to 15 percent[26-28]. Few studies have compared TEM to transanal excision for early rectal cancer. The University of Minnesota reported a retrospective analysis of their experience with transanal excision and TEM. Recurrence rates for TEM were lower when compared with transanal excision (9% *vs* 33%, $P < 0.001$)[29]. Sengupta *et al*[6] performed a meta-analysis that demonstrated recurrence rates from 4.2% to 25% for lesions excised by TEM. For pT1 lesions, recurrence rates have been reported as ranging between 0%-12.5%[30].

In this study, the comparison between transanal local excision and endoscopic resection in the patients with early rectal cancer of equal grade showed that, in the selected patients, the two procedures were equally safe and effective with regard to treatment, outcome and disease recurrence.

The results of this study suggest that endoscopic resection can be considered as a treatment option for patients with early rectal cancer. Radical surgery, transanal excision and the associated complications might thus be avoided in high risk groups such as the elderly and those with significant co-morbidity.

The limitations of this study include the following; (1) the number of patients that underwent endoscopic resection or transanal excision was small, (2) the follow period was short (3) and the study design was retrospective and non-randomized. However, to the best of our knowledge, this is the first report to compare endoscopic resection and transanal excision as treatments for early rectal cancers.

In conclusion, endoscopic resection was safe and effective for the treatment of early rectal cancers; the outcomes were comparable to patients undergoing a transanal excision. In addition, the endoscopic resection had the advantage of a shorter hospital recovery.

COMMENTS

Background

Screening colonoscopy enables us to detect early colorectal cancer, which is demanding relative non-invasive treatment strategy. This study compared the results of two non-invasive methods for early rectal cancer; transanal excision and colonoscopic resection.

Research frontiers

Transanal endoscopic microsurgery (TEM) have been gaining the attention for the treatment option of early rectal cancer.

Innovations and breakthroughs

This is the first study which compared the results of the transanal resection with that of the endoscopic resection. Endoscopic resection is safe and effective for the treatment of early rectal cancer and comparable to the outcomes of the transanal resection.

Applications

These results mean that the two non-invasive methods might be the options for the early rectal cancer in clinical practice. The feasibility and accessibility should be evaluated according to the site within the rectum. The comparative study are needed between TEM and endoscopic resection.

Peer review

This is an interesting paper focused on effectiveness of endoscopic resection for early rectal cancer comparing to transanal resection. Although this paper has limitations due to retrospective, non-randomized and small numbers based design, it will contribute to readers in the field of therapeutic endoscopy. For more benefit, a number of points clarifying and certain statements require further justification.

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S- Editor Zhang HN **L- Editor** Herholdt AV **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.61

World J Gastrointest Endosc 2009 October 15; 1(1): 61-64
ISSN 1948-5190 (online)

BRIEF ARTICLE

Subserosal injection of hyaluronic acid may prevent perforation after endoscopic resection

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Received: March 23, 2009 Revised: August 26, 2009
Accepted: September 2, 2009
Published online: October 15, 2009

Abstract

AIM: To investigate the protective effect of subserosal injection of hyaluronic acid (HA) after endoscopic resection (ER) using *ex vivo* and *in vivo* studies.

METHODS: As the first examination, technical application of subserosal injection was tested 10 times using resected porcine stomachs. As the second examination, ER was applied to make six mucosal defects per stomach in three live minipigs and thermal damage was given on the proper muscle layer by using hemostatic forceps. Following the thermocoagulation, 1 mL of normal saline and HA, respectively, was injected targeting the subserosal layer in two mucosal defects each and the rest kept no injection as the control. The minipigs were recovered from the anesthesia and kept fasting until euthanasia which was carried out around 24 h after the procedures.

RESULTS: *Ex vivo* study revealed that complete and partial subserosal injection was possible two (20%) and four (40%) times, respectively. *In vivo* study revealed that no postoperative perforation occurred at any point of the thermocoagulation. Apparent retention of hyaluronic acid was identified at only two (33%) points where HA was injected.

CONCLUSION: This study failed to show preventative effects of subserosal injection of HA on postoperative perforation due to technical faults. However, this concept has a possibility to change strategy of ER with further technical innovation.

Key words: Subserosal injection; Endoscopic submucosal dissection; Endoscopic mucosal resection; Animal model; Thermal injury; Perforation

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Niimi K, Fujishiro M, Kodashima S, Ono S, Goto O, Yamamichi N, Koike K. Subserosal injection of hyaluronic acid may prevent perforation after endoscopic resection. *World J Gastrointest Endosc* 2009; 1(1): 61-64 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/61.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.61

INTRODUCTION

Owing to the remarkable development in therapeutic endoscopy, epithelial neoplasms in the gastrointestinal (GI) tract those fulfill the node-negative criteria of each organ have been endoscopically resected, especially in Japan[1,2]. Endoscopic mucosal resection (EMR), that is inject, cut technique or inject, suck, cut technique, is a conventional method applied for a small and non-ulcer-

ative neoplasms and endoscopic submucosal dissection (ESD), that is inject, mucosal incision, submucosal cut technique with electrosurgical knife, is a relatively novel method applied for a large or ulcerative neoplasms[3]. When the target becomes more complex, complications accompanying these techniques frequently occurred.

Most commonly-encountered complications are bleeding and perforation and these complications are divided into intraoperative and postoperative ones. Bleeding can be managed by thermocoagulation or endoscopic clipping and, even if the attempts fail, blood transfusion can rescue disturbed patient's condition in almost all cases as a final consideration in both of intraoperative and postoperative occasions. In terms of perforation, it is now considered that the intraoperative perforation can be successfully managed without surgical rescue when endoscopic closure of the perforation is completed[4-6]. However, postoperative perforation still needs surgical rescue because gut contents are poured out into the abdominal cavity at the time of notification and endoscopic procedures to close the perforation is quite risky with deteriorated conditions of the patients. Although the reason for postoperative perforation is still an open question, one of the major reasons may be excessive thermal injury to the remnant gut wall (the proper muscle layer) at the site of mucosal resection during the operation, which results in necrotic perforation.

Hyaluronic acid is a thick substance with high viscosity that is widely found in connective tissues. The current approved indications for its use in clinical practice in many countries, including Japan, Europe and the United States, are for intra-articular injections for osteoarthritis, as well as in eye surgery[7]. In Japan, it is also approved for submucosal injection material to lift the lesion from the proper muscle layer during endoscopic resection[8,9]. From the viscous nature of hyaluronic acid, we hypothesized that subserosal injection through the proper muscle layer after endoscopic resection might prevent from postoperative perforation. So we conducted this animal study to investigate whether our hypothesis was acceptable or not.

MATERIALS AND METHODS

As the first examination, two resected porcine stomachs within a few hours after euthanasia was obtained from a butcher to validate the technical application of the injection needle in the subserosal layer after endoscopic resection. The resected stomachs were set on a training system for endoscopic procedure (Figure 1) after washing the residue and mucus on the mucosal surface by normal saline. A slim upper gastrointestinal endoscope (XQ230, Olympus, Tokyo, Japan) was inserted in the stomach and a standard ESD technique[10] by using a flex knife (KD-630L, Olympus) as an electrosurgical knife and normal saline as submucosal injection fluid was performed to make ten mucosal defects in total, about 3 cm in diameter, in different locations of the gastric bodies. Through the exposed proper muscle layer, 1 mL of 0.4% hyaluronic acid preparation (Mucoup, Johnson & Johnson Co., Tokyo, Japan) (HA) was injected targeting the subserosal layer by 23-gauge disposable injection needle (NM-200L-0423, Olympus) and the technical availability of subserosal injection was investigated.

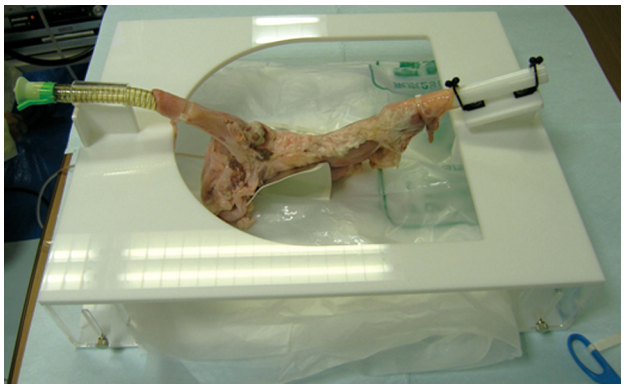

Figure 1 Training system for endoscopic procedure by using a resected stomach.

For the second examination, three living minipigs (Sus scrofa; Miniature Swine) were used for an overnight survival study to elucidate the preventive effect of subserosal injection of hyaluronic acid for postoperative perforation. On the first day, endoscopic procedures were performed for the minipigs under general anesthesia after overnight fasting. An endoscope with two instrumental channels (GIF-2TQ240, Olympus) was used for the following entire examination. The stomachs were sufficiently inflated with air after the residue and mucus were washed out with tap water which was splashed from the instrumental channel.

After these preparations, endoscopic mucosal resection (EMR) was applied to make six mucosal defects per stomach with a standard EMR technique by using normal saline injection and an electrocautery snare. The electrosurgical unit used was VIO 300D (ERBE Elektromedizin, Tübingen, Germany), which employed a special coagulation current, soft coagulation current. After more than 30 min of the EMR procedure when the normal saline injected for EMR in the submucosal layer was absorbed into surrounding tissues, thermal damage was given on the proper muscle layer by using hemostatic forceps (Coagrasper, Olympus) at the settings of soft coagulation mode, effect 5, 50 watts for 10 s. The muscular damage imitated thermal damage for treatment of non-bleeding and bleeding vessels on the proper muscle layer during and immediately after endoscopic resection[11].

Following the thermocoagulation, 1 mL of normal saline and HA, respectively, was injected targeting the subserosal layer through the proper muscle layer by using the injection needle in two mucosal defects each to elucidate protective effects of postoperative perforation. The rest kept no injection as the control. The minipigs were recovered from the anesthesia and kept fasting until euthanasia which was carried out around 24 h after the procedures.

The retrieved stomachs were cut on the points of coagulation and fixed with formalin and embedded in par-

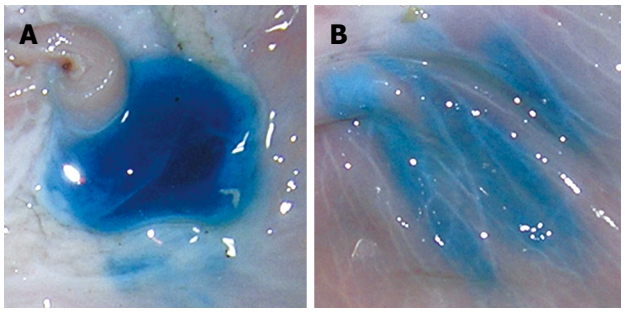

Figure 2 Subserosal injection of hyaluronic acid. A: Complete retention; B: Partial retention.

Table 1 Subserosal injection after thermocoagulation on mucosal defect of endoscopic resection

	Perforation, %	Extent of muscular damage				Identification of subserosa (%)
		0	< 50%	> 50%	100%	
Normal saline (n = 6)	0	1	1	1	3	0
Hyaluronic acid (n = 6)	0	1	1	1	3	33
Non-injection (n = 6)	0	1	1	1	3	0

affin. A histological section was made from each block, stained with hematoxylin and eosin, and examined tissue damage microscopically.

RESULTS

Ex vivo study by using the resected stomachs revealed that precise placement of HA in the subserosal layer was possible twice among ten trials. The rest was partial subserosal retention with intra-muscular and submucosal retention four times, intra-muscular and submucosal retention without subserosal retention twice, and no retention due to needle placement outside the wall twice (Figure 2).

In vivo study of the minipigs revealed that transmural tissue damage due to thermocoagulation was observed in 50% (3/6), 50% (3/6), and 50% (3/6) of the points where saline, HA, and nothing were injected, respectively. However, no postoperative perforation occurred at any point of the thermocoagulation. In terms of possible protective effects of postoperative perforation by subserosal injection, apparent identification of the subserosal layer, which was expected to be retaining of injected material, was observed at only two points where HA was injected (Table 1). The representative histological sections of each group were shown in Figure 3.

DISCUSSION

This study did not reveal the usefulness of subserosal injection through the proper muscle layer after endoscopic resection to prevent from postoperative perforation. The

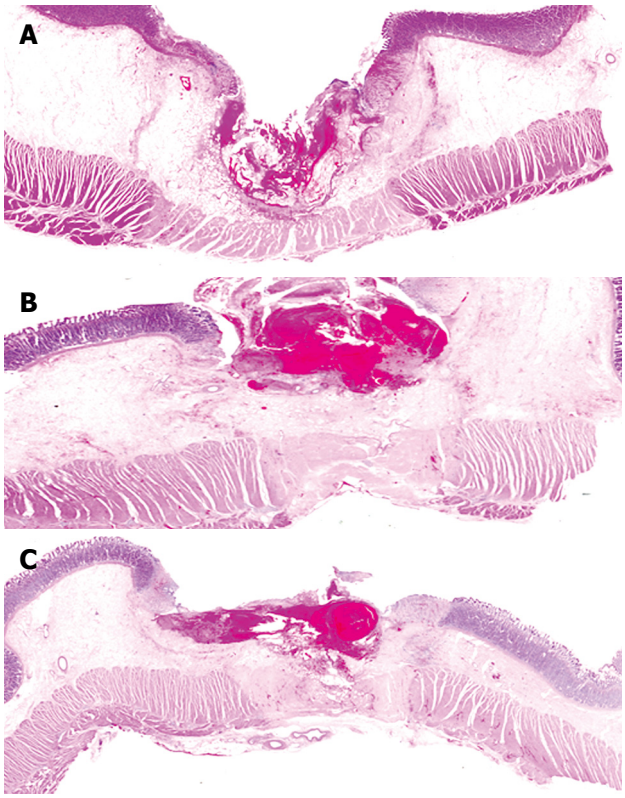

Figure 3 Representative histological sections at 24 h after the applications. A: No injection; B: Saline injection; C: Hyaluronic acid injection.

biggest fault of our pilot study may be an estimate that appropriate placement of hyaluronic acid in the subserosal layer were surely possible by using a commonly-used injection needle. However, in the *ex vivo* study, only 20% (2/10) and 40% (4/10) of injection, completely and partially, respectively, succeeded in subserosal placement of hyaluronic acid. When the placement was not validated, it was natural not to obtain reliable results from the *in vivo* study. So we have realized that technical innovation to put hyaluronic acid in the subserosal layer precisely is firstly necessary to advance our study.

Another fault may be the duration for survival after application of thermocoagulation. We considered that duration of 24 h were enough to lead to postoperative perforation. However, as shown in this study, no postoperative perforation was observed, although transmural damage was observed in 50% (9/18) of thermocoagulation. So longer duration, such as 2 d or more after thermocoagulation may be necessary to result in postoperative perforation even in case of transmural damage. Because the same application of thermocoagulation was impossible in the *in vivo* setting, it was acceptable to result that only half of the application had transmural damage. The disadvantage may be overcome when more cases were tested.

Although there were these faults in our pilot study, we believe that this study is meaningful in terms of a new foothold to cope with the rare but serious complication, postoperative perforation. When the protective effect on tissue destruction is elucidated by precise placement

of hyaluronic acid into subserosal layer, there are several breakthroughs in addition to preventative effects on postoperative perforation in the field of endoscopic resection as follows: First, little possibility of postoperative perforation even in the small intestine which has the thinnest wall in the GI tract may result in intensive treatments of bleeding or non-bleeding visible vessels on the mucosal defect during and after mucosal resection. This should lead to a less frequency of postoperative bleeding[12]. Closure of the mucosal defect after endoscopic resection may be unnecessary for the fear of postoperative perforation, although preventative effect on postoperative bleeding should be considered as another possible indication. Second, the targets for endoscopic resection may be technically extended into non-lifting lesions which stick on the proper muscle layer without fear of transmural thermal injury, because detachment of these lesions just on the proper muscle layer or at the level of internal muscle layer is necessary. Third, retention of the substance into the subserosal layer may lead to not only protective effect of tissue destruction, but also acceleration of healing process, although there is no supportive data so far. Mixture of several promising molecules such as growth factors may be useful for healing of the injured site.

In summary, this study failed to show preventative effects of subserosal injection of hyaluronic acid on postoperative perforation. The main reason is technical difficulty in precise placement of hyaluronic acid into the subserosal layer. However, technical innovation in the near future enables to place it precisely, which has a possibility to change strategy of endoscopic resection in the GI tract.

COMMENTS

Background

Endoscopic resection of gastrointestinal tumors can replace surgical organ resection to some extent. Due to the technical limitation, however, some serious complications concerning endoscopic resection may occur.

Research frontiers

One of rare but serious complications of endoscopic resection is postoperative perforation. The possible cause is transmural tissue damage due to thermocoagulation and there is no knowledge to prevent it so far.

Innovations and breakthrough

This study shows the first attempt to make subserosal injection of hyaluronic acid and its preventative effect on postoperative perforation.

Applications

Although technical refinement should be necessary, the concept to make subserosal injection is promising.

Terminology

Endoscopic mucosal resection: Endoscopic resection by the following sequences: marking, submucosal injection, snaring, and cut. Endoscopic submucosal dissection: Endoscopic resection by the following sequences: marking, submucosal injection, mucosal incision, and submucosal dissection. Hyaluronic acid: Non-antigenic thick substance for human with high viscosity that is widely found in human connective tissues.

Peer review

There is novelty and innovation in the research field and this study may change the strategy of endoscopic resection in the gastrointestinal tract with further efforts.

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S- Editor Zhang HN **L- Editor** Negro F **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.65

World J Gastrointest Endosc 2009 October 15; 1(1): 65-67
ISSN 1948-5190 (online)

CASE REPORT

Stenting of strictures close to the upper esophageal sphincter with the Polyflex stent

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Received: February 21, 2009 Revised: March 6, 2009
Accepted: March 13, 2009
Published online: October 15, 2009

Abstract

Stent insertion in strictures in the upper cervical esophagus present special difficulties, such as patient discomfort and worry due to continuous neck globus sensation and a metallic taste. Additionally, the endoscopist needs to have great skill to properly adjust the proximal stent end. We present the experience of stenting high cervical esophageal strictures with a self-expanding plastic stent (Polyflex), in three tumoral and one postoperative benign stenosis. Dysphagia disappeared and the endoprosthesis was well tolerated. The Polyflex stent seems to be suitable for insertion in the upper esophagus.

Key words: Polyflex; Dysphagia; Esophageal stent

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García-Cano J, Muñoz-Sánchez M, Morillas-Ariño J. Stenting of strictures close to the upper esophageal sphincter with the Polyflex stent. *World J Gastrointest Endosc* 2009; 1(1): 65-67 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/65.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.65

INTRODUCTION

Cervical esophageal strictures are a therapeutic challenge. Despite the fact that endoscopic dilation will solve most of the benign stricture cases and small fistulas will eventually heal, some difficult to manage, severe strictures will remain in some patients. In addition, palliation of dysphagia in tumoral stenosis frequently needs some kind of stenting apart from other therapeutic modalities such as radiotherapy.

The use of self-expanding metal stents (SEMS) in cervical stenosis or fistulas is somewhat limited due to severe cervical pain, globus sensation, bleeding, migration and patient intolerance. Additionally, the endoscopist needs to have great skill to properly adjust the proximal stent end. Recently, a self-expanding plastic stent (SEPS), namely Polyflex, was designed for palliation of strictures in the digestive tract[1]. We present the experience of stenting four high cervical esophageal strictures with the Polyflex endoprosthesis.

CASE REPORT

Patient characteristics are shown in Table 1. Tumoral strictures were caused by primary esophageal cancer in two occasions and metastasis/compression of lung cancer in one case (patient 4, Table 1). In Figure 1A a tumoral stricture in the cervical esophagus, close to the upper esophageal sphincter is shown. The benign post-

Table 1 Characteristics of patients with cervical esophageal strictures stented with the Polyflex endoprosthesis

Patient	Gender/age (yr)	Type of stricture	Outcomes after Polyflex stenting
1	Male/63	Benign postoperative	Spontaneous stent migration after two months. Stricture permanent dilated
2	Female/79	Tumoral	Spontaneous stent migration after chemotherapy. Asymptomatic. No need for further stenting
3	Male/80	Tumoral	Asymptomatic until death several months after
4	Male/53	Tumoral	Asymptomatic until death several months after

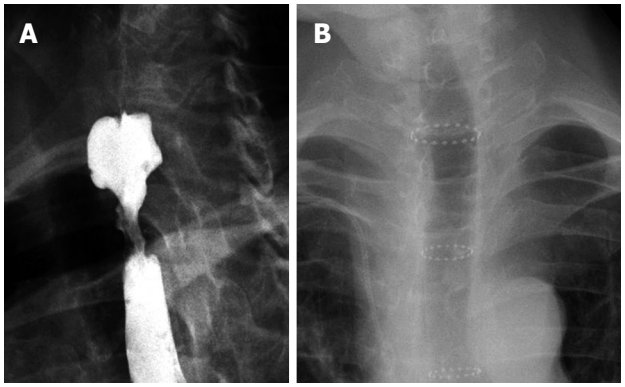

Figure 1 Radiograph of the stricture and Polyflex in the upper esophagus. A: Malignant stricture; B: Polyflex.

operative stricture was due to esophagectomy for mid-portion esophageal cancer. Dysphagia was severe in all patients who were virtually unable to drink liquids. The sizes of the Polyflex employed were 9 cm length and 16 mm width (with 20 mm in the upper flared portion).

Polyflex insertion was monitored endoscopically, as previously reported by us, for peptic strictures in the lower esophagus[2]. Briefly, the insertion manoeuvre was as follows, an ultrathin gastroscope (Pentax EG-1870 K) with an outer diameter of 6 mm was passed into the stomach. A Savary guide wire was then inserted through the working channel and left inside the gastric cavity, and the ultrathin gastroscope was withdrawn. Dilation was performed with Savary bougies or neumatic balloons, to a diameter of 10-12 mm. Next, the Polyflex, after being loaded into the applicator, was passed over the guide wire, traversing the stricture. Below the distal tip of the pusher, the blue radio-opaque marks of the upper part of the stent were seen. A mark with a felt-tipped pen can be made on the pusher to indicate the level of the upper part of the SEPS. This level was maintained as the stent was released several centimeters above the Killian´s mouth.

Figure 2A shows the Polyflex stent, loaded into the applicator that has passed into the esophagus and is visualized with an ultrathin gastroscope positioned alongside the applicator in the hypopharynx. The vocal cords lay before the applicator but are not seen from this position. A blue mark has been made on the distal tip of the pusher, corresponding to the upper level of the stent. During the release manoeuvre this blue mark has to be kept several centimeters above the Killian's mouth. The outer sheath of the applicator is gently removed,

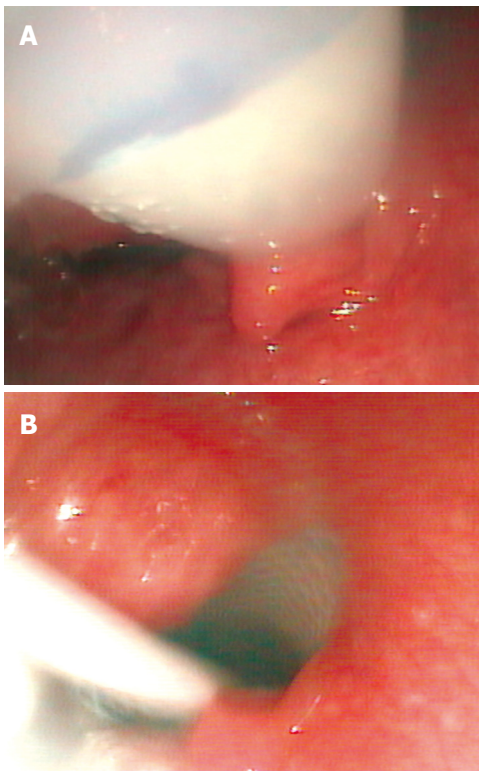

Figure 2 Endoscopic Polyflex stent and release. A: Undeployed Polyflex traversing the stricture; B: Polyflex immediately after release.

while keeping the upper end of the stent in the desired position above the stricture, until complete deployment of the Polyflex has been achieved.

Therefore, the key point for proper placement is to maintain the proximal end of the stent in all cases immediately below the Killian's mouth and check the stent release with the ultrathin endoscope placed in the hypopharynx.

After suitable complete Polyflex deployment the upper part of the stent is typically positioned just below the Killian's mouth. In Figure 2B complete Polyflex release is seen. The plastic rod on which the folded stent was mounted is still visible from the hypopharynx.

After insertion only mild pain was observed in one patient. Dysphagia disappeared and patients were able to eat. Radiographs were taken at the end of the procedure and for follow up when necessary. In Figure 2B a Self-expanding plastic stent (Polyflex, 9 cm length × 16 mm diameter, 20 mm in the upper flared portion) has been placed in the upper esophagus. Nearly the entire endoprosthesis is radiolucent, except for three crowns of ra-

diopaque material placed at both ends and in the middle of the stent (Figure 1B).

Stent migration occurred in one neoplastic stricture after chemotherapy and in the benign stricture after achieving permanent dilation. Thus no further stenting was necessary. On follow up radiographs stents were seen in the stomach and were easily removed endoscopically. Stricture dilation was also assessed during these endoscopies. The remaining two patients having tumoral stenosis died several months after stent insertion without complaining of dysphagia. As they were able to eat and had many other medical problems, doctors in charge did not check stent position on follow up radiographs.

DISCUSSION

Stent insertion in strictures in the upper cervical esophagus presents special difficulties, such as patient discomfort and worry due to continuous neck globus sensation and a metallic taste. Nevertheless, SEMS have been employed in this setting in specialized tertiary centers, emphasizing that physician experience with stent placement is important and is likely to influence patient outcome in this particularly challenging group of patients where precision in stent deployment is essential[3].

The Polyflex endoprosthesis, a SEPS, was made available several years ago, as an adequate stent to achieve and maintain patency in benign or malignant gastrointestinal strictures[4]. The Polyflex stent has the advantage of easy removal. In the event of incorrect insertion, it can be extracted and reinserted during the same session. This is one of the most important factors in its increasingly widespread use, apart from having much less granulation tissue reaction at the ends of the endoprosthesis than SEMS. These facts make plastic stents removable.

In contrast to older esophageal plastic stents, the Polyflex stent is a self-expanding endoprosthesis. Consequently, it is inserted at a smaller diameter, requiring minimal stricture dilation prior to the procedure. When compared to SEMS, plastic stents have the disadvantage of a so-called "memory" or the tendency to revert to their original shape (length, diameter) after they have been compressed to facilitate insertion. SEMS are manufactured and then packed in the "reduced" size, ready for insertion. In contrast, SEPS must be loaded into the introducing device immediately before insertion because a longstanding contraction damages the plastic material. This procedure can appear complex initially but is easily performed once experience has been gained.

Although this study is limited to a small number of patients, tolerance to Polyflex in the upper esophagus appeared to be good and suitable for managing these strictures. Furthermore, if the Polyflex is not properly adjusted during insertion, it can be extracted, loaded again into the applicator and reinserted during the same session. This is an important fact in complex cases or when the endoscopist does not have extensive experience.

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S- Editor Zhang HN **L- Editor** Lalor PF **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.68

World J Gastrointest Endosc 2009 October 15; 1(1): 68-71
ISSN 1948-5190 (online)

CASE REPORT

Curative ESD for intraepithelial esophageal carcinoma with leiomyoma mimicking submucosal invasive carcinoma

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Author contributions: Niimi K drafted the article and Fujishiro M revised it intensively; All the authors managed the patient, gave the intellectual comments on the critical revision and approved the final version.

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Received: February 21, 2009 Revised: March 22, 2009
Accepted: March 29, 2009
Published online: October 15, 2009

Abstract

This case report presents a 65-year-old man who developed early esophageal cancer with leiomyoma treated by endoscopic submucosal dissection (ESD). There have been several reports of co-existing superficial esophageal cancer and leiomyoma treated by endoscopic mucosal resection. However, there is no previous report describing the co-existing lesion treated by ESD. In order to determine treatment strategies for esophageal cancer, accurate endoscopic evaluation of the cancerous depth is essential. In the present case, the combination of endoscopic ultrasonography and narrow-band imaging system with magnifying endoscopy was extremely useful to evaluate the superficial esophageal cancer with leiomyoma, which lead to the appropriate treatment, ESD.

Key words: Endoscopic submucosal dissection; Submucosal tumor; Esophageal neoplasms; Narrow-band imaging magnifying endoscopy; Endoscopic ultrasonography

Peer reviewer: Philip Wai Yan Chiu, Associate Professor, Department of Surgery, Institute of Digestive Disease, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

Niimi K, Kodashima S, Ono S, Goto O, Yamamichi N, Fujishiro M. Curative ESD for intraepithelial esophageal carcinoma with leiomyoma mimicking submucosal invasive carcinoma. *World J Gastrointest Endosc* 2009; 1(1): 68-71 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/68.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.68

INTRODUCTION

Although esophageal carcinoma and submucosal tumors (SMTs) like leiomyoma are common diseases of the esophagus, the coexistence of those tumors in the same location is extremely rare[1-4]. In this situation, it is very important to diagnose the component of SMT-like protrusion as cancerous invasion into the submucosal layer or a true SMT, because the succeeding treatment may be quite different between them. In this case report, we present a case of intraepithelial esophageal carcinoma with leiomyoma, which has been successfully diagnosed preoperatively by using endoscopic ultrasonography (EUS) and narrow-band imaging (NBI) magnifying endoscopy and treated by endoscopic submucosal dissection (ESD) as a curative treatment.

CASE REPORT

An asymptomatic 65-year-old man with habits of heavy smoking and alcohol consumption underwent esophagogastroduodenoscopy as a health checkup, which revealed an esophageal tumor in the middle thoracic esophagus (Figure 1A). Endoscopic biopsy taken from the lesion, which was clearly identified as nonstaining area by chromoendoscopy with iodine staining, demonstrated a squamous cell carcinoma (Figure 1B). The proximal edge of

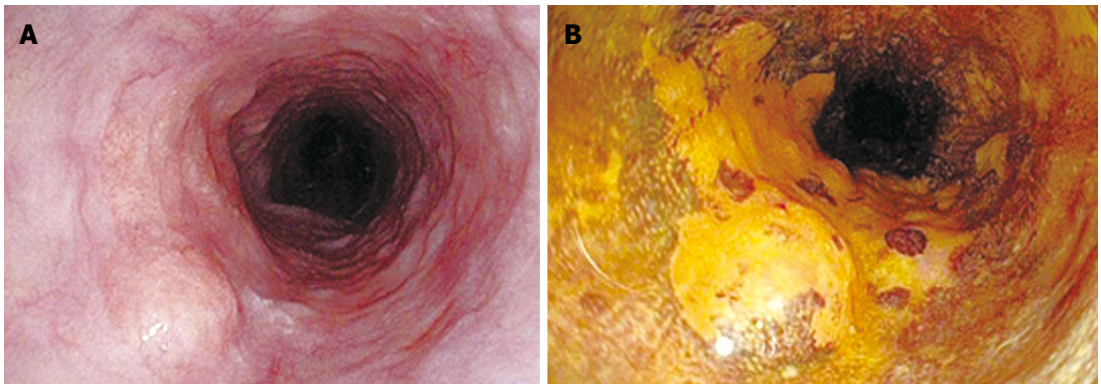

Figure 1 Esophageal tumor in the middle thoracic esophagus. A: Conventional endoscopy; B: Chromoendoscopy with iodine staining.

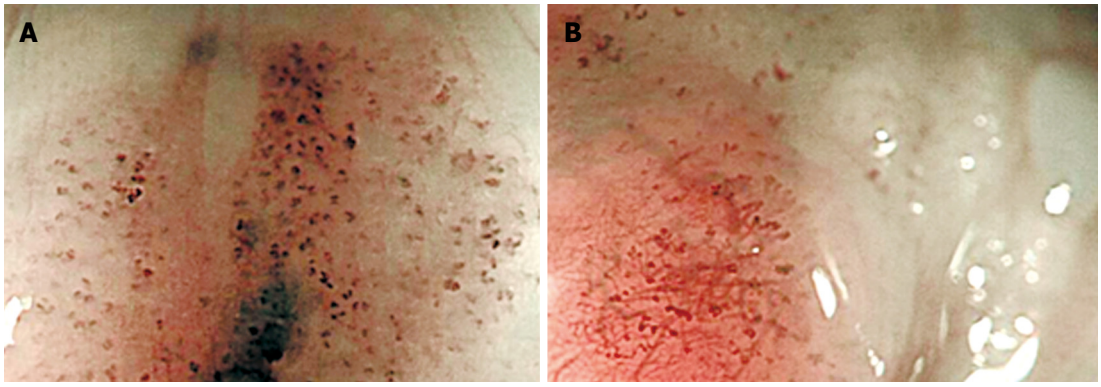

Figure 2 Esophageal tumor in the middle thoracic esophagus by magnifying endoscopy with narrow band imaging. A: Dilated and elongated intrapapillary capillary loops on the intraepithelial carcinoma; B: Dilated and elongated intrapapillary capillary loops on the submucosal tumor.

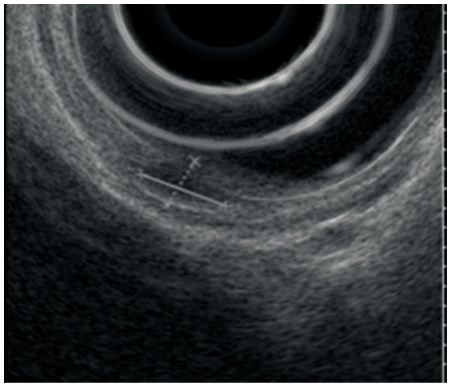

Figure 3 A hypoechoic tumor (4.2 mm × 2.6 mm) in the muscularis mucosae covered by intraepithelial layer by endoscopic ultrasonography.

Figure 4 Splash-needle.

the lesion consisted of SMT-like protrusion, which was quite difficult to differentiate cancerous invasion from a true SMT with a conventional white-light or chromoendoscopy. The differentiation between them was very important to select a treatment for the lesion, so additional thorough endoscopic examinations were performed. Novel image enhanced magnifying endoscopy with NBI was conducted for the entire lesion at first, which revealed dilated and elongated intrapapillary capillary loop (IPCL) even on the protrusion, indicated intraepithelial carcinoma (Figure 2). EUS demonstrated a hypoechoic tumor in the muscularis mucosae (MM) covered with intraepithelial layer, which was typical finding of leiomyoma, originated from MM (Figure 3)[5]. From these examinations, preoperative diagnosis of intraepithelial carcinoma with leiomyoma was obtained and ESD was performed as a curative treatment for this lesion after written informed consent was provided from the patient.

Procedural detail of ESD was described elsewhere[6]. In brief, splash-needle (DN-2618A, Pentax Co., Tokyo, Japan) (Figure 4) was used as an electrosurgical knife for marking, mucosal incision, and submucosal dissection and hyaluronic-acid containing solution was used for

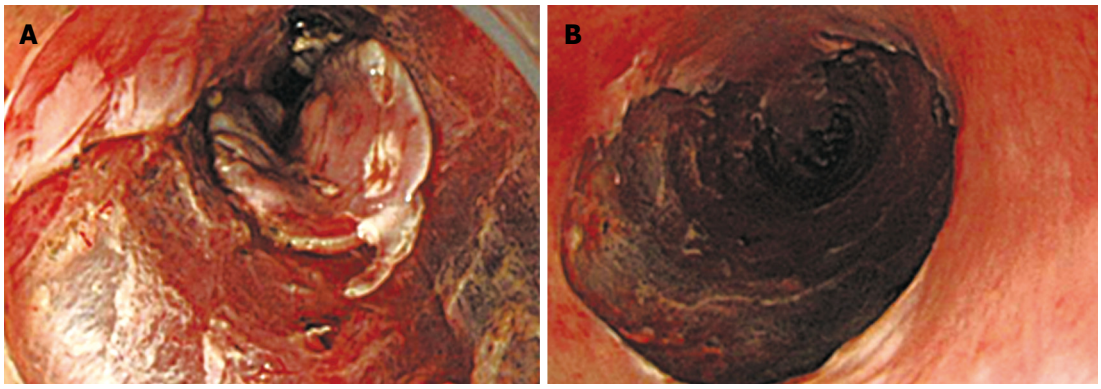

Figure 5 Esophageal endoscopic submucosal dissection. A: During submucosal dissection. B: Mucosal defect after the procedure.

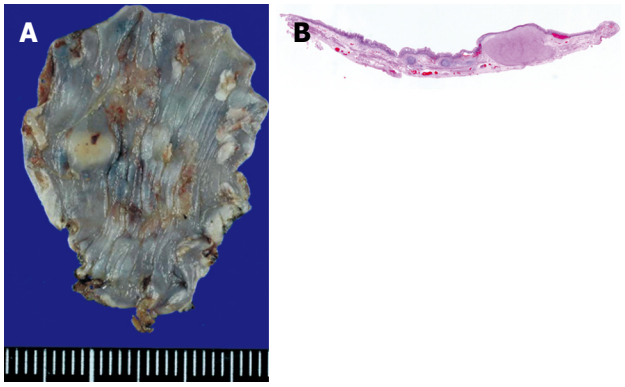

Figure 6 Resected specimen. A: Macroscopic examination reveals a shallow depression, 34 mm × 26 mm in size in the center of the specimen, with a hard nodule, 5 mm in size, at the proximal edge of the depression; B: Histological examination reveals an intraepithelial esophageal carcinoma overlying a leiomyoma originating from the muscularis mucosae.

submucosal fluid cushion[7,8]. ESD was completed without complications and the esophageal carcinoma with leiomyoma was resected in an en bloc fashion (Figure 5). The resected specimen contained a shallow depression, 34 mm × 26 mm in size in the center, with a hard nodule, 5 mm in size, at the proximal edge and histological diagnosis of an intraepithelial esophageal carcinoma overlying a leiomyoma originating from the MM layer was made (Figure 6).

DISCUSSION

Endoscopic diagnosis plays a central role for deciding therapeutic strategy of esophageal squamous cell carcinoma. Especially, it is crucial to differentiate between intramucosal carcinomas without and with invasion into the MM layer, because this is a cut-off line to differentiate between absolutely node-negative and possible node-positive carcinomas, which means that it is also a cut-off line whether endoluminal surgery is curatively performed or not. Traditional diagnostic modalities are only white-light endoscopy, chromoendoscopy with iodine staining, and EUS. EUS is considered to be a powerful tool to diagnose the depth of cancerous invasion, but the accuracy is reported to be at most 74%[9]. A recently developed image enhanced endoscopy, NBI, is very promising to diagnose the cancerous depth, when magnifying endoscopy is combined with the technology. Detail inspection of IPCLs on the mucosal surface by using magnifying endoscopy with NBI revealed an extremely accurate view into cancerous depth especially among superficial esophageal squamous cell carcinomas[5]. In the present case, the findings that there were only dilatation and elongation of IPCLs without severe destruction or large neovascular formation were quite helpful to diagnose the intraepithelial carcinoma with leiomyoma.

In conclusion, we experienced a case of intraepithelial esophageal carcinoma with leiomyoma mimicking submucosal invasive carcinoma, which is successfully diagnosed with combination of EUS and magnifying endoscopy with NBI. By the reliable preoperative diagnosis, the patient could avoid radical esophagectomy with lymph node dissection and treated curatively by ESD with preservation of the esophageal physiology.

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S- Editor Li JL **L- Editor** Alpini GD **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v1.i1.72

World J Gastrointest Endosc 2009 October 15; 1(1): 72-75
ISSN 1948-5190 (online)

CASE REPORT

Colonoscopy polypectomy management in Glanzmann's thrombasthenia

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Received: January 16, 2009 Revised: March 2, 2009
Accepted: March 9, 2009
Published online: October 15, 2009

Abstract

Glanzmann's thrombasthenia (GT) is a rare autosomal recessive bleeding syndrome characterized by abnormal Glycoprotein Ⅱb/Ⅲa complex (GⅡb/Ⅲa) on platelets with resultant abnormality in platelet aggregation. There is very little information regarding polypectomy management in GT. We report a single patient with this rare disease, who underwent sequential endoscopic management of large colon polyps. Polypectomy in our GT patient was complicated by immediate and delayed bleeding. Multiple clips used after standard cautery polypectomy for a polyp 10 mm or larger in our GT patient, was most effective in preventing immediate and delayed post-polypectomy bleeding than other known therapeutic approaches. We favor preemptive use of multiple clips in large polypectomy defects for GT patients and we may argue the added cost may be offset by the reduction in the need for blood products, and by averting or shortening potential hospitalizations.

Key words: Glanzmann's thrombasthenia; Polypectomy; Post-polypectomy bleeding

Peer reviewers: Carlos Robles-Medranda, MD, Head of the Endoscopy Division, Ecuadorian Institute of Digestive Disease (IECED), San Antonio Clinic, Av. Reales Tamarindo y Tennis Club, Portoviejo-Manabi-Ecuador, Casilla 13-01-266, Ecuador; Rami Eliakim, Professor, Chair of Medicine, Head, Department of Gastroenterology, Rambam Health Care Campus, Haifa 31096, Israel

Raina D, Movva A, Rahhal F, Abderrahim K, Schade R, Chamberlain SM. Colonoscopy polypectomy management in Glanzmann's thrombasthenia. *World J Gastrointest Endosc* 2009; 1(1): 72-75 Available from: URL: http://www.wjgnet.com/1948-5190/full/v1/i1/72.htm DOI: http://dx.doi.org/10.4253/wjge.v1.i1.72

INTRODUCTION

Glanzmann's thrombasthenia (GT) is a rare autosomal recessive bleeding syndrome characterized by an absence of platelet aggregation secondary to an abnormality in the Glycoprotein Ⅱb/Ⅲa complex (GⅡb/Ⅲa)[1]. The disease is characterized by impaired platelet aggregation stemming from defective fibrinogen binding to GPⅡb/Ⅲa and clinically manifests as a bleeding diathesis. We report a patient with Glanzmann's thrombasthenia who bled following colonic polypectomy and review the role of clips in endoscopic hemostasis for post-polypectomy bleeding in GT.

CASE REPORT

A 52-year-old African American female was referred by her primary care physician for a diagnostic colonoscopy to evaluate anemia and hemoccult positive stools. This patient was diagnosed with GT at the age of 17 after experiencing frequent nosebleeds and menorrhagia. Since menopause at age 48, the patient had no further bleeding episodes. She had no previous surgery except for dental extraction for which she had received platelet

Table 1 Blood products used and length of hospital stay

Colonoscopy	Number of clips placed/polyp size	Delayed post procedure hematochezia	Pre procedure blood products and or AMA[a]	Post procedure blood products	Factor rVIIa[e]	LOS[f]
Colonoscopy with polypectomy. Diagnostic (C1)	Two/10 mm	Self limiting	None	2 units of PP[d], 4 units of PRBC[c], AMA[a]	None	9 d
Colonoscopy with polypectomy (C2)	None/5-6 mm	None	2 units of HLA P[b], 2 units of PRBC[c], and AMA[a]	None	None	3 d
Colonoscopy with polypectomy (C3)	Single/15 mm	Severe	2 units of HLA P[b], 1 unit of PRBC[c], AMA[a]	16 units of PP[d], 6 units of PRBC[c], AMA[a]	RVIIae 80 mcg/kg, Q2 h for a total of 5 doses	11 d
Colonoscopy for hematochezia (C4)	Four/prior 15 mm polyp site	None				1 d

[a]Aminocaproic acid; [b]HLA matched platelets; [c]Packed red blood cells; [d]Pheresed platelets; [e]Recombinant activated factor seven; [f]Length of stay in hospital.

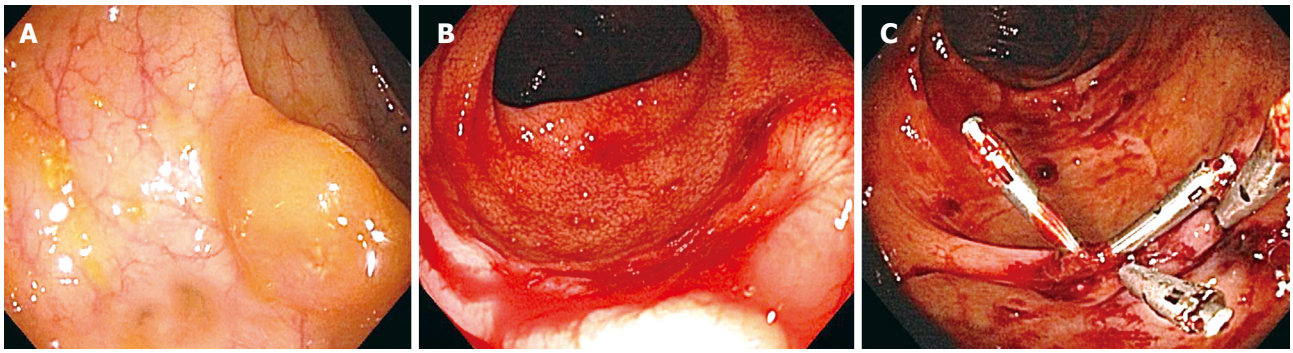

Figure 1 Colonoscopic findings of polyp bleeding and hemostasis. A: Right sided sessile large polyp; B: Post polypectomy bleeding; C: Multiple clips placed and immediate hemostasis achieved.

transfusion. She reported no family history of colon cancer or polyps but had an older sister with a diagnosis of GT. She underwent four sequential colonoscopies over 9 mo as enumerated below.

All the colonoscopic examinations were performed in a standard fashion (Olympus CF-H180 A/L endoscopes) at our university medical center endoscopy suite under the direct supervision and assistance of a single gastroenterology-attending physician (SC). Anesthesia services provided propofol during all procedures. Blood products, antifibrinolytic agents and procedural timing were managed by the hematology service.

DISCUSSION

Colonoscopy 1

The first procedure was performed when the patient had baseline hemoglobin of 10 mg/dL. No blood products were given prior to the procedure. The colonoscopy revealed multiple sessile polyps. The two largest sessile polyps, 10 mm and 15 mm each, were noted in the right colon. The 10 mm sessile polyp was completely removed using a saline-assisted technique in combination with Endoloop and standard cautery (A blend of 10 watts of cutting power and 30 joules of coagulation energy, Valleylab electrosurgical unit, Tyco Healthcare, Boulder, CO). Immediate post- polypectomy bleeding was observed and successfully controlled with 2 Triclips (Cook Endoscopy Medical GI Endoscopy, Bloomington, IN). Further polypectomies were deferred. The histological examination of the polyp revealed a sessile serrated adenoma with no dysplasia. Subsequently the patient presented to the hospital with delayed (after 3 d) self-limiting hematochezia and a decrease in hemoglobin that responded adequately to two units of packed red blood cells (PRBC). Surgical opinion was obtained for further management of the residual large polyps. They recommended endoscopic surveillance (Table 1).

Colonoscopy 2

The second colonoscopy was planned (10 d after C1) with pre-procedure blood products (Table 1). A day prior to the procedure the patient received aminocaproic acid and HLA matched platelets (Table 1). Hot biopsy polypectomies were performed to remove ten smaller approximately 4-5 mm polyps from the left side of the colon. The 15 mm polyp on the right side of the colon was left in place at this time to help localize any potential post-polypectomy bleeding. No immediate or delayed bleeding occurred. All polyps were hyperplastic on histology (Table 1).

Colonoscopy 3

The pre-procedure HLA-matched platelets and antifibrinolytics were given the same day prior to the third colonoscopy performed 7 mo after C2. The 15 mm right-sided polyp was tattooed with 4cc of India ink and removed with a saline assisted technique (Figure 1A). No

immediate bleeding noted, though a single QuickClip (QuickClip 2, Olympus, Center Valley, PA) was placed at the post-polypectomy site to close the defect. Two other smaller polyps 7 mm and 9 mm in size were removed from the left colon using standard electrocautery, with no clips applied. Three days later the patient was admitted with hematochezia and a three-gram drop in hemoglobin (Table 1).

Colonoscopy 4

Hematochezia was severe, presenting as intermittent large bloody 4 to 5 bowel movements per day. Over the next 7 d, bleeding failed to stop and the patient required daily replacement with several units of packed red blood cells, platelets and intravenous aminocaproic acid. The patient also received intravenous recombinant factor Ⅶa and prothrombin concentrate complex, but the hematochezia was persistent.

The fourth colonoscopy on day 10 post-procedure (C3) identified an active bleeding site in the right colon at the tattooed 15 mm post-polypectomy site (Figure 1B). Previously placed QuickClip was not identified. Dual therapy with epinephrine injection and placement of 4 Resolution Clips (Boston Scientific, Natick, MA) achieved immediate hemostasis (Figure 1C). No further episodes of colonic bleeding occurred (Table 1).

GT, originally described in 1918, is a rare disorder characterized by prolonged bleeding time, normal platelet count, and absent macroscopic platelet aggregation[2,3]. The basis for defective platelet function is a deficiency or dysfunction of platelet membrane GⅡb/Ⅲa complex (α 2b β3 integrin)[2,3]. The bleeding noted in GT is predominantly mucocutaneous, while purpura, epistaxis, gingival hemorrhage, and menorrhagia are nearly constant features; gastrointestinal bleeding and hematuria are less common. In most cases, bleeding symptoms manifest rapidly after birth, but diagnosis is often delayed. Diagnosis may be suspected in patients with mucocutaneous bleeding with absent platelet aggregation in response to all physiologic stimuli, and a normal platelet count and morphology[4].

Transfusion of platelets is the standard of therapy for bleeding once conservative measures fail. It is however, limited by the development of alloantibodies to GⅡb/Ⅲa complex and or /HLA complex[5]. HLA matched platelet transfusion or leukocyte depleted platelet transfusion may lessen that problem. Recombinant activated factor seven (rFⅦa; NovoSeven_; Nordisk A/S, Bagsvaerd, Denmark) is reported as an effective alternative in managing severe bleeding episodes especially in patients at risk or with a history of alloimmunization[6]. A review based on a large international survey included 103 GT patients who experienced severe bleeding episodes during 34 surgical and invasive procedures[6,7]. It was previously reported that rFⅦ was effective in achieving hemostasis in approximately two thirds of the cases[6,7]. However, on subgroup analysis it was determined that gastrointestinal bleeding was difficult to control with rFⅦ. A recent case report further highlighted that gastrointestinal bleeding can occur after polypectomy in GT patients, and may ultimately require surgical intervention[8].

This is in contrast to an older case report in which pre-procedure platelet transfusion and aminocaproic acid was effective in preventing post-polypectomy bleeding[9]. This suggests that one has to maximize local hemostatic therapy, especially in gastrointestinal bleeds arising from polypectomies in GT patients.

Post-polypectomy bleeding as a major complication after colonoscopy has been reported to occur after approximately 1%-6% of polypectomies[7,8]. Delayed bleeding can present within days up to 2 wk post procedure[10,11]. To minimize post-polypectomy hemorrhage, techniques such as submucosal injection of saline or the use of detachable nylon loop are employed before completion of polypectomy as was done in this case[1,14]. Prophylactic clip application for prevention of post-polypectomy hemorrhage by closure of mucosal defects after polypectomy has also been reported[15]. In our patient four colonoscopies were performed. When examined retrospectively this allows us to analyze the several techniques attempted to prevent and treat post-polypectomy bleeding in GT. Post-polypectomy bleeding was significant when a single clip was applied as compared to two clips when adjusted for polyp size and site. Our observation is that in a patient with GT, multiple versus single hemostatic clips may have a more significant role in preventing or limiting post-polypectomy bleeding and it is effectiveness in achieving hemostasis once that happens. Depth of bite or retention rate may differ between different types of clips, whether that can help explain the difference in severity of post-polypectomy hemorrhage would be unknown. Studies in animal models have shown that Resolution Clips retain longer at site of application compared to Tri-clips though no difference was noted in hemodynamic stability in bleeding ulcers[16,17]. Longer retention has been shown in clinical setting when Resolution Clips were used to close post-polypectomy defects[18]. Whether a certain type of clip can improve hemostasis is not known, but this needs to be weighed against the fact that longer retention may be a limitation for residual polyp removal.

In conclusion, colonic polypectomy in GT patients may be complicated by immediate or delayed bleeding. The single previous GT case report suggested a protective effect of platelet transfusion and aminocaproic acid in preventing post-polypectomy bleeding. Another study implied that severe bleeding could be stopped by use of rFⅦ. However, we conclude that for polyps 10 mm or larger the addition of mechanical therapy, with multiple clips after standard cautery polypectomy, may be effective in preventing immediate and delayed post-polypectomy bleeding in patients with GT. The cost of preemptive multiple clips at post-polypectomy site may be offset by a reduction in need for blood products and by averting or shortening potential hospitalizations.

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S- Editor Li JL **L- Editor** Alpini GD **E- Editor** Ma WH

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2009 October 15; 1(1): I
ISSN 1948-5190 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Endoscopy*

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

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World J Gastrointest Endosc 2009 October 15; 1(1): I
ISSN 1948-5190 (online)

Meetings

Events Calendar 2009

August 14-16, 2009
Bell Harbor Conference Center, Seattle, Washington, United States
Practical Solutions for Successful Management
http://www.asge.org/index.aspx?id=5040

September 23-26, 2009
Beijing International Convention Center (BICC), Beijing, China
19th World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists (IASGO)
http://iasgo2009.org/en/index.shtml

September 27-30, 2009
Taipei, China
Asian Pacific Digestive Week
http://www.apdwcongress.org/2009/index.shtml

October 23-28, 2009
San Diego, CA
American College of Gastroenterology Annual Scientific Meeting

November 21-25, 2009
London, UK
Gastro 2009 UEGW/World Congress of Gastroenterology
www.gastro2009.org

Global Collaboration for Gastroenterology

For the first time in the history of gastroenterology, an international conference will take place which joins together the forces of four pre-eminent organizations: Gastro 2009, UEGW/WCOG London. The United European Gastroenterology Federation (UEGF) and the World Gastroenterology Organization (WGO), together with the World Organisation of Digestive Endoscopy (OMED) and the British Society of Gastroenterology (BSG), are jointly organizing a landmark meeting in London from November 21-25, 2009. This collaboration will ensure the perfect balance of basic science and clinical practice, will cover all disciplines in gastroenterology (endoscopy, digestive oncology, nutrition, digestive surgery, hepatology, gastroenterology) and ensure a truly global context; all presented in the exciting setting of the city of London. Attendance is expected to reach record heights as participants are provided with a compact "all-in-one" programme merging the best of several GI meetings. Faculty and participants from all corners of the earth will merge to provide a truly global environment conducive to the exchange of ideas and the forming of friendships and collaborations.

World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2009 October 15; 1(1): I-IV
ISSN 1948-5190 (online)

Instructions to authors

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

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Patent (list all authors)

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

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