

# World Journal of *Gastrointestinal Endoscopy*

*World J Gastrointest Endosc* 2015 October 10; 7(14): 1114-1156





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## Contents

Biweekly Volume 7 Number 14 October 10, 2015

### REVIEW

- 1114 Colorectal endoscopic submucosal dissection: Recent technical advances for safe and successful procedures

*Yamamoto K, Michida T, Nishida T, Hayashi S, Naito M, Ito T*

### MINIREVIEWS

- 1129 Peroral endoscopic myotomy: An emerging minimally invasive procedure for achalasia

*Vigneswaran Y, Ujiki MB*

- 1135 Endoscopic retrograde cholangiopancreatography-related perforations: Diagnosis and management

*Vezakis A, Fragulidis G, Polydorou A*

### ORIGINAL ARTICLE

#### Prospective Study

- 1142 Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy vs mucosal cutting biopsy

*Ikehara H, Li Z, Watari J, Taki M, Ogawa T, Yamasaki T, Kondo T, Toyoshima F, Kono T, Tozawa K, Ohda Y, Tomita T, Oshima T, Fukui H, Matsuda I, Hirota S, Miwa H*

### CASE REPORT

- 1150 Laparoscopic endoscopic cooperative surgery as a minimally invasive treatment for gastric submucosal tumor

*Namikawa T, Hanazaki K*



## Contents

*World Journal of Gastrointestinal Endoscopy*  
Volume 7 Number 14 October 10, 2015

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*World Journal of Gastrointestinal Endoscopy*

ISSN  
ISSN 1948-5190 (online)

LAUNCH DATE  
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PUBLICATION DATE  
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## Colorectal endoscopic submucosal dissection: Recent technical advances for safe and successful procedures

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**Conflict-of-interest statement:** Authors have no conflict of interests to declare for this article.

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Received: May 27, 2015

Peer-review started: May 29, 2015

First decision: July 6, 2015

Revised: August 27, 2015

Accepted: September 7, 2015

Article in press: September 8, 2015

Published online: October 10, 2015

### Abstract

Endoscopic submucosal dissection (ESD) is very useful in *en bloc* resection of large superficial colorectal tumors but is a technically difficult procedure because the colonic wall is thin and endoscopic maneuverability is poor because of colonic flexure and extensibility. A high risk of perforation has been reported in colorectal ESD. To prevent complications such as perforation and unexpected bleeding, it is crucial to ensure good visualization of the submucosal layer by creating a mucosal flap, which is an exfoliated mucosa for inserting the tip of the endoscope under it. The creation of a mucosal flap is often technically difficult; however, various types of equipment, appropriate strategy, and novel procedures including our clip-flap method, appear to facilitate mucosal flap creation, improving the safety and success rate of ESD. Favorable treatment outcomes with colorectal ESD have already been reported in many advanced institutions, and appropriate understanding of techniques and development of training systems are required for world-wide standardization of colorectal ESD. Here, we describe recent technical advances for safe and successful colorectal ESD.

**Key words:** Endoscopic submucosal dissection; Colorectal tumors; Mucosal flap; Clip-flap method

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**Core tip:** Endoscopic submucosal dissection (ESD) is useful for *en bloc* resection of large colorectal tumors but is a technically difficult procedure. Good visualization of the submucosal layer is crucial for safely and successfully performing colorectal ESD because poor visualization of the operative field may result in perforation or unexpected bleeding. Creating a mucosal flap solves these problems; however, it is the

process that requires the most skill in this procedure. To facilitate the mucosal flap creation, we developed the clip-flap method, which is simple and very effective for colorectal ESD. We described recent advances in colorectal ESD techniques and devices.

Yamamoto K, Michida T, Nishida T, Hayashi S, Naito M, Ito T. Colorectal endoscopic submucosal dissection: Recent technical advances for safe and successful procedures. *World J Gastrointest Endosc* 2015; 7(14): 1114-1128 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i14/1114.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i14.1114>

## INTRODUCTION

Endoscopic submucosal dissection (ESD) was recently developed for *en bloc* resection of early stage gastrointestinal neoplasms with negligible risk of lymph node metastasis<sup>[1-5]</sup>. Higher rates of *en bloc* resection of large colorectal tumors have been reported with colorectal ESD than with endoscopic mucosal resection (EMR); however, colorectal ESD confers an increased risk of perforation<sup>[6-10]</sup>. A high degree of technical skill and the development of specific strategies for colorectal ESD are required because of the anatomical characteristics of the colon, namely being a long and winding tube with a thinner wall than other regions of the gastrointestinal tract<sup>[4,6]</sup>. To prevent complications such as perforation and uncontrollable bleeding, it is crucial to maintain good visualization of the submucosal layer to be dissected<sup>[4,11,12]</sup>. Therefore, the mucosal flap creation is the key procedure<sup>[12]</sup>, although this process is technically challenging. To facilitate the mucosal flap creation, we recently developed the clip-flap method in which an endoclip is initially substituted for the mucosal flap<sup>[13-15]</sup>. Several types of endoknives were developed and properly utilizing them according to the requirements is also important. In this review, recent advances in techniques using various devices in colorectal ESD will be described.

## INDICATION FOR COLORECTAL ESD

Before performing colorectal ESD, the determination of the indications for ESD by preoperative examination is highly important. EMR using a snare remains the main treatment for superficial colorectal tumors. However, EMR is not adequate for *en bloc* resection of flat lesions larger than 20 mm in diameter because incomplete removal and local recurrence are occasionally observed<sup>[16,17]</sup>. The indications for ESD are therefore considered for a tumor when using EMR for *en bloc* resection is difficult. The guidelines on the indications for colorectal ESD were published in Japanese and Spanish academic societies of gastrointestinal endoscopy<sup>[18,19]</sup>. Basically, the indications for ESD are colorectal tumors for which endoscopic *en bloc* resection is required but *en*

*bloc* resection with EMR is difficult to apply. The primary objective lesions are large colorectal tumors, such as the laterally spreading tumor granular type (LST-G) with a large nodule or the laterally spreading tumor non-granular type (LST-NG)<sup>[20,21]</sup>, which are suspected to be intramucosal or with slightly invaded submucosal cancers > 20 mm in diameter in the preoperative examinations. Large protruding lesions are also indications for colorectal ESD<sup>[18,19]</sup>. However, an abundance of caution is required to treat large protruding lesions because even experienced endoscopists sometimes cannot avoid discontinuation of submucosal dissection due to severe submucosal fibrosis and retracted muscle<sup>[22]</sup>. Even if the size of the tumor is less than 20 mm, mucosal lesions with submucosal fibrosis, which cannot be resected with EMR, can be the indications for ESD.

In contrast, the technical simplicity of EMR can permit its utilization for colorectal tumors > 20 mm in diameter when the preoperative diagnosis is adenoma or mucosal cancer in adenoma<sup>[18-20]</sup>, although piecemeal mucosal resection includes the problem of a high local recurrence rate<sup>[20]</sup>. Magnifying chromoendoscopy for pit pattern observation<sup>[23]</sup> and magnifying image-enhanced endoscopy (narrow band imaging<sup>[24,25]</sup> or blue laser imaging<sup>[26]</sup>, etc.) are useful for preoperative differential diagnosis of adenoma, intramucosal cancer, and submucosal invasive cancers. It is better to avoid preoperative biopsy if the endoscopic treatment is planned to be performed because biopsy often causes submucosal fibrosis, complicating further endoscopic treatment<sup>[18]</sup>. In addition, the endoscope maneuverability should be analyzed before performing ESD because poor endoscope maneuverability may cause incomplete resection or complications<sup>[27,28]</sup>.

## METHOD FOR SAFE AND SUCCESSFUL ESD

### Preparation and oral intake

Bowel preparation is required for adequate visualization of the operative field and as prophylaxis against bacterial peritonitis in case of perforation. Patients are restricted to a low-fiber diet on the day before colorectal ESD and are instructed to orally consume 10 mL picosulfate after the last meal on the day before the procedure. Two-four liters of an electrolyte solution is orally administrated before the procedure<sup>[11,29]</sup>.

In contrast, no food or drink is allowed on the day of the procedure or the following day. Provided that there are no signs or symptoms of complications, patients will begin drinking water on day 1 and have light meals (rice porridge) on day 2. Meals are upgraded to normal food with alcohol excluded from day 2 until day 3-5 or the date of hospital discharge<sup>[30-32]</sup>.

### Sedation and patient's position

Light or conscious sedation is appropriate for colorectal ESD because deep sedation makes alteration of the patient's position difficult and often leads to severe



respiratory fluctuations<sup>[11]</sup>. At our institution, midazolam (2 mg) and pethidine (17.5-35 mg) is initially intravenously administered. Light sedation is maintained with additional administration of midazolam or pethidine during the procedure. In cases where a long procedure duration is expected, the use of dexmedetomidine may be useful in maintaining good sedation levels<sup>[33,34]</sup>. Use of a carbon dioxide (CO<sub>2</sub>) insufflation system (UCR; Olympus Co., Tokyo, Japan) is extremely helpful for reducing the patient's discomfort and risk of peritonitis in case of perforation<sup>[35-37]</sup>. Excessive air present during the procedure decreases the endoscope maneuverability, but carbon dioxide can be quickly absorbed<sup>[35-37]</sup>. Yoshida *et al.*<sup>[38]</sup> reported that CO<sub>2</sub> insufflation during colorectal ESD was safe even for patients with obstructive ventilator disturbance.

Scopolamine butylbromide (10 mg) is administered to all patients except those contraindicated because of reduced bowel movement immediately prior to the procedure. Additional doses may be administered during the procedure. Administration of intravenous glucagon<sup>[39]</sup> or intraluminal peppermint oil<sup>[40]</sup> may be useful for patients who are contraindicated for scopolamine.

The patient's position is critical in performing successful colorectal ESD. In principle, the lesion should be moved upward as far as possible against the force of gravity prior to ESD and followed by a postural change to take advantage of the counter-traction of gravity<sup>[4,11,41,42]</sup>. The direction of gravity can be understood by the pooling of water or indigo carmine dye<sup>[11]</sup>. However, the intestinal lumen may become narrower or broader on alteration of the patient's position due to the movement of air. ESD becomes particularly challenging in narrowed lumen. Therefore, it is recommended that ESD should be commenced after each position (supine, prone, left lateral decubitus position, and right lateral decubitus position) has been adequately assessed as far as possible. In case of large lesions, changing the patient's position during the procedure is often required to ensure optimal operative field<sup>[4]</sup>.

### Selection of endoscope

ESD is generally performed using a single-channel colonoscope. At our institution, PCF-H290I or CF-H290I (Olympus), which have a water-jet function, are currently predominantly used because the water-jet function is convenient for hemostasis during ESD. Moreover, a gastroendoscope (GIF-HQ290, GIF-Q260J; Olympus) may be used for lesions in the rectum or distal sigmoid colon because the shorter endoscope can be easily operated in such locations<sup>[11,43]</sup>. In addition, a gastroendoscope can be used to approach lesions from the oral side in retroflexion more easily than with a conventional colonoscope.

Endoscope maneuverability is crucial to precisely perform ESD. ESD is challenging in cases of poor endoscope maneuverability, although experts can overcome these difficulties in most cases. Straightening of the endoscope is important for maintaining good

endoscope maneuverability. Single-balloon<sup>[44]</sup> (OBCU; Olympus) or double-balloon endoscopy systems<sup>[45,46]</sup> (PB-20; Fujifilm Co., Tokyo, Japan) may be useful in cases of extremely poor maneuverability.

### Distal attachments (Hoods)

The use of distal attachments is essential in safely performing colorectal ESD. The cutting area can be broadened and visualized with the use of distal attachments during the procedure. The shapes of distal attachments for colorectal ESD are mainly divided into straight types (D-201; Olympus, Figure 1A) and tapered types. Straight distal attachments allow larger working spaces for the operation of endoknives or forceps; however, the submucosal layer must be cut more deeply to insert the attachment under the exfoliated mucosa compared with tapered distal attachments. At our institution, a distal attachment (F-050/020, M-02/03/01; Top Corp., Tokyo, Japan, Figure 1B and C), which is slightly tapered, is attached to the tip of the endoscope. Small-caliber tip transparent hoods (ST-hood; Fujifilm) (Figure 1D) are useful for accessing narrow cutting areas<sup>[4,47]</sup>. Furthermore, this distal attachment is used for the tunnel<sup>[41,48]</sup> or pocket-creation method<sup>[49]</sup>.

### Endoknives and high-frequency generators

Various types of endoknives are used for colorectal ESD. Short-needle knives are the most widely used type of endoknife for colorectal ESD. The DualKnife<sup>[50]</sup> (Olympus, Figure 2A) is a short-needle endoknife that has a small disk at the tip of a short needle. The FlushKnife BT<sup>[51]</sup> /FlushKnife (Fujifilm, Figure 2B), Jet B-knife (Zeon Medical, Tokyo, Japan, Figure 2C)<sup>[52]</sup>, and Splash needle (Pentax Medical, Tokyo, Japan) are all short-needle knives with a water-jet function that enable submucosal injection without requiring the injection needle to be changed. The HookKnife<sup>[53]</sup> (Olympus, Figure 2D) has a hook on the tip that enables hooking and cutting of submucosal tissue. The HookKnife is particularly useful when the tangential approach is difficult or submucosal fibrosis is present because the submucosal tissue can be easily hooked and cut with this endoknife. The SBknife Jr<sup>[54-56]</sup> (Sumitomo Bakelite, Tokyo, Japan, Figure 2E) and Clutch Cutter<sup>[57]</sup> (Fujifilm) (Figure 2F) are scissor-type endoknives that have a rotation function. Scissor-type endoknives can be easily operated in the manner of forceps even by inexperienced operators. In addition, it can be efficiently operated even in cases when the tangential approach is difficult or endoscope maneuverability is extremely poor, because the submucosal tissue can be dissected simply by grasping, lifting, and applying an electrical current. The ITknife-nano (Olympus, Figure 2G) is an endoknife with an insulator on the tip of the blade that was developed for colorectal or esophageal ESD. Its use may allow increased dissection speeds<sup>[21]</sup> because it has a long blade between the insulated-tip and the sheath. The Mucosectom<sup>[58]</sup> (PENTAX, Figure 2H and I) and Swanblade (PENTAX, Figure 2J) have blades on

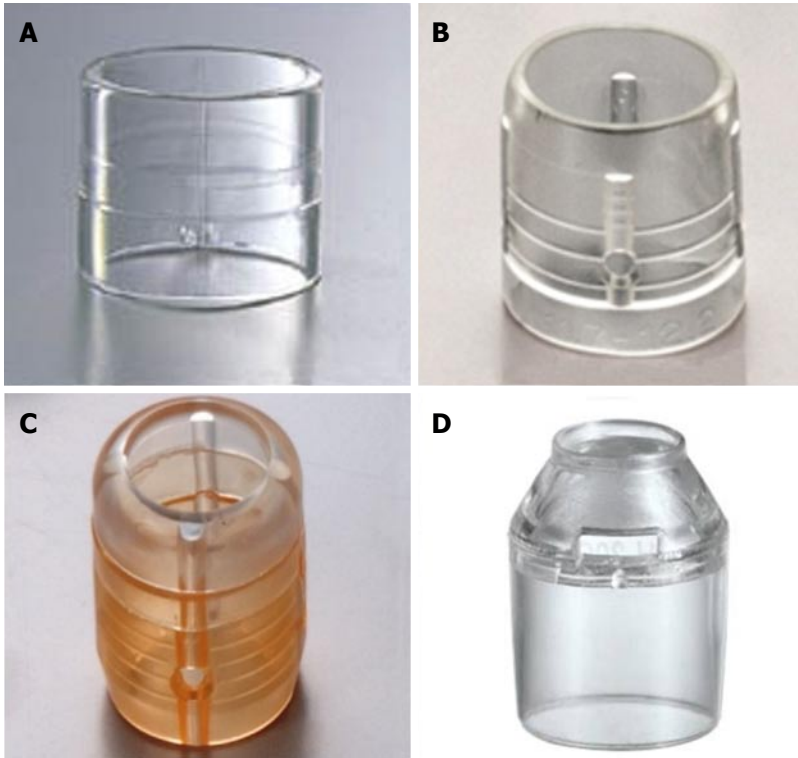


Figure 1 Distal attachments for colorectal endoscopic submucosal dissection. A: D-201; B: F-050; C: M-02; D: Short ST-hood.

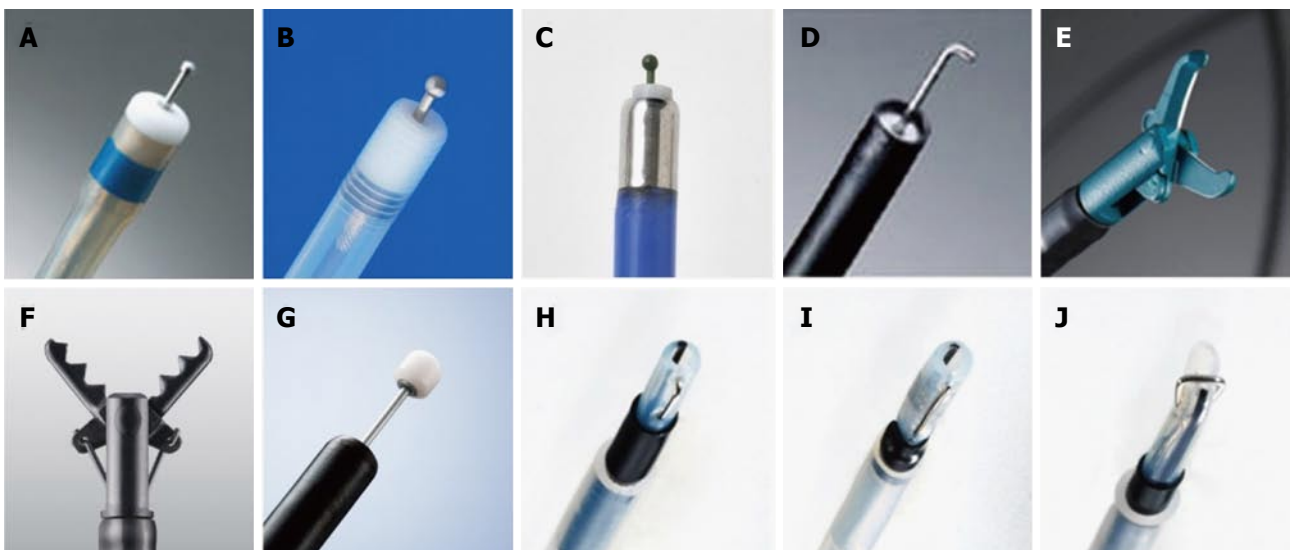


Figure 2 Various types of endoknives used for colorectal endoscopic submucosal dissection. A: DualKnife; B: FlushKnife BT; C: Jet B-knife; D: Hookknife; E: SBknife Jr; F: Clutch cutter; G: ITknife-nano; H: Mucosectom-short blade; I: Mucosectom-long blade; J: Swanblade.

an insulated rod that has a rotation function. These endoknives were developed for the safe and rapid dissection of the submucosal layer. At our institution, the FlushKnife BT (DK2618JB15/20) is predominantly used. According to the specific situation, other endoknives may be used in conjunction.

A high-frequency generator with an automated control system is required for ESD. At our institution, the VIO 300D (Erbe Elektromedizin GmbH, Tübingen, Germany) is predominantly used. ICC-200 (Erbe) or ESG-100 (Olympus) are also used for colorectal ESD.

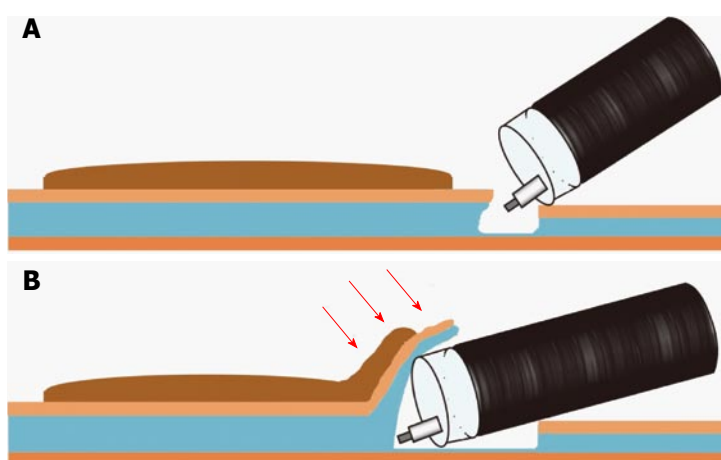
The settings on each instrument when using short-needle knives (FlushKnife BT, DualKnife) and hemostatic forceps (FD-410LR, FD-411QR; Olympus) are shown in Table 1<sup>[11,50,59]</sup>.

#### Strategies for improving safety and efficacy of ESD

ESD is usually initiated either from the anal side of the lesion in a forward direction or from the oral side in retroflexion<sup>[11,43]</sup>. There are benefits and limitations to both methods. Dissection from the anal side can be performed in almost all cases; however, endoscope

**Table 1** Setting of high-frequency generators for colorectal endoscopic submucosal dissection using Flush Knife BT, Dual Knife, and hemostatic forceps (FD-410LR, FD-411QR)

Device	Mucosal incision	Submucosal dissection	Hemostasis
FlushKnifeBT with VIO 300D (at our institution) with ICC 200 (at our institution)	Endocut I, effect 2, duration 3, interval 3 Endocut, effect 2-3, 80-120 W	Forced coag, effect 2, 40-50 W Swift coag, effect 2, 40-50 W Forced coag, 40-50 W Endocut, effect 2-3, 80-120 W	Forced coag, effect 2, 40-50 W Swift coag, effect 2, 40-50 W Forced coag, 40-50 W
DualKnife with VIO 300D <sup>[49]</sup> with ESG-100 <sup>[59]</sup>	Dry cut, effect 2, 30 W Pulse-cut-slow, 50 W	Swift coag, effect 4, 30 W Forced coag, effect 2	Swift coag, effect 4, 30 W Forced coag, effect 2
Hemostatic forceps FD-410LR with VIO 300D <sup>[11]</sup> with ICC 200 (at our institution) with ESG-100 <sup>[59]</sup>			Soft coag, effect 5, 50 W Soft coag, 80 W
FD-411QR with VIO 300D (at our institution)			Soft coag, 80 W Soft coag, effect 6, 80-100 W

**Figure 3** Schema of the mucosal flap. A: After injecting a solution in the submucosal layer, mucosal incision and deeper cut are made; B: Continuing to dissect the submucosal layer allows the creation of the "mucosal flap" (Red arrows point to the "mucosal flap"). Inserting the distal attachment under the mucosal flap provides good counter-traction to the submucosal layers and allows good visualization of the operative field. Therefore, completion of the mucosal flap facilitates subsequent submucosal dissection.

maneuverability is somewhat unstable, and the treatment of the mucosa just beyond a haustrum or a colonic flexure is occasionally challenging. Dissection from the oral side in retroflexion requires adequate space with a broad lumen; however, endoscope maneuverability is comparatively stable using this method<sup>[11,60]</sup>. The method selection by endoscopists largely depends on the institutions' established procedures and lesion location. At our institution, dissection from the anal side is predominantly performed and dissection from the oral side in retroflexion is occasionally performed in cases where approaching from anal side is difficult.

In either case, it is important to start dissecting the submucosa immediately proximal to the tip of the endoscope to avoid complications, such as perforation and unexpected bleeding, caused by blind procedures. Therefore, insertion of a distal attachment under the exfoliated mucosa of the lesion side is a crucial step in safely and effectively dissecting the submucosal layer. The lesional exfoliated mucosa is called the mucosal flap (Figure 3B)<sup>[12,61]</sup>. Formation of the mucosal flap facilitates safe and sequential dissection.

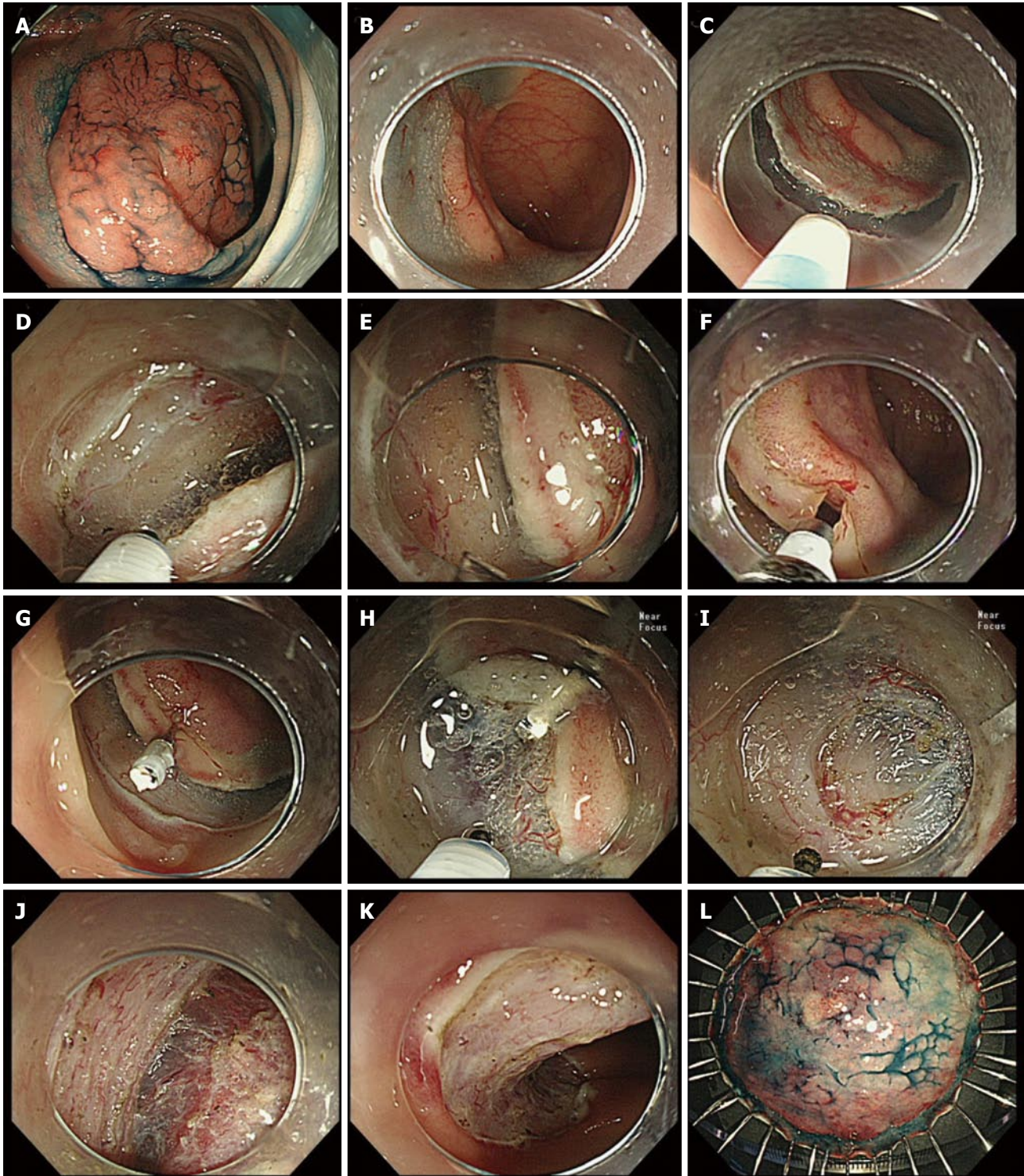
#### **Submucosal injection, mucosal incision, and deeper cut**

While approaching from the anal side, a solution is injected in the submucosal layer of the anal side of the

lesion and then the lesion tends to be more tangentially approached and more easily dissected (Figure 4B). Saline, 0.4% sodium hyaluronate solution (MucoUp; Johnson and Johnson, Tokyo, Japan) (Sigmavisc; Hyaltech Ltd., Livingston, United Kingdom), or 10% glycerin with a small amount of indigo carmine dye and 0.001% epinephrine are usually used as the injected solution<sup>[11,41,47,62]</sup>. Sodium hyaluronate solution is the most long-acting agent that can be locally injected for colorectal ESD<sup>[63]</sup>. Suvenyl (2% hyaluronate, Chugai, Tokyo, Japan) or Artz (1% hyaluronate, Seikagaku Corp. Tokyo, Japan) may be used after coordinating their concentrations<sup>[4,47,63]</sup>.

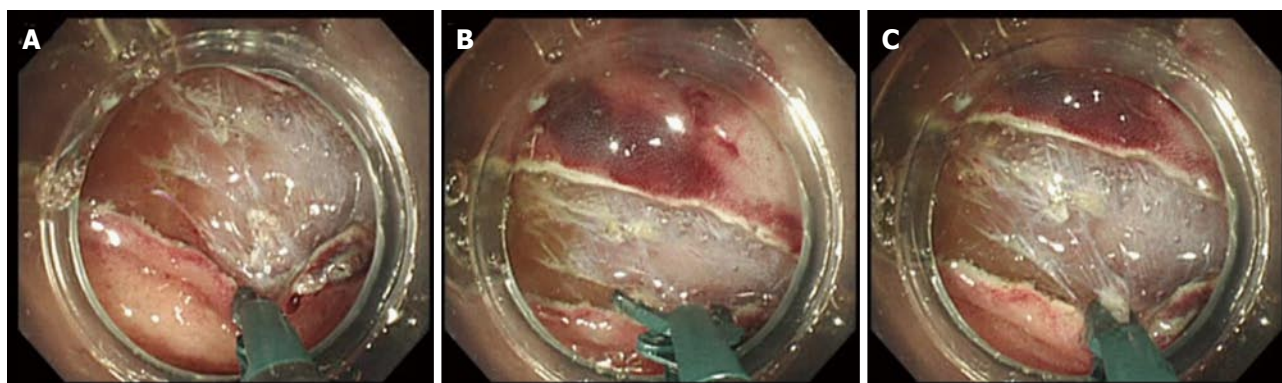
Following submucosal injection, the mucosa adjacent to the lesion is incised with an adequate margin before incision of the submucosal layer. A complete or partial circumferential mucosal incision is initially made according to the institutions' established procedures or characteristics of the lesion. A partial circumferential mucosal incision has recently been introduced at an increasing number of institutions because initial complete circumferential mucosal incision can make insertion of the distal attachment under the exfoliated mucosa difficult because of the loss of mucosal tension caused by extensive mucosal incision<sup>[4,11,30]</sup>. At our institution, a partial circumferential mucosal incision





**Figure 4** Endoscopic submucosal dissection of a laterally spreading tumor, non-granular type lesion using the clip-flap method. A: A 45 mm, LST-NG was located at the sigmoid colon. The patient was first positioned so that the bowel wall containing the lesion was uppermost, and this maximizes the assistance of gravity during ESD; B: Submucosal injection was performed from the anal side; C: Mucosal incision from the anal side was made using FlushKnife BT; D: Deeper cut of the anal side was made; E: The submucosal layer could not be adequately visualized because it was hidden by the exfoliated mucosa at this region. Insertion of the distal attachment under the exfoliated mucosa was difficult because of the tight space between the exfoliated mucosa and muscle, despite the condition after submucosal injection; F: After the width of endoclip's prongs was slightly narrowed, the edge of the exfoliated mucosa was clipped with an endoclip while lifting the exfoliated mucosa with the prongs of the endoclip, so that the deep layer of the submucosa was not grasped by the endoclip; G: The endoclip was attached to the exfoliated mucosa. The tail end of the endoclip attached to the mucosa slightly fell toward the intestinal lumen due to gravity, allowing the attachment to be easily inserted under the endoclip; H: The distal attachment was inserted under the endoclip, and then mucosa and the submucosal layer were elevated by the endoclip. The submucosal layer could be clearly visualized and dissected with the endoknife under the direct vision; I: The distal attachment could be inserted under the exfoliated mucosa by cutting the vasculature; J: Following mucosal flap formation, the submucosal layer could be dissected more easily; K: Dissection was completed following complete circumferential incision without any complications. Artificial ulcer after ESD; L: Resected specimen. Histopathological examination confirmed intramucosal cancer, and margin (-). LST-NG: Laterally spreading tumor, non-granular type; ESD: Endoscopic submucosal dissection.





**Figure 5** Three steps of safe submucosal dissection using a scissor-type endoknife (SBknifeJr) in case of a vertical approach. A: The endoscope was rotated and the exfoliated mucosa was turned down with a tip of an endoknife to clearly visualize the submucosal layer to be dissected along with the scissor tips; B: The edges of the scissor-type endoknife was opened; C: The submucosal layer under the exfoliated mucosa could be safely dissected by grasping and pulling up with the endoknife before application of an electrical current. Repeating these procedures led to the creation of the mucosal flap and successful endoscopic submucosal dissection.

from the anal side is usually made (Figure 4C) because it allows widening of the gap between lesional and non-lesional mucosa and greater ease of insertion of the distal attachment under the exfoliated mucosa. In partially circumferential mucosal incision, a complete circumferential mucosal incision is made after the creation of the mucosal flap.

At our institution, mucosal incision with the FlushKnife BT is performed with the endocut I mode. Deeper cut of the submucosal layer is performed with the forced coagulation or swift coagulation mode.

### Creation of the mucosal flap

Insertion of the distal attachment under the exfoliated mucosa is critical in allowing dissection of the submucosal layer while maintaining a good operative field. However, adequate visualization of the submucosal area at the beginning of the dissection is difficult because it is commonly hidden under the exfoliated mucosa. Poor visualization of the submucosal layer to be dissected may cause perforation and unexpected bleeding. To enhance visualization and ensure safe dissection of the submucosal layer, a mucosal flap must be created. Insertion of the distal attachment under the mucosal flap elevates the mucosal flap and provides counter-traction to the submucosal layer that allows easier dissection (Figure 4J). Therefore, creation of the mucosal flap is the most important step of the ESD procedure<sup>[12]</sup>; however, this process requires the most technical skill. The presence of submucosal fibrosis or vasculature often hinders smooth dissection and vertical approaches make creation of the mucosal flap more challenging. Changing the type of endoknife (Figure 5A-C) or using a tapered-type distal attachment may have utility in cases where the creation of the mucosal flap proves difficult.

### The Clip-flap method

To facilitate the mucosal flap creation, we developed the clip-flap method, in which an endoclip is substituted for

the mucosal flap until the flap is completed<sup>[13-15]</sup>. The basic procedure is as follows.

After submucosal injection, the mucosa adjacent to the lesion on the anal side is incised with an adequate margin and then the submucosal layer is cut deeply (Figure 4A-E). The edge of the exfoliated mucosa is clipped with an endoclip (EZ Clip, HX-610-135; Olympus; Figure 4F and G) while lifting the exfoliated mucosa with the prongs of the endoclip, so that the deep layer of the submucosa is not grasped by the endoclip. The distal attachment is inserted under the endoclip, and then the endoclip is lifted with the distal attachment. Consequently, the exfoliated mucosa is pulled up by the endoclip, allowing clear visualization and effective dissection of the submucosal layer by counter-traction using the endoclip (Figure 4H and I). In addition, the distal attachment can be easily inserted under the endoclip when the tail end of the endoclip is directed toward the intestinal lumen (Figure 4G) by using gravity after a postural change or temporarily lifting the endoclip with the endoknife.

Other than a single endoclip (Figure 4G and H), a cross pattern of endoclips created by attaching one endoclip to another endoclip is used to provide good counter-traction according to the situations<sup>[14]</sup>. We use the EZ clip in the clip-flap method because it can be easily rotated, and it has a joint between the metal prongs and sheath, most of which is made of plastic. The joint may be utilized as a step difference with which to hook it to the distal attachment. A long endoclip may be inappropriate because it can be a hindrance in a narrow lumen.

In our experience, the clip-flap method was effective in most cases, even in the presence of submucosal fibrosis or with a vertical approach, but can be difficult to use in some situations. When lesions are located within a very narrow lumen, such as in the anal tube, just beyond the colonic flexure, or when endoscope maneuverability is extremely poor, attaching the endoclip to the exfoliated mucosa and inserting the



distal attachment under the endoclip may be difficult<sup>[14]</sup>.

The clip-flap method is very simple and requires no special equipment other than common rotatable endoclips. Furthermore, various types of distal attachments, including a tapered type, can be used in the clip-flap method.

The endoscopists may apply the clip-flap method or change the endoknife or distal attachment according to the situation, when inserting the distal attachment under the exfoliated mucosa is difficult.

### Submucosal dissection

Following mucosal flap formation, adequate visualization of the submucosal layer to be dissected is ensured by lifting the mucosal flap with the distal attachment. Many vessels are present in the submucosal layer. Bleeding worsens the translucency of submucosal layer and makes dissection of the submucosal layer much more challenging after bleeding. Thick vessels are pre-coagulated with hemostatic forceps using the soft coagulation mode and cut after precoagulation with an endoknife<sup>[12]</sup>. Fat tissue is occasionally observed in the submucosal layer, and the translucent layer to be dissected is found below submucosal fat tissue. The deep submucosal layer should be dissected to determine the presence or absence of massive malignant submucosal invasion<sup>[12]</sup>.

At our institution, submucosal dissection is predominantly performed with the FlushKnife BT using forced or swift coagulation mode. Forced coagulation mode is superior to swift coagulation mode for hemostasis but inferior for incision. Therefore, we initially use forced coagulation mode and change to swift coagulation mode in cases where the submucosal tissue cannot be easily incised with forced coagulation mode because of submergence, fat rich tissue, fibrosis, or burnt tissue. Endocut I mode can also be used for incision of burnt tissue or tissue with severe fibrosis.

Submucosal fibrosis is an important factor that has a large impact on the technical difficulty of dissection<sup>[10,27,64-66]</sup>. Submucosal fibrosis complicates dissection by losing the translucency of the submucosal layer or narrowing the space between the mucosa and muscle. Furthermore, the presence of submucosal fibrosis is often preoperatively unexpected. Endoscopists must dissect the submucosal layer more carefully in cases of submucosal fibrosis because submucosal fibrosis increases perforation risk. Additional submucosal injection of solution widens the gap between the exfoliated mucosa and muscle layer and enhances the safety of submucosal dissection. A short needle knife with a water-jet function, such as FlushKnife BT, is very useful in these situations because it enables repeated submucosal injection without changing the injection needle<sup>[12,51,67,68]</sup>. A HookKnife or scissor-type endoknife, which enable the endoscopists to resect the submucosal tissue while pulling up on it, may also be useful in those situations<sup>[55]</sup>.

## SUCCESS RATES AND COMPLICATIONS

Single- and multi-center studies of colorectal ESD have reported *en bloc* resection rates of 61%-99.3%, perforation rates of 0%-20.4%, and bleeding rates ranging from 0% to 11.9% (Table 2)<sup>[8-10,12,14,29,52,54,56,62,64,65,69-88]</sup>. Numerous studies regarding colorectal ESD were reported in Japan where colorectal ESD was initially developed; furthermore, the reports from some other Asian countries and Western countries are continuously increasing. Direct comparison of treatment outcomes is difficult because the technical difficulty of ESD is greatly affected by tumor location, tumor size, the presence of submucosal fibrosis, and endoscope maneuverability. In addition, in some studies, treatment outcomes do not include data of earlier stage of colorectal ESD. However, recent single- and multi-center studies have reported improved treatment outcomes compared with previous studies<sup>[6,61,72,86,89]</sup>. Nakajima *et al.*<sup>[86]</sup> recently reported a comparatively high *en bloc* resection rate (94.5%) and low perforation rate (2.0%) of colorectal ESD in a Japanese large multi-center prospective study. The development of various devices and improvement of the endoscopist's skill appear to have contributed to recent improvements in treatment outcomes<sup>[21,52,55,90,91]</sup>. Probst *et al.*<sup>[62]</sup> reported low perforation rate (1.9%) and permissible *en bloc* resection rate (81.6%) of colorectal ESD in a European single-center study. Furthermore, higher *en bloc* resection rate (96.2%) in their late stage was reported compared with that in their early (60.0%) and middle stage (88.0%). These data reveal that colorectal ESD may be widely spread even in European countries where ESD experience is low.

In contrast, some studies have compared the local recurrence rates after EMR and ESD for large colorectal tumors (Table 3)<sup>[92-96]</sup>. Those studies demonstrated that local recurrence rates after ESD were significantly lower than after EMR because of the high *en bloc* resection rates with ESD despite the larger tumor sizes compared with EMR<sup>[92,93,95,96]</sup>. Oka *et al.*<sup>[96]</sup> reported that piecemeal resection was the most important risk factor for local recurrence regardless of EMR or ESD in a large multicenter prospective study. Most local recurrences of mucosal lesions may be addressed with additional endoscopic treatment; however, close follow-up colonoscopy is required to detect local recurrence after piecemeal resection<sup>[92-96]</sup>, even with ESD.

Perforation is a major complication of colorectal ESD; however, most cases of perforation can be conservatively treated by closure with endoclips (Figure 6A and B). However, endoscopists should give particular attention to the risks of perforation because open or laparoscopic surgery may be required for bacterial peritonitis, particularly with delayed perforations<sup>[77,85,97]</sup>. Larger lesional size, submucosal fibrosis, colonic location, and less experienced ESD operators have all been reported as risk factors for perforation during colorectal ESD<sup>[10,27,28,77,87]</sup>.

**Table 2** Previous reports of treatment outcomes following colorectal endoscopic submucosal dissection

Ref.	Year	Country	Study design	No. of cases	Tumor size (mm)	<i>En bloc</i> resection rate (%)	Complete <i>en bloc</i> resection rate (%)	Perforation (%)	Bleeding (%)
Fujishiro <i>et al</i> <sup>[69]</sup>	2007	Japan	S, R	200	29.9	91.5	70.5	6	1
Tamegai <i>et al</i> <sup>[70]</sup>	2007	Japan	S, R	71	32.7	98.6	95.6	1.4	
Hurlstone <i>et al</i> <sup>[29]</sup>	2007	United Kingdom	S, R	42		78.6	73.8	2.4	11.9
Taku <i>et al</i> <sup>[8]</sup>	2007	Japan	M, R	43				14	
Zhou <i>et al</i> <sup>[9]</sup>	2009	China	S, R	74	32.6	93.2	89.2	8.1	1.3
Iizuka <i>et al</i> <sup>[71]</sup>	2009	Japan	S, R	38	39	61	58	8	
Isomoto <i>et al</i> <sup>[64]</sup>	2009	Japan	S, R	292	26.8	90.1	79.8	8.2	0.7
Hotta <i>et al</i> <sup>[72]</sup>	2010	Japan	S, R	120	35	93.3	85	7.5	
Niimi <i>et al</i> <sup>[73]</sup>	2010	Japan	S, R	310	28.9	90.3	74.5	4.8	1.6
Matsumoto <i>et al</i> <sup>[65]</sup>	2010	Japan	S, R	203	32.4		85.7	6.9	
Yoshida <i>et al</i> <sup>[74]</sup>	2010	Japan	S, R	250	29.1	86.8	81.2	6	2.4
Tanaka <i>et al</i> <sup>[75]</sup>	2010	Japan	M, R	8303			83.8	4.8	1.6
Oka <i>et al</i> <sup>[76]</sup>	2010	Japan	M, R	688				3.3	1.7
Saito <i>et al</i> <sup>[77]</sup>	2010	Japan	M, P	1111	35	88		4.9	1.5
Kim <i>et al</i> <sup>[10]</sup>	2011	South Korea	S, R	108	27.6		78.7	20.4	
Shono <i>et al</i> <sup>[78]</sup>	2011	Japan	S, R	137	29.2	89.1	85.4	3.6	
Uraoka <i>et al</i> <sup>[79]</sup>	2011	Japan	S, R	202	39.9	91.6		2.5	0.5
Takeuchi <i>et al</i> <sup>[80]</sup>	2012	Japan	S, R	348	30	91.1		2.3	4.6
Probst <i>et al</i> <sup>[62]</sup>	2012	Germany	S, R	82	45.5	81.6	69.7	1.9	7.9
Toyonaga <i>et al</i> <sup>[112]</sup>	2012	Japan	S, R	1143		99.3		1.4	1.2
Homma <i>et al</i> <sup>[54]</sup>	2012	Japan	M, R	102	32.4	100		1	
Tseng <i>et al</i> <sup>[81]</sup>	2013	Taiwan	S, R	92	37.2	90.2	89.1	12	0
Thorlacius <i>et al</i> <sup>[82]</sup>	2013	Sweden	S, R	29	26	72	69	6.9	3.4
Hülagü <i>et al</i> <sup>[83]</sup>	2013	Turkey	S, R	44	30	77.3		4.5	9.1
Hsu <i>et al</i> <sup>[84]</sup>	2013	Taiwan	S, R	50	33	86	82	6	0
Saito <i>et al</i> <sup>[52]</sup>	2013	Japan	S, R	806	37	90		2.8	1.9
Lee <i>et al</i> <sup>[85]</sup>	2013	South Korea	S, R	1000	24.1	97.5		5.3	0.4
Nakajima <i>et al</i> <sup>[86]</sup>	2013	Japan	M, P	816		94.5		2	2.2
Hori <i>et al</i> <sup>[87]</sup>	2014	Japan	S, P	247	35	93.1	92.3	2	0.4
Bialek <i>et al</i> <sup>[88]</sup>	2014	Poland	S, R	37	37	86.5	81.1	0	5.7
Nawata <i>et al</i> <sup>[56]</sup>	2014	Japan	S, R	150		98.6	91.3	0	0
Yamamoto <i>et al</i> <sup>[14]</sup>	2015	Japan	S, R	119	32.5	97.5	90.8	0.8	1.7

S: Single center; M: Multicenter; R: Retrospective study; P: Prospective study.

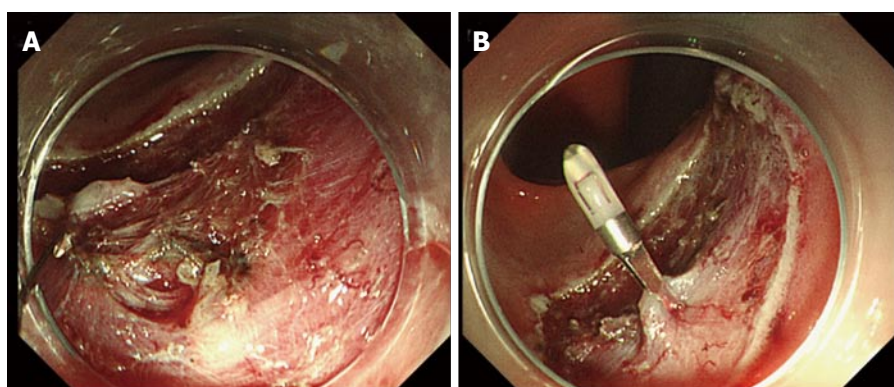
**Table 3** Comparison of local recurrence rates after endoscopic mucosal resection and endoscopic submucosal dissection for removal of large colorectal tumors from previous single-center or multicenter studies

Ref.	Study design	Recurrence rate after EMR ( <i>En bloc</i> resection with EMR) (Tumor size with EMR)	Recurrence rate after ESD ( <i>En bloc</i> resection with ESD) (Tumor size with ESD)	P value
Saito <i>et al</i> <sup>[92]</sup>	S, R	14.0%; 33/228 (33%; 74/228) (28 ± 8 mm)	2%; 3/145 (84%; 122/145) (37 ± 14 mm)	$P < 0.0001$ $P < 0.0001$ $P = 0.0006$
Tajika <i>et al</i> <sup>[93]</sup>	S, R	15.4%; 16/104 (48.1%; 50/104) (25.5 ± 6.8 mm)	1.2%; 1/85 (83.5%; 71/85) (31.6 ± 9.0 mm)	$P = 0.002$ $P < 0.001$ $P < 0.001$
Terasaki <i>et al</i> <sup>[94]</sup>	S, R	8.0%; 14/176 (39.3%; 70/178)	0%; 0/56	
Lee <i>et al</i> <sup>[95]</sup>	S, R	25.7%; 29/113 (42.9%; 60/140) (21.7 ± 3.5 mm)	0.8%; 2/257 (92.7%; 291/314) (28.9 ± 12.7 mm)	$P < 0.001$ $P < 0.001$ $P < 0.001$
Oka <i>et al</i> <sup>[96]</sup>	M, P	6.8%; 55/808 (53.2%; 430/808) (32.8 ± 15.7 mm)	1.4%; 10/716 (95.0%; 680/716) (39.6 ± 18.6 mm)	$P < 0.01$ $P < 0.01$

S: Single center; M: Multicenter; R: Retrospective study; P: Prospective study; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; Tumor size: Mean ± SD.

Post-operative bleeding is less common with colorectal ESD than with gastric ESD and can conser-

vatively managed with hemostatic forceps or endoscopic clipping in the majority of cases<sup>[77,85]</sup>.



**Figure 6 Management of perforation by clipping.** A: Perforation occurring during colorectal endoscopic submucosal dissection; B: Perforation closure using an endoclip.

Abdominal pain or fever due to electrocoagulation syndrome after ESD is occasionally observed, particularly in the proximal colon, and when conservatively managed<sup>[98]</sup>. The occurrence of adverse events may cause an extension in hospital stay<sup>[31,32,98]</sup>.

## CURRENT STATUS AND FUTURE PERSPECTIVES

The safety and success rates of colorectal ESD have recently improved to favorable levels predominantly in advanced institutions in Japan, some Asian, and a few Western countries. However, colorectal ESD is still a technically difficult procedure for majority of endoscopists, and development of training systems is required for world-wide adoption of colorectal ESD<sup>[99,100]</sup>. ESD for rectal and smaller lesions, which is less technically difficult, is suitable for initial adoption of colorectal ESD. Substantial experience of gastric ESD, which is less technically challenging than colorectal ESD, is highly useful for performing colorectal ESD; however, it is difficult in Western countries because of the low morbidity rate of gastric cancer. EMR with circumferential mucosal incision may be option in cases where ESD cannot be successfully performed<sup>[101]</sup>. Before performing colorectal ESD, ESD training using animal models or observing the performance of procedure by ESD experts at other institutions have been shown to be extremely useful in improving operator skill<sup>[102-104]</sup>.

In contrast, some cases are challenging even for experts in colorectal ESD, particularly because of the poor endoscope maneuverability or poor visualization of the operative field due to colonic flexure. Colonic flexure and extensibility commonly causes paradoxical movement of the endoscope. Therefore, double- or single-balloon endoscopy systems have recently been introduced for colorectal ESD at several institutions<sup>[44-46]</sup> because these endoscopy systems enable the endoscope to be straightened more easily than conventional endoscopy. Ohya *et al.*<sup>[44]</sup> reported that a short-type single-balloon overtube through which

a thin conventional endoscope can be introduced was useful for colorectal ESD, particularly for poor endoscope maneuverability in the proximal colon.

Sinker-assisted ESD<sup>[105]</sup>, magnet anchor-guided ESD<sup>[106]</sup>, clip with line-assisted ESD<sup>[107,108]</sup>, clip with rubber- or spring-assisted ESD<sup>[109,110]</sup>, clip-band ESD<sup>[111]</sup>, a double-channel scope method<sup>[112,113]</sup>, and a double endoscopic intraluminal procedure<sup>[114,115]</sup> have all been described as traction systems that facilitate ESD. Each system has a unique traction system that utilizes specialized equipment to provide counter-traction<sup>[107]</sup>. Because these traction systems are somewhat complicated or commercially unavailable, they are not widely used in colorectal ESD at present. The improvement of these traction systems or development of new tractions systems or devices<sup>[116]</sup> may facilitate improvements in the safety or efficacy of colorectal ESD in the future.

## CONCLUSION

In this review, we have described the technical aspects and recent progresses in colorectal ESD. Maintaining good visualization of the operative field is the most important for safely and successfully performing colorectal ESD. Developments of various devices, novel procedures, and appropriate strategies have resulted in the recent improvement of the treatment outcome in colorectal ESD. Further development of training systems or devices will promote world-wide standardization of colorectal ESD.

## ACKNOWLEDGMENTS

We would like to thank Dr. Takashi Toyonaga, Dr. Yoshinori Morita, and CE Ken Yoshimura, all at Kobe University Hospital, Japan, for their technical advice.

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**P- Reviewer:** Matsumoto K, Yoshida N **S- Editor:** Song XX  
**L- Editor:** A **E- Editor:** Wu HL



## Peroral endoscopic myotomy: An emerging minimally invasive procedure for achalasia

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**Conflict-of-interest statement:** Dr. Yalini Vigneswaran and Dr. Michael B Ujiki have no conflicts of interest that are related to the work submitted here for publication.

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Received: May 28, 2015  
Peer-review started: May 31, 2015  
First decision: August 18, 2015  
Revised: August 25, 2015  
Accepted: September 7, 2015  
Article in press: September 8, 2015  
Published online: October 10, 2015

### Abstract

Peroral endoscopic myotomy (POEM) is an emerging

minimally invasive procedure for the treatment of achalasia. Due to the improvements in endoscopic technology and techniques, this procedure allows for submucosal tunneling to safely endoscopically create a myotomy across the hypertensive lower esophageal sphincter. In the hands of skilled operators and experienced centers, the most common complications of this procedure are related to insufflation and accumulation of gas in the chest and abdominal cavities with relatively low risks of devastating complications such as perforation or delayed bleeding. Several centers worldwide have demonstrated the feasibility of this procedure in not only early achalasia but also other indications such as redo myotomy, sigmoid esophagus and spastic esophagus. Short-term outcomes have showed great clinical efficacy comparable to laparoscopic Heller myotomy (LHM). Concerns related to postoperative gastroesophageal reflux remain, however several groups have demonstrated comparable clinical and objective measures of reflux to LHM. Although long-term outcomes are necessary to better understand durability of the procedure, POEM appears to be a promising new procedure.

**Key words:** Endoscopy; Achalasia; Peroral endoscopic myotomy; Myotomy

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**Core tip:** With recent advancements in endoscopic techniques and technology, peroral endoscopic myotomy, also known as peroral endoscopic myotomy (POEM), has emerged as a promising minimally invasive procedure for treating achalasia. POEM uses the technique of endoscopic submucosal dissection to create a myotomy and palliate symptoms of achalasia. Although long-term outcomes are still needed, short-term outcomes show good safety and efficacy of the procedure that are comparable to laparoscopic Heller myotomy. In this review we will review the technical details of the procedure itself as well as the reported outcomes.



Vigneswaran Y, Ujiki MB. Peroral endoscopic myotomy: An emerging minimally invasive procedure for achalasia. *World J Gastrointest Endosc* 2015; 7(14): 1129-1134 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i14/1129.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i14.1129>

## INTRODUCTION

Achalasia is a rare motility disorder of the esophagus that is characterized by non-relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophagus. No cure exists for this idiopathic disease and thus treatment is aimed at palliation of the esophagus to allow for adequate emptying of the esophagus and improvement of symptoms. Palliation requires disruption of the LES, which has been traditionally accomplished by botulinum toxin injection, balloon dilation or surgical myotomy. Endoscopic botulinum toxin treatment is not often the therapy of choice in these patients, due to the short-term therapeutic effect in this chronic disease. Pneumatic balloon dilation forcefully disrupts the sphincter fibers and although several groups have demonstrated efficacy with this technique, dilation is still associated with a significant risk of perforation<sup>[1]</sup>. Surgical myotomy has been conventionally performed laparoscopically by dividing the LES above and below, known as a laparoscopic Heller myotomy (LHM) and typically performed with concurrent anti-reflux procedure. Reports of long-term outcomes have shown the superior efficacy of LHM and thus are often the therapy of choice in many of these patients. However with the advances in technology and endoscopic techniques, this concept of a surgical myotomy has led to the development of an endoscopic approach, peroral endoscopic myotomy (POEM).

## HISTORY AND DEVELOPMENT OF POEM

The use of endoscopic treatment for achalasia was first reported in a case series in 1980 by Ortega *et al*<sup>[2]</sup>. In this series of 17 patients, an endoscopic myotomy was performed using a modified needle knife to directly dissect through the mucosa into the muscular layer to perform a myotomy. Although showing good outcomes, at the time the technique was thought to be unsafe because a direct mucosal approach not only resulted in poor visualization of the muscular layer, but also could result in mediastinal contamination from luminal content. Additionally with limited available devices, the use of the needle knife did not allow for precise and controlled movement, which could potentially lead to high risks of perforation as well as injury to nearby structures. Although abandoned at that time, several decades later the evolution of natural orifice transluminal endoscopic surgery (NOTES) allowed for improvements in endoscopic techniques and technology that subsequently lead to the development of what we

now know of as POEM.

As the growth of NOTES procedures continued, submucosal endoscopy developed as a method to not only work below the mucosa to remove mucosal disease, but also to safely enter sterile cavities by creating a mucosal flap to minimize contamination<sup>[3,4]</sup>. In 2007 using a pig mode, Parischa *et al*<sup>[5]</sup> reported submucosal tunneling with a balloon dilator to create a mucosal flap and a distal esophageal myotomy effectively reducing LES pressure. This addressed the first problem of direct dissection through the mucosa and risk of mediastinal contamination, but the use of the balloon dilator has limitations, due to the inability to accurately position within the wall as well as the associated risks of injury. However in 2010, Inoue *et al*<sup>[6]</sup> reported a modified technique and presented the first case series of successfully performed POEM in humans. The two important alterations included: (1) the use of electrosurgery for the endoscopic submucosal dissection rather than a balloon dilator, which is described below; and (2) the use of a triangle-tip knife for muscle dissection, which allowed for precise dissection under direct visualization. Variations of this technique are now performed by specialized centers worldwide for the treatment of achalasia.

## OPERATIVE TECHNIQUE

Under general anesthesia patients are positioned supine. POEM places these patients at high risk for subcutaneous emphysema and accumulation of gas in the body cavities thus CO<sub>2</sub> should be used for insufflation and if possible positive pressure ventilation should be maintained at pressures higher than that of endoscopic insufflation to reduce the risk of these complications. Initial evaluation of the esophagus and stomach with a high-definition standard upper endoscope is performed to identify the gastroesophageal junction (GEJ). Once the GEJ is identified, an overtube is placed over the endoscope and dissecting cap placed on the endoscope. Approximately 10-15 cm proximal to the GEJ, the mucosa is injected with a mixture of methylene blue, saline, and epinephrine to create a mucosal bleb. Most groups perform this on the anterior aspect of the esophagus, however there may be variation to this positioning. If the patient is presenting for redo myotomy, the operator should typically perform the procedure on the right lateral aspect of the esophagus to avoid the previous myotomy site. The mucosotomy is then made to enter the submucosal space.

The submucosal tunnel is created from the mucosotomy along the lesser curvature to 2-3 cm distal to the GEJ where blanching is identified on the stomach side. The method to dissect this space is based on operator preference. The use of electrosurgery allows for a controlled dissection, with the use of either a triangular-tip knife (Olympus, Center Valley, PA, United States) or a T-type hybrid knife (ERBE, Tubingen, Germany). The alternative option is balloon dilation to develop



**Table 1** Complications after peroral endoscopic myotomy

Complication	Treatment
Mucosal injury	After completion of myotomy, mucosal defects should be closed to minimize risk of leak with clips or suturing device
Full thickness injury	Although certain centers have demonstrated safety with full thickness myotomy, if occurs at site of mucosotomy the operator must consider closure of this myotomy site to prevent potential leakage
Gas escape related complications	
Subcutaneous emphysema	Observation
Pneumomediastinum	Observation, unless physiologic symptoms
Pneumothorax	Small volume closely observed with oxygen only. Volume > 30% may require decompression
Pneumoperitoneum	Large volume or physiologic symptoms requires decompression of the abdomen with Veress needle insertion
Pleural effusion	Small volume can be observed and will absorb. Larger volumes with symptoms require drainage
Bleeding	Most common at the GEJ or distal on stomach side due to increased vascularity. Supportive care and transfusions, endoscopic re-exploration if warranted for hemostasis
Leak/mediastinitis	Depending on time of presentation and extent of perforation will determine the interventions required, which may be as simple as endoscopic treatment or as severe as invasive surgical treatment

GEJ: Gastroesophageal junction.

the plane, however this is a less controlled method, as previously discussed.

The myotomy is started 2-3 cm distal to the mucosotomy and continued to the end of the tunnel at 2-3 cm distal to the GEJ. A partial myotomy is most commonly performed by careful dissection of the circular fibers only, avoiding the longitudinal fibers to avoid entry into the mediastinum. However several groups have explored the option of a complete myotomy through the longitudinal fibers as well<sup>[7,8]</sup>. The mucosotomy is then closed to avoid leak with the use of endoscopic clips or an endoscopic suturing device. After completion of the procedure, the scope should easily traverse the GEJ. The scope can be then removed and patient extubated and recovered.

## COMPLICATIONS AND ADVERSE EVENTS

This invasive endoscopic procedure is not without risks and should only be performed at centers that are capable of treating these complications. Additionally POEM requires operators with specific surgical and endoscopic skills as well as a good understanding of esophageal motility disorders and the available interventions. All standard operative procedures should be followed, including appropriate preoperative evaluation and risk stratification of the patient. The most common complications encountered during or after POEM are listed in Table 1.

Inadvertent mucosotomy is a relatively common complication, especially early in the operators experience, due to the challenges in technique of submucosal tunneling. Although the clinical implications of mucosal injuries are unclear, most centers would recommend closing any defects prior to completion of the procedure to avoid any potential leaks. This is similar to full-thickness muscular injuries that in particular occur at the site of the initial mucosotomy.

Complications related to the insufflation are fairly

common. These complications can be minimized by the use of CO<sub>2</sub> rather than room air, due to the quick diffusion of CO<sub>2</sub>, and by also maintaining low insufflation pressures if possible. The subsequent complications due to insufflation are listed in Table 1 and in most cases have minimal clinical sequelae. However depending on the degree of gas accumulation in these cavities, the patient may require decompression as described in Table 1. All operators performing POEM should be aware of these risks and capable of treating them.

Similarly pleural effusions may commonly occur and depending on the degree of fluid accumulation and patient symptoms, may or may not require intervention. Delayed bleeding appears to be a rare complication of POEM (0.8%-2.7%)<sup>[9,10]</sup>, but if diagnosed must be promptly intervened on. Lastly the most feared complication, esophageal leak with reported rates from 0% to 5.6%<sup>[7,11,12]</sup>, can be a devastating complication if occurs. If the patient is slow to recover there should be high suspicion for gastrointestinal leak and appropriate work up with either endoscopy or imaging. The time to diagnosis of the leak in addition to the extent of the leak will largely determine the required interventions.

## SHORT TERM OUTCOMES

Most centers perform this new procedure under institutional review board oversight as suggested by the NOSCOP POEM White Paper Committee<sup>[13]</sup> and thus several groups have published their initial outcomes. These preliminary results demonstrate highly skilled endoscopists can safely perform the procedure and short-term data suggests promising efficacy. Table 2 summarizes the reported outcomes seen by the experienced centers around the world.

Most centers evaluate efficacy based on symptomatic relief as measured by the Eckardt score and measure clinical success as Eckardt score  $\leq$  3. All of the centers described in Table 2 demonstrated significant improvement in Eckardt scores after POEM. At mean follow up from 1.5 to 12 mo, 89%-100% of patients

**Table 2** Reported outcomes for Large Volume Single Centers after peroral endoscopic myotomy

Ref.	Study size	Myotomy thickness/length	Morbidity	Follow up (mo)	Clinical outcome - before/after	Manometry before/after	Postop PPI
Inoue <i>et al</i> <sup>[14]</sup> 2013	300	Partial 14.1 cm	Pneumothorax 0.3% Mucosal Injury - 2.0%	12	Eckardt - 6.13/1.33 98.2% success	27.3/13.4	4.9%
Ren <i>et al</i> <sup>[10]</sup> 2012	119	Partial 9.2 cm	Pneumothorax - 25.2% Pneumoperitoneum - 39.5% Bleeding 0.8%	3	98.3% success	NA	NA
Friedel <i>et al</i> <sup>[15]</sup> 2013	45	Full 9 cm	Mucosal Injury - 20% Pneumoperitoneum - 13%	3	Eckardt - 7.8/0.4 95% success	NA	NA
Bhayani <i>et al</i> <sup>[9]</sup> 2014	37	Partial	Perforation - 10.8% Bleeding - 2.7%	6.8	Eckardt - 5.4/1.2 Dysphagia - 0%	41/16	NA
Vigneswaran <i>et al</i> <sup>[17]</sup> 2014	37	Partial 12.8 cm	Perforation - 5.4% Mucosal Injury - 2.7%	11.3	Eckardt - 6.8/0.6 100% success	29.1/NA	22%
Hungness <i>et al</i> <sup>[12]</sup> 2013	18	Partial 9 cm	Perforation - 5.6%	6	Eckardt - 7/1 89% success	19/9	NA
von Renteln <i>et al</i> <sup>[7]</sup> 2012	16	Partial and full 12 cm	Perforation - 0% Pneumoperitoneum - 50%	3	Eckardt - 8.8/1.4 94% success	27.2/11.8	6.3%

NA: Not available; PPI: Proton pump inhibitor.

received clinical success from POEM treatment<sup>[7,9-12,14,15]</sup>. Several centers also routinely use manometry postoperatively to evaluate the diagnostic outcomes after POEM, which revealed significant improvement in LES resting pressures<sup>[9,12,14]</sup>. When compared to patients undergoing a standard LHM, patients undergoing POEM had similar symptomatic relief and manometry findings<sup>[9,11,12,16]</sup>. Additionally quality of life improvements after POEM seem to be comparable to reported outcomes after LHM<sup>[17]</sup>. All of these results are promising, but only provide short-term results. Further observation is required to determine the durability of POEM outcomes at long-term follow up.

In addition to the durability, postoperative reflux after POEM has and continues to be a concern with the long-term outcomes. LHM, the gold standard for treatment of achalasia, has a reported occurrence of gastroesophageal reflux (GERD) anywhere from 20% to 100% after surgical myotomy without fundoplication<sup>[18,19]</sup>. This iatrogenic reflux due to the extensive disruption of the LES has lead to routine performance of an anti-reflux procedure in concurrence with the Heller myotomy. Thus without an anti-reflux procedure, GERD after POEM is an important endpoint for efficacy. Objective measures of GERD after POEM such as erosive esophagitis have been found at rates of 6%-40%<sup>[6,7,12,20]</sup> and abnormal pH studies at rates of 20%-40%<sup>[9,21]</sup>. Clinically, 4.9%-33%<sup>[6,7,12,20]</sup> of these patients have reflux symptoms and 4.9%-22% of patients appear to be restarted on proton pump inhibitor therapy after POEM<sup>[7,14,17]</sup>. However, all of these objective and clinical findings appear to be equivalent to LHM with fundoplication in several series<sup>[9,11,12,22]</sup>. The leading theory for possible comparable reflux outcomes is related to the maintained hiatal anatomy after POEM. With an endoscopic approach to the myotomy, the opportunity to preserve the longitudinal muscle fibers as well as not disrupting the GEJ innervation or the diaphragm and the phrenoesophageal ligament, may in fact be enough to avoid significantly worse GERD. However these reported

outcomes of GERD are fairly short-term results and are difficult to compare to LHM outcomes because of the highly variable reported outcomes of reflux after LHM with fundoplication in the literature itself.

## SPECIAL PATIENT COHORTS

Certain special patient cohorts have been studied as possible indications for POEM. These include patients with a previous failed Heller myotomy or POEM, sigmoid type achalasia, spastic esophagus and the pediatric patient. Due to the rarity of these cases, outcomes are not well understood but initial reports discussed below are encouraging.

### Redo myotomy

Patients with failed LHM are difficult to treat. Traditionally patients who fail myotomy can be candidates for additional interventions including repeat Heller myotomy and as a last resort esophagectomy. However due to scarring and adhesive disease that develops around the GEJ from the initial operation, these redo cases can be quite challenging. Moreover, although repeat Heller myotomy is often successful, 20%-30% of patients will undergo this relatively risky procedure and still fail after second Heller myotomy<sup>[23,24]</sup>. Thus, POEM provides a unique opportunity to potentially treat these patients without enduring a challenging and involved operation. Several centers including our own have reported the use of POEM to treat patients with failed Heller myotomy. Initial outcomes show the procedure is safe and at short-term follow-up has 90%-100% success<sup>[25-27]</sup>. Even with previous fundoplication, the procedure is performed in these patients almost identical to patients without previous myotomy with exception of the location of the second myotomy. The recommendation is to avoid the previous myotomy that is conventionally performed anterior and to perform the repeat myotomy right lateral on the esophagus. Similar outcomes have been observed in those patients with previous POEM

presenting for redo POEM<sup>[28]</sup>.

### Sigmoid esophagus

Sigmoid-shaped esophagus is often seen in advanced achalasia cases and can be a complicated disease to treat. Although initial approaches to treatment are debatable, most would advocate for treating these patients with myotomy before discussing esophagectomy<sup>[29-32]</sup>. The use of POEM in these advanced staged patients has been reported with good feasibility and short-term success<sup>[6,33]</sup>. However, due to the anatomical changes in the esophagus these cases are particularly challenging, especially when developing the submucosal space, and should only be performed by highly experienced operators.

### Spastic esophagus

Spastic disorders of the esophagus are characterized by abnormal contractility of the esophagus and can be divided into spastic achalasia, diffuse esophageal spasm, and hypercontractile or jackhammer esophagus. These motility disorders are difficult to treat and often long-term clinical success is only accomplished with surgical myotomy<sup>[34]</sup>. Treating these patients with POEM is safe and at initial short term follow up is efficacious<sup>[35,36]</sup>. In a recent multicenter study which included 73 patients with spastic esophagus, when an extended myotomy was performed with POEM, 93% clinical success was observed at an average of 8 mo<sup>[37]</sup>. However as with POEM in the typical achalasia patient, longer term studies are necessary to understand the durability of these treatments.

### Pediatric patients

Though rare, achalasia presenting in pediatric patients can lead to significant problems with malnutrition and subsequently mental and physical development. These patients are not good candidates for endoscopic therapies due to short term durability with the growing child and the gold standard of treatment is surgical myotomy. Chen *et al.*<sup>[38]</sup> demonstrated POEM can be safely performed for pediatric patients and in 27 patients showed 100% clinical success at an average of 25 mo and thus can be considered in a pediatric patient.

## CONCLUSION

POEM is an emerging new technique for treating achalasia that evolved from the era of NOTES. POEM may also expand the therapeutic options for patients with challenging esophageal disease due to the growing indications, including patients with previous myotomy, sigmoid esophagus and spastic esophagus. Short-term results from experienced centers allow for cautious optimism with this minimally invasive technique, however questions remain as to long-term durability and subsequent GERD. Patients offered POEM should be counseled about our limited knowledge of long-term outcomes as well as the potential risk of GERD.

Continued observation of long-term outcomes will be necessary as we continue to understand this procedure.

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P- Reviewer: Ramchandani M S- Editor: Ji FF  
L- Editor: A E- Editor: Wu HL





## Endoscopic retrograde cholangiopancreatography-related perforations: Diagnosis and management

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**Conflict-of-interest statement:** No author has conflict of interest related to the manuscript.

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Received: April 27, 2015

Peer-review started: April 30, 2015

First decision: July 25, 2015

Revised: July 31, 2015

Accepted: September 7, 2015

Article in press: September 8, 2015

Published online: October 10, 2015

### Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has become an important therapeutic modality for biliary and pancreatic disorders. Perforation is one of the most feared complications of ERCP and endoscopic sphincterotomy. A MEDLINE search was performed

from 2000-2014 using the keywords "perforation", "ERCP" and "endoscopic sphincterotomy". All articles including more than nine cases were reviewed. The incidence of ERCP-related perforations was low (0.39%, 95%CI: 0.34-0.69) with an associated mortality of 7.8% (95%CI: 3.80-13.07). Endoscopic sphincterotomy was responsible for 41% of perforations, insertion and manipulations of the endoscope for 26%, guidewires for 15%, dilation of strictures for 3%, other instruments for 4%, stent insertion or migration for 2% and in 7% of cases the etiology was unknown. The diagnosis was made during ERCP in 73% of cases. The mechanism, site and extent of injury, suggested by clinical and radiographic findings, should guide towards operative or non-operative management. In type I perforations early surgical repair is indicated, unless endoscopic closure can be achieved. Patients with type II perforations should be treated initially non-operatively. Non-operative treatment includes biliary stenting, fasting, intravenous fluid resuscitation, nasogastric drainage, broad spectrum antibiotics, percutaneous drainage of fluid collections. Non-operative treatment was successful in 79% of patients with type II injuries, with an overall mortality of 9.4%. Non-operative treatment was sufficient in all patients with type III injuries. Surgical technique depends on timing, site and size of defect and clinical condition of the patient. In conclusion, diagnosis is based on clinical suspicion and clinical and radiographic findings. Whilst surgery is usually indicated in patients with type I injuries, patients with type II or III injuries should be treated initially non-operatively. A minority of them will finally require surgical intervention.

**Key words:** Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Perforation

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**Core tip:** Perforation is one of the most feared complications of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy. The



incidence of ERCP-related perforations is low (0.39%) with an associated mortality of 7.8%. Endoscopic sphincterotomy is responsible for 41% of perforations and endoscope manipulations for 26%. The mechanism, site and extent of injury, suggested by clinical and radiographic findings, should guide towards operative or non-operative management. Classification into types permits a tailored approach to management. Whilst surgery is usually indicated in patients with type I injuries, patients with type II or III injuries should be treated initially non-operatively. A minority of them will finally require surgical intervention.

Vezakis A, Fragulidis G, Polydorou A. Endoscopic retrograde cholangiopancreatography-related perforations: Diagnosis and management. *World J Gastrointest Endosc* 2015; 7(14): 1135-1141 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i14/1135.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i14.1135>

## INTRODUCTION

In the era of minimally invasive therapy, endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy has become an important therapeutic modality for the treatment of biliary and pancreatic disorders. Although considered as a safe procedure, it is associated with complications such as pancreatitis, bleeding and perforation. The incidence of ERCP-related complications is 5%-10% and the overall mortality 0.1%-1%<sup>[1-5]</sup>.

Perforation is one of the most feared complications of ERCP and sphincterotomy. In a review of 21 prospective studies<sup>[6]</sup>, addressing ERCP complications, between 1987-2003, perforations occurred in 101 patients (0.6%, 95%CI: 0.48-0.72) with a perforation related mortality of 9.90% (95%CI: 3.96-15.84).

Traditionally, the standard treatment for iatrogenic duodenal perforations has been early surgical repair. Recently, non operative management of ERCP-related perforations has increased. However, it is difficult to evaluate the efficacy of different treatments, because of the rarity of the complication and there is no consensus for optimal management.

This review aims to evaluate the incidence, diagnosis and treatment of ERCP-related perforations.

## RESEARCH

A MEDLINE search was performed from 2000-2014 using the keywords "perforation", "ERCP" and "endoscopic sphincterotomy". All articles including more than nine cases were reviewed. No randomized controlled trial could be identified.

## CLASSIFICATION

There are two proposed classifications of ERCP-

related perforations. In 1999, Howard *et al*<sup>[7]</sup> classified perforations into three distinct types: type I, guidewire perforation; type II, periampullary perforation; type III, duodenal perforation remote from the papilla. In 2000 Stapfer *et al*<sup>[8]</sup> classified ERCP-related perforations into four types, based on the mechanism, anatomical location and severity of injury, which may predict the need for surgery. The Stapfer classification is the most commonly used and it divides perforations into: Type I, lateral or medial wall duodenal perforation; type II, perivaterian injuries; type III, distal bile duct injuries related to guidewire-basket instrumentation and type IV, retroperitoneal air alone. Type IV is questionable and it is not a true perforation. Due to the excess compression of air in the duodenum, air bubbles can leak through the sphincterotomy area outside the duodenal lumen, into the retroperitoneal space. The presence of retroperitoneal air is a common finding after endoscopic sphincterotomy. CT scan, when used routinely after ERCP and sphincterotomy, may detect retroperitoneal air in 13% to 29% of patients<sup>[9,10]</sup>. In the absence of symptoms, it has no clinical significance and these patients do not require any further intervention.

## INCIDENCE AND RISK FACTORS

Reviewing 18 studies<sup>[8,11-27]</sup>, between 2000-2014 (mainly retrospective), addressing only ERCP-related perforations, including 142847 patients, the incidence was 0.39% (95%CI: 0.34-0.69). According to Stapfer classification, type I counted 25%, type II 46% and type III 22%. The overall mortality was 7.8% (95%CI: 3.80-13.07) (Table 1).

A multivariate analysis to reveal risk factors was performed in two studies<sup>[4,14]</sup>. Precut, Billroth II gastrectomy and intramural injection of contrast medium were significant risk factors for retroperitoneal duodenal perforation by Loperfido *et al*<sup>[4]</sup>. In Enns *et al*<sup>[14]</sup>'s study, factors existing prior to ERCP which predicted perforation included sphincter of Oddi dysfunction and a dilated common bile duct. Predictive factors related to ERCP itself included duration of procedure, biliary stricture dilation and performance of a sphincterotomy. Precut didn't reach statistical significance in that study.

## ETIOLOGY

The mechanism of injury is mentioned in 573 patients from 18 studies<sup>[8,11-15,17-23,25-29]</sup> (Table 2). Endoscopic sphincterotomy was responsible for 41% of perforations, insertion and manipulations of the endoscope for 26%, guidewires for 15%, dilation of strictures for 3%, other instruments for 4%, stent insertion or migration for 2% and in 7% of cases the etiology was unknown.

## DIAGNOSIS

Early diagnosis and prompt treatment during the endoscopic procedure are vital for a better outcome<sup>[7,30]</sup>.

**Table 1** Incidence of perforations and overall mortality

Ref.	Design	n	Perforations (%)	Types <sup>1</sup>				Mortality (%)	
				I	II	III	IV		
Assalia <i>et al</i> <sup>[11]</sup> , 2007	Prosp	3104	22 (0.70)	2	17	2		1	(4.5)
Avgerinos <i>et al</i> <sup>[12]</sup> , 2009	Retro	4358	15 (0.34)	9	3		1	3	(20)
Dubecz <i>et al</i> <sup>[13]</sup> , 2012	Retro	12232	11 (0.08)	7	3	1		2	(18)
Enns <i>et al</i> <sup>[14]</sup> , 2002	Case control	9314	33 (0.35)	5	13	15		1	(3)
Fatima <i>et al</i> <sup>[15]</sup> , 2007	Retro	12427	75 (0.60)	8	26	35	6	5	(6.6)
Jin <i>et al</i> <sup>[16]</sup> , 2013	Retro	22998	59 (0.26)	17	36	6		5	(8.4)
Kayhan <i>et al</i> <sup>[17]</sup> , 2004	Retro	3124	17 (0.54)	2	15			-	-
Kim <i>et al</i> <sup>[18]</sup> , 2011	Retro	7638	13 (0.17)	4	5	4		0	(0)
Kim <i>et al</i> <sup>[19]</sup> , 2012	Retro	11048	68 (0.61)	13	31	22		4	(5.8)
Knudson <i>et al</i> <sup>[20]</sup> , 2008	Retro	4919	32 (0.65)	6	11	7		0	(0)
Kwon <i>et al</i> <sup>[21]</sup> , 2012	Retro	8381	53 (0.63)	21	24	8		3	(5.6)
Li <i>et al</i> <sup>[22]</sup> , 2012	Retro	8504	16 (0.45)	7	5	4		0	(0)
Mao <i>et al</i> <sup>[23]</sup> , 2008	Retro	2432	9 (0.37)	8	1			0	(0)
Miller <i>et al</i> <sup>[24]</sup> , 2013	Retro	1638	27 (1.60)	5	12	5	5	9	(33)
Morgan <i>et al</i> <sup>[25]</sup> , 2009	Retro	12817	24 (0.18)	12	12			1	(4.1)
Polydorou <i>et al</i> <sup>[26]</sup> , 2011	Retro	9880	44 (0.44)	7	30	5	2	2	(4.5)
Stapfer <i>et al</i> <sup>[8]</sup> , 2000	Retro	1413	14 (0.99)	5	6	3		2	(14)
Wu <i>et al</i> <sup>[27]</sup> , 2006	Retro	6620	30 (0.45)	5	11	7		5	(16)
Total		142847	562 (0.39)	143 (25%)	261 (46%)	124 (22%)		43/545	(7.8)

<sup>1</sup>Classification of types is assumed, because not all studies clearly defined the type of perforation according to Stapfer classification<sup>[8]</sup>.

**Table 2** Assumed etiology of perforations

Ref.	Endo scope	ES	Guide wire	Dilation of strictures	Other instruments	Stent insertion or migration	Unknown
Alfieri <i>et al</i> <sup>[28]</sup> , 2013	6	15	1				8
Assalia <i>et al</i> <sup>[11]</sup> , 2007	2	17	2			1	
Avgerinos <i>et al</i> <sup>[12]</sup> , 2009	9	3					3
Dubecz <i>et al</i> <sup>[13]</sup> , 2012	7	3	1				
Enns <i>et al</i> <sup>[14]</sup> , 2002	5	13	13	2			
Fatima <i>et al</i> <sup>[15]</sup> , 2007	8	11	24	5	9	7	11
Krishna <i>et al</i> <sup>[29]</sup> , 2011	11	1	2				
Kayhan <i>et al</i> <sup>[17]</sup> , 2004	2	15					
Kim <i>et al</i> <sup>[18]</sup> , 2011	4	3	4		2		
Kim <i>et al</i> <sup>[19]</sup> , 2012	13	25	23		2		5
Knudson <i>et al</i> <sup>[20]</sup> , 2008	6	11			4	3	8
Kwon <i>et al</i> <sup>[21]</sup> , 2012	21	24	2	6			
Mao <i>et al</i> <sup>[23]</sup> , 2008	-	8			1		
Li <i>et al</i> <sup>[22]</sup> , 2012	7	5			4		
Morgan <i>et al</i> <sup>[25]</sup> , 2009	12	12					
Polydorou <i>et al</i> <sup>[26]</sup> , 2011	7	30	2	2	3		
Stapfer <i>et al</i> <sup>[8]</sup> , 2000	5	6	3				
Wu <i>et al</i> <sup>[27]</sup> , 2006	5	11	7				7
Total (%)	130 (25)	213 (41)	84 (16)	15 (3)	25 (5)	11 (2)	42 (8)

ES: Endoscopic sphincterotomy.

ERCP-related perforations can usually be diagnosed during ERCP, from the endoscopic view or using fluoroscopy. In a review of 437 cases from 15 studies<sup>[8,12-15,17-24,26,27]</sup> the diagnosis was made during ERCP in 73% of cases (Table 3). The definition of delayed diagnosis was inconsistent between studies, but it was considered to be associated with worst prognosis<sup>[11,16,22]</sup>. Type I perforations can be diagnosed from direct visualization of the retroperitoneal space (Figure 1) or the abdominal cavity. In doubtful cases with bleeding and not clear endoscopic view, the use of fluoroscopy with or without contrast injection can confirm the

diagnosis. Type II perforations can be suspected after a large or wrong direction sphincterotomy and can be confirmed by fluoroscopy. Fluoroscopy will reveal the presence of retroperitoneal air, especially around the right kidney with delineation of kidney margin (Figure 2) and occasionally the outlining of psoas muscle. The injection of contrast can also show leaking from the sphincterotomy site. Type III perforations can be diagnosed by the unusual passage of the guide wire or by the injection of contrast.

At the end of every endoscopic procedure, thorough control for any possible perforation should be performed.

**Table 3** Time to diagnosis of endoscopic retrograde cholangiopancreatography related perforations

Ref.	During ERCP (%)	After ERCP
Avgerinos <i>et al</i> <sup>[12]</sup> , 2009	4 (26)	11
Dubecz <i>et al</i> <sup>[13]</sup> , 2012	5 (45)	6
Enns <i>et al</i> <sup>[14]</sup> , 2002	28 (84)	5
Fatima <i>et al</i> <sup>[15]</sup> , 2007	45 (60)	30
Kayhan <i>et al</i> <sup>[17]</sup> , 2004	17 (100)	0
Kim <i>et al</i> <sup>[18]</sup> , 2011	10 (77)	3
Kim <i>et al</i> <sup>[19]</sup> , 2012	46 (95)	2
Knudson <i>et al</i> <sup>[20]</sup> , 2008	11 (34)	21
Kwon <i>et al</i> <sup>[21]</sup> , 2012	39 (73)	14
Li <i>et al</i> <sup>[22]</sup> , 2012	16 (100)	0
Mao <i>et al</i> <sup>[23]</sup> , 2008	8 (88)	1
Miller <i>et al</i> <sup>[24]</sup> , 2013	18 (66)	9
Polydorou <i>et al</i> <sup>[26]</sup> , 2011	42 (95)	2
Stapfer <i>et al</i> <sup>[8]</sup> , 2000	13 (93)	1
Wu <i>et al</i> <sup>[27]</sup> , 2006	19 (63)	11
Total	321(73)	116

ERCP: Endoscopic retrograde cholangiopancreatography.

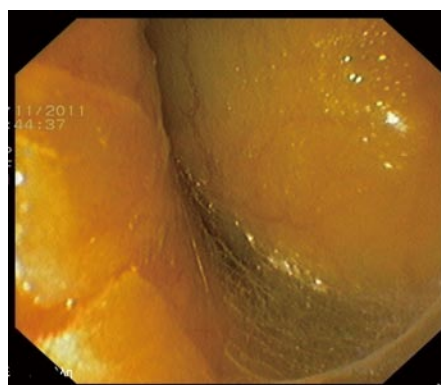
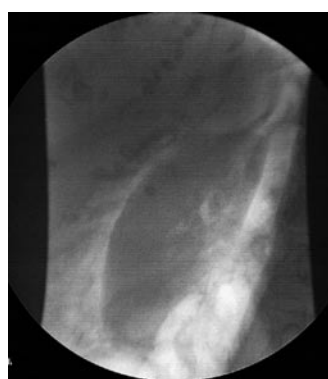
**Table 4** Comparison of different types of stents used for type II, III perforations

	Technical success	Biliary drainage	Covering the perforation	Repeat ERCP for removal	Cost
SEMS	+++	+++	+++	Y	+++
Plastic biliary stents	+++	++	+	Y	+
Nasobiliary drain	+++	+	—	N	+

SEMS: Covered self expanding metallic biliary stents; Y: Yes; N: No; ERCP: Endoscopic retrograde cholangiopancreatography.

The endoscopist should inspect the circumference of the duodenum carefully and check the X-ray for the presence of retroperitoneal air. This concern is especially true when the procedure is technically difficult; needle-knife pre-cut has been performed; there are variations in the usual anatomy due to previous operative interventions; strictures are dilated. If there is high suspicion contrast medium can be infused through the endoscope to facilitate identification of the injury.

Patients with undetected leaks can present hours after the ERCP with pain, fever and leukocytosis. In cases of intraperitoneal type I perforations, the diagnosis is usually obvious with severe pain and signs of peritonitis. When a patient experiences severe pain after ERCP, a differential diagnosis between acute pancreatitis and perforation should be made. In cases of retroperitoneal perforations the diagnosis is not so obvious. The patient may complain of mild epigastric pain but signs of peritonitis may develop after several hours or may not develop at all, depending on the size of the leak. The presence of subcutaneous emphysema may be evident from the first hours, especially at right abdominal wall, back or even cervix. Tachycardia is a constant finding, but it can be caused by other factors including pain. Leukocytosis and fever are often seen

**Figure 1** Endoscopic view of the retroperitoneal space after an endoscope-related perforation.**Figure 2** Retroperitoneal air delineating kidney margin after a sphincterotomy-related perforation.

12 h or more after completion of the procedure. A mild elevation of serum amylase levels is caused from the absorption of pancreatic fluid from the retroperitoneal space.

In cases with suspicion of perforation, a CT scan with oral contrast should be obtained. The presence of retroperitoneal air can also be detected by plain films, but CT scan is more sensitive<sup>[10,31]</sup>, it may demonstrate the leak and the presence of fluid collections.

## TREATMENT

After the recognition of an ERCP-related perforation, the first dilemma is conservative treatment or surgery. That depends on the mechanism of injury, site and degree of leak and patient condition<sup>[28,32]</sup>. Endoscope related perforations (type I) should be referred for immediate surgery, unless endoscopic closure can be achieved. Endoscopic closure using fibrin glue, endoloops and endoclips or an over the scope clipping device has been described<sup>[33-36]</sup>.

In cases of endoscopic sphincterotomy related perforations (type II), when diagnosed during the procedure, biliary drainage is essential in order to prevent leakage of bile into the perforation site. In Enns study<sup>[14]</sup>, 5/13 patients with type II injuries were managed successfully either with plastic biliary stents

**Table 5 Outcome after initial non-surgical management of type II and III perforations**

Ref.	Type II				Type III		
	<i>n</i>	Surgery (%)	Mortality (%)		<i>n</i>	Surgery (%)	Mortality (%)
			After surgery	Overall			
Assalia <i>et al</i> <sup>[11]</sup> , 2007	17	2 (11)	1 (50)	1 (6)	2	0	0
Enns <i>et al</i> <sup>[14]</sup> , 2002	13	2 (15)	0	0	15	0	0
Kim <i>et al</i> <sup>[18]</sup> , 2011	3	1 (33)	0	0	4	0	0
Kwon <i>et al</i> <sup>[21]</sup> , 2012	24	0	0	1 (4)	7	0	0
Li <i>et al</i> <sup>[22]</sup> , 2012	5	0	0	0	4	0	0
Mao <i>et al</i> <sup>[23]</sup> , 2008	8	3 (37)	0	0	1	0	0
Miller <i>et al</i> <sup>[24]</sup> , 2013	9	7 (77)	5 (71)	6 (66)	5	0	0
Morgan <i>et al</i> <sup>[25]</sup> , 2009	12	0	0	0			
Polydorou <i>et al</i> <sup>[26]</sup> , 2011	30	6 (20)	0	0	5	0	0
Stapfer <i>et al</i> <sup>[8]</sup> , 2000	5	3 (60)	1 (33)	1 (20)	3	0	0
Wu <i>et al</i> <sup>[27]</sup> , 2006	11	5 (45)	4 (80)	4 (36)	7	0	0
Total	137	29 (21)	11 (38)	13 (9.4)	53	0	0

or percutaneous transhepatic biliary drainage. In Alfieri *et al*<sup>[28]</sup>'s study, 12/30 patients with early diagnosis were successfully treated conservatively with nasobiliary drainage.

Several case series have reported the use of fully covered self expandable metallic stents (SEMS) in sphincterotomy related perforations. SEMS have the advantage of covering the laceration and permit free flow of bile into the duodenum instead of into the retroperitoneal space. It seems better to use a covered SEMS because plastic stents or nasobiliary drains may not prevent bile flow into the perforation site completely. SEMS can also be used later with a repeat ERCP when the leak persists<sup>[37-40]</sup>. The advantages and disadvantages of different types of stents are shown in Table 4.

When a sphincterotomy related perforation is diagnosed after the procedure it should be assessed by a CT scan with contrast orally to demonstrate the degree of leak. Major contrast leak is an indication for immediate surgery, whilst minimal or no leak can be treated non-operatively<sup>[30,32]</sup>. Non-operative treatment includes nil by mouth, nasogastric tube, intravenous fluid resuscitation, broad spectrum antibiotics, repeat endoscopy for stenting in selected cases, and radiologic interventions for percutaneous drainage of fluid collections. Total parenteral nutrition is recommended in undernourished patients or when adequate enteral feeding will be impeded for at least seven days<sup>[41]</sup>. Generally, indications for surgery are: Major contrast leak; sepsis despite non-surgical treatment; presence of peritonitis or retroperitoneal fluid collections not amenable to percutaneous drainage; unsolved problems like stones or retained hardware (baskets)<sup>[28,30,32,41]</sup>. The clinical condition of the patient should be the key factor determining the mode of treatment<sup>[14,28,42]</sup>. Knudson *et al*<sup>[20]</sup> devised a clinical index score to predict the need for operative intervention. This 4-point scoring system assigned 1 point for each of the following: fever, tachycardia, guarding on examination and leukocytosis. The odds ratio for requiring operative management in patients with a score of greater than or equal to 3 was

40 (5.3-303.1,  $P < 0.001$ ). In two studies<sup>[15,26]</sup> applying multivariate logistic regression analysis only ASA score and site of perforation remained significant for predicting operative treatment.

Reviewing 11 studies<sup>[8,11,14,18,21-27]</sup>, after initial non-surgical treatment, surgery was required in 29/137 (21%) of patients with type II perforations, with an overall mortality of 9.4% (Table 5). The mortality of patients who required surgery was high (38%). Non-surgical management was successful in all patients with type III perforations (Table 4). In a recent review<sup>[32]</sup> conservative management was successful in 92.9% of patients with both types of injuries, treated initially non-operatively, with a final mortality of 0.6%.

In the available literature there are no prospective comparative studies between surgical techniques for ERCP-related perforations. Surgical technique depends on site and size of defect, timing of surgery and clinical condition of the patient.

The main goal of immediate surgery is to repair the perforation and diversion of bile and gastric fluid, if required. Endoscope related duodenal perforations (type I) can be closed primarily in one or two layers, following debridement of devitalized tissue. The closure should be oriented transversely in order to avoid compromising the duodenal lumen. In cases with large defects the options are jejunal serosal patch closure or tube duodenostomy. Leak from the duodenal closure line is a major concern and duodenal diversion should be suggested in large defects or delayed diagnosis. The rationale is to divert the gastrointestinal content and proteolytic enzymes from the duodenal repair site. In sphincterotomy related perforations (type II), a non-operative approach is successful in nearly 80% of cases. When the clinical condition of the patient or the size of the leak requires immediate surgery, a transduodenal approach and repair, by performing sphincteroplasty within 24 h, has been described with good results<sup>[43]</sup>.

The main goals of delayed surgery are to control sepsis, to repair the perforation if possible, and diversion, if required<sup>[28,30,32,43,44]</sup>. Delayed surgery is performed in patients who remain septic despite non-



operative treatment, and debridement and drainage of the retroperitoneal space is required. That can be achieved by an extraperitoneal approach (right posterior laparostomy)<sup>[28]</sup> or transperitoneal approach when cholecystectomy, common bile duct exploration with T-tube placement or diversion techniques are required. The perforation site cannot be found in 16% to 80% in delayed surgery<sup>[24,27,44]</sup> or the tissues are too edematous for primary repair. The transduodenal approach is not indicated for delayed surgery.

Diversion of gastric and duodenal fluid is mandatory and can be achieved by: placement of a nasogastric or nasoduodenal tube; tube duodenostomy; pyloric exclusion and gastrojejunostomy; gastrojejunostomy alone; T-tube placement for bile diversion; duodenal diverticulization<sup>[7,8,11,12,15,20,23,25,27,29]</sup>. Duodenal diverticulization consists of Billroth II gastrectomy, placement of a decompressive catheter into the duodenum, closure of duodenal wound and drainage<sup>[45]</sup>. The main drawback of duodenal diverticulization is that it is an extensive procedure which may be inappropriate in septic, unstable patients. Pyloric exclusion is a less invasive alternative. This procedure consists of duodenal wound repair, closure of the pylorus with a running suture or by stapling and gastrojejunostomy. Pyloric exclusion is a less extensive procedure, less time consuming, causes less physiological disturbances and it is advocated by most clinicians, when duodenal diversion is required.

In conclusion, ERCP-related perforation is uncommon (0.39%), but it is associated with an overall mortality of 7.8%. Early diagnosis and treatment are essential for a better outcome. The mechanism, site and extent of injury, suggested by clinical and radiographic findings, should guide towards conservative or surgical management. In type I perforations early surgical repair is indicated, unless endoscopic closure can be achieved. Patients with type II perforations should be treated initially non-operatively. Non-operative treatment is successful in 79% of patients with an overall mortality of 9.4%. Non-operative treatment is sufficient in all patients with type III injuries. Surgical technique depends on size and site of defect, timing and clinical condition of the patient.

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P- Reviewer: Chen CH, Changela K, Tantau A S- Editor: Ji FF  
L- Editor: A E- Editor: Wu HL



## Prospective Study

## Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy vs mucosal cutting biopsy

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**Author contributions:** Ikehara H and Li Z contributed equally to this work; Watari J and Miwa H designed and performed the research study; Ikehara H, Li Z, Taki M, Kondo T, Tozawa K performed the procedures; All the authors helped to collect the data; Matsuda I and Hirota S diagnosed the histology; Watari J performed statistical analysis and wrote the paper.

**Institutional review board statement:** This study was approved by the Institutional Review Board at Hyogo College of Medicine, Nishinomiya, Japan.

**Informed consent statement:** All patients in the study gave informed consent for the procedures.

**Conflict-of-interest statement:** None.

**Data sharing statement:** The technical appendix, statistical code, and dataset are available from the corresponding author ([watarij@hyo-med.ac.jp](mailto:watarij@hyo-med.ac.jp)). Consent for data sharing was not obtained from the participants, but the presented data are anonymized and the risk of identification is low.

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Received: April 19, 2015

Peer-review started: April 21, 2015

First decision: June 3, 2015

Revised: June 21, 2015

Accepted: September 7, 2015

Article in press: September 8, 2015

Published online: October 10, 2015

### Abstract

**AIM:** To compare the usefulness of endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) without cytology and mucosal cutting biopsy (MCB) in the histological diagnosis of gastric submucosal tumor (SMT).

**METHODS:** We prospectively compared the diagnostic yield, feasibility, and safety of EUS-FNAB and those of MCB based on endoscopic submucosal dissection. The cases of 20 consecutive patients with gastric SMT  $\geq 1$  cm in diameter, who underwent both EUS-FNAB and MCB were investigated.

**RESULTS:** The histological diagnoses were gastrointestinal stromal tumors ( $n = 7$ ), leiomyoma ( $n =$



6), schwannoma ( $n = 2$ ), aberrant pancreas ( $n = 2$ ), and one case each of glomus tumor, metastatic hepatocellular carcinoma, and no-diagnosis. The tumors' mean size was 23.6 mm. Histological diagnosis was made in 65.0% of the EUS-FNABs and 60.0% of the MCBs, a nonsignificant difference. There were no significant differences in the diagnostic yield concerning the tumor location or tumor size between the two methods. However, diagnostic specimens were significantly more frequently obtained in lesions with intraluminal growth than in those with extraluminal growth by the MCB method ( $P = 0.01$ ). All four SMTs with extraluminal growth were diagnosed only by EUS-FNAB ( $P = 0.03$ ). No complications were found in either method.

**CONCLUSION:** MCB may be chosen as an alternative diagnostic modality in tumors showing the intraluminal growth pattern regardless of tumor size, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

**Key words:** Submucosal tumor; Endoscopic ultrasonography-guided fine-needle aspiration biopsy; Gastrointestinal stromal tumor; Mucosal cutting biopsy; Endoscopic submucosal dissection

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**Core tip:** We prospectively compared the diagnostic yield and the safety between endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) without cytology and mucosal cutting biopsy (MCB) based on endoscopic submucosal dissection. Although no significant difference in histological diagnosis was found between EUS-FNAB and MCB, diagnostic specimens were significantly more frequently obtained in the lesions with intraluminal growth compared to those with extraluminal growth by the MCB method. All submucosal tumors (SMTs) with extraluminal growth were diagnosed only by EUS-FNAB. No complications were found in either method. Therefore, MCB may be chosen as an alternative diagnostic modality in tumors showing intraluminal growth, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

Ikehara H, Li Z, Watari J, Taki M, Ogawa T, Yamasaki T, Kondo T, Toyoshima F, Kono T, Tozawa K, Ohda Y, Tomita T, Oshima T, Fukui H, Matsuda I, Hirota S, Miwa H. Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy vs mucosal cutting biopsy. *World J Gastrointest Endosc* 2015; 7(14): 1142-1149 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i14/1142.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i14.1142>

## INTRODUCTION

Gastric submucosal tumors (SMTs) including gastroin-

testinal stromal tumors (GISTs), leiomyomas, schwannomas, aberrant pancreas and more are frequently identified during routine upper endoscopies. Although endoscopic ultrasonography (EUS) is a useful modality for diagnosing gastric SMTs<sup>[1]</sup>, it is not always possible to differentiate a GIST from a leiomyoma or schwannoma by EUS, especially when the tumor originated from the muscularis propria layer. GISTs are rare neoplasms that account for only 0.1%-3% of all gastrointestinal (GI) malignancies<sup>[2-4]</sup>, whereas they represent approximately 80% of GI mesenchymal tumors<sup>[5]</sup>. As GISTs are potentially malignant, histological diagnosis by an EUS-fine-needle aspiration biopsy (FNAB) is recommended<sup>[6,7]</sup>. It is thus very important to discriminate these lesions from benign SMTs originating from the muscularis propria, such as leiomyomas and schwannomas. However, it may be difficult to arrive at the correct histological diagnosis with only a standard endoscopic biopsy, because the surface of an SMT is covered with normal epithelium.

EUS-FNAB is a reliable, useful and suitable method for the histological evaluation of SMTs<sup>[8-10]</sup>. Although EUS-FNAB is used widely, only a limited number of cases are subjected to this method, even in hospitals specializing in gastroenterology. In addition, EUS-FNAB systems including an echoendoscope and its observing system are very expensive and require not only experienced pathologists but also cytology technicians capable of handling and processing biopsy specimens<sup>[7]</sup>. The successful diagnostic rate for SMT by an EUS-FNAB combined with cytology has been reported to be relatively high (83%), but the success rate for histology is not satisfactory (50%)<sup>[9,11-13]</sup>. An alternative modality for the histological diagnosis of SMTs is thus needed.

Endoscopic submucosal dissection (ESD) was developed in Japan in the 2000s<sup>[14]</sup> and has since been widely adopted for the treatment of superficial gastric neoplasms. By applying this method, Lee *et al.*<sup>[15]</sup> described cases in which an ESD-associated technique rather than EUS-FNAB was useful for the tissue sampling of SMTs. The applications of several similar methods for the histological diagnosis of gastrointestinal (GI) SMTs were also reported: mucosal cutting biopsy (MCB), a mucosal incision-assisted biopsy technique, and an "unroofing" biopsy based on endoscopic mucosal resection (EMR)<sup>[16-20]</sup>.

A comparison of the histological diagnostic yield of SMTs between EUS-FNAB without its combination with cytology and MCB has not been published, to our knowledge. The aim of the present study was to prospectively compare the diagnostic yield of gastric SMTs and the feasibility, safety and complications between EUS-FNAB and MCB by performing both diagnostic modalities simultaneously for the same SMT patients.

## MATERIALS AND METHODS

### Patients

Between May 2012 and February 2015 in our depart-



ment, both EUS-FNAB and MCB were prospectively performed for 20 consecutive patients with gastric SMTs  $\geq 1$  cm in diameter which were diagnosed by EUS (UM2000, UM-2R and 3R; Olympus Optical Corp., Tokyo) prior to the EUS-FNAB and MCB procedures. If the EUS finding of SMT showed mainly inward or outward growth from the gastric wall, the lesion was judged as intraluminal or extraluminal growth, respectively. Since hyperechoic lesions on EUS that originate from the submucosal layer are generally diagnosed as lipoma, these lesions were excluded from the study. All patients were admitted on the day of EUS-FNAB and MCB, and were usually discharged the day after the procedures. Thus the hospital stay for the patients without any clinical complications was generally 1 d, based on the clinical protocol at our hospital.

Written informed consent was obtained from all patients prior to the study, and the study design was approved by the Ethics Committee of Hyogo College of Medicine (No. 1710).

#### **Operators of the EUS-FNAB and MCB procedures**

Operator skill may affect the diagnostic yield and the complications of these procedures. In Japan, endoscopists receive board certification from the Japan Gastroenterological Endoscopy (JGES) after 5 years of training in a JGES-approved educational institution of endoscopy and after passing an examination administered by the JGES. Accordingly, the EUS-FNAB and MCB procedures in the present study were performed by expert endoscopists with board certification from the JGES. The same endoscopist performed the EUS-FNAB and MCB in a given patient.

#### **EUS-FNAB procedure**

The EUS-FNAB procedure was performed first with the patient under conscious sedation by midazolam with or without pethidine. The EUS-FNAB procedure was performed by expert endoscopists. Fundamentally, a convex linear-array echoendoscope (GF-UCT260; Olympus Optical) connected to an observing system (UM-ME1; Olympus Optical) was used in this procedure. A 22-gauge needle (EchoTip ProCore High Definition Ultrasound Biopsy Needle; Cook Japan, Tokyo) was used to obtain specimens for the histological analysis. After properly targeting the mass, the endoscopist punctured the lesion with the needle. Thereafter, the inner needle was pulled out, and the endoscopist moved the needle back and forth 20 times while applying suction using the connected 10-mL syringe. The EUS-FNAB was performed by making 1 to 4 passes, at the discretion of the endoscopist. That is, when the endoscopist judged that grossly visible material was obtained, the procedure was stopped.

The obtained material was immediately and directly exposed to 10% formalin, and then processed as a tissue block for histopathological evaluation using hematoxylin-eosin and immunohistochemistry (IHC) staining. Cytology was not performed as an on-site

cytologist was not available in this procedure, and a cell block for confirmatory IHC was also not prepared.

#### **Mucosal cutting biopsy**

Immediately following the EUS-FNAB in each patient, an MCB was performed. The MCB technique was as follows: first, saline was injected into the submucosa and then mucosal cutting was performed using a needle-knife (KD-1L-1; Olympus Optical). Under direct vision of the SMT, several biopsy specimens were taken using conventional biopsy forceps (Radial Jaw™ 4; Boston Scientific, Natick, MA). One to six biopsy samples were taken at the discretion of the operators. As in the EUS-FNAB procedure, when the endoscopist judged that grossly visible material was obtained, the procedure was stopped. Thereafter, the mucosal incision was closed with hemoclips (EZ Clip™; Olympus Optical) to prevent post-procedure bleeding (Figure 1) and to reduce the risk of ulceration that may cause peritoneal dissemination.

The patient's oral intake was allowed starting the morning after the day of the procedure, and then the patient was discharged. A proton pump inhibitor was administered for 2 wk after the procedure.

IHC staining of the samples obtained by both methods was performed using the following antibodies: c-kit, CD34, S100 protein, and desmin. Patients diagnosed with a GIST were offered surgical resection.

#### **Analysis parameters**

We evaluated the diagnostic yield and post-procedure bleeding and other complications between the EUS-FNAB and MCB methods, and we tried to determine the causes of nondiagnostic cases.

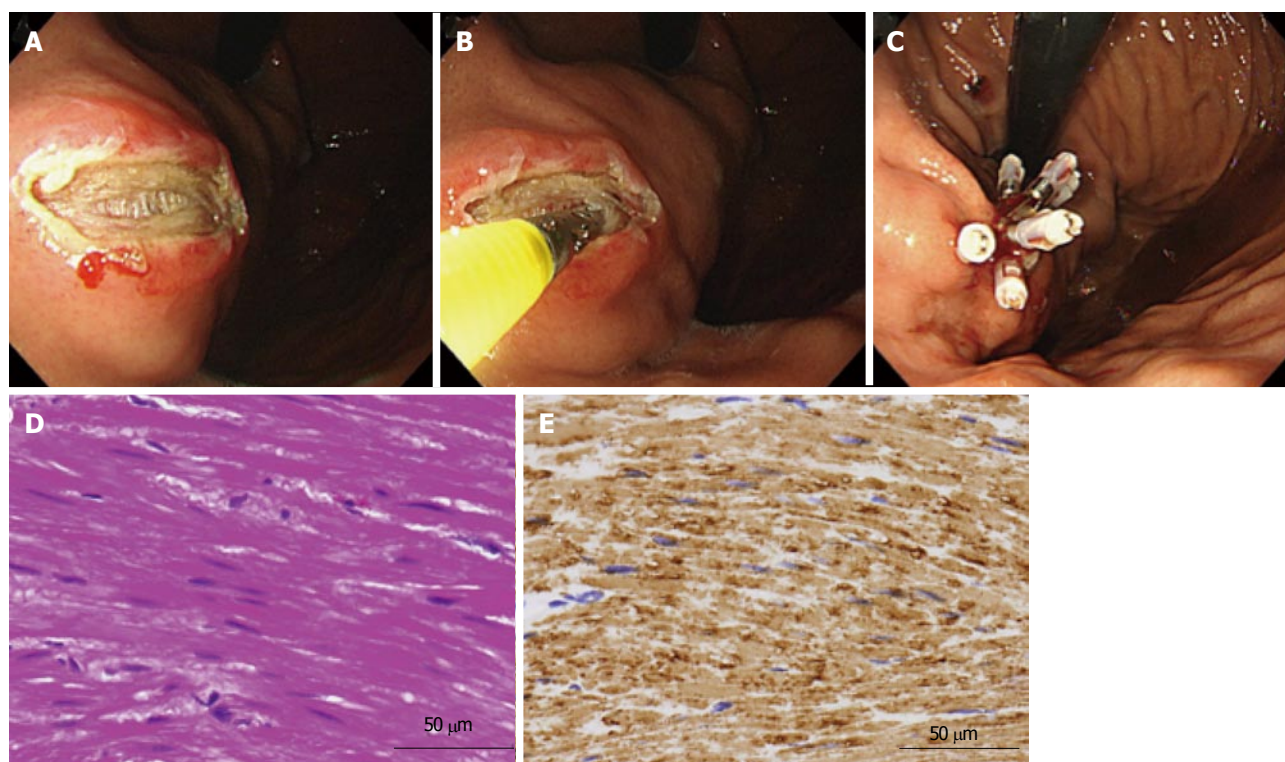
#### **Statistical analysis**

The data were assessed by Welch's *t* test between two groups, and the chi-square test or Fisher's exact test was used to examine differences between two proportions. Statistical significance was defined as a *P* value  $< 0.05$ . Statistical analyses were performed with GraphPad Prism5 software (GraphPad Software, La Jolla, CA).

## **RESULTS**

#### **Patient characteristics and clinicopathological data of SMTs**

Table 1 provides the characteristics of the 20 patients and a summary of the targeted SMTs. All patients underwent EUS prior to the EUS-FNAB and MCB procedures and were diagnosed as having a gastric SMT originating from the submucosal (third layer) or the muscularis propria layer (fourth layer). The mean age of the patients was  $61.8 \pm 12.5$  years (range 39-77 years), and women accounted for 50.0% of the patients. The tumors had a mean size of 23.6 mm (range 10-57). Among the 20 cases, four showed extraluminal growth on EUS. The histological diagnoses were GIST



**Figure 1** Mucosal cutting biopsy of a submucosal tumor with intraluminal growth in the lesser curvature of the corpus. A: The mucosal incision was made by a needle-knife after an injection of saline; B: Biopsy specimen obtained from the tumor using biopsy forceps under direct observation; C: The incision was closed with hemoclips; D: Histological examination of the biopsied specimen showing a spindle cell without mitotic figures (HE); E: Immunohistochemical staining was positive for desmin. This lesion was diagnosed histologically as a leiomyoma.

**Table 1** Summary of the 20 patients with submucosal tumors who underwent endoscopic ultrasonography-guided fine-needle aspiration biopsy and mucosal cutting biopsy

Age, mean $\pm$ SD (yr)	61.8 $\pm$ 12.5
Male: Female	10:10
Tumor location (upper/middle/lower)	11/8/1
Tumor size $\pm$ SD (range) (mm)	23.6 $\pm$ 11.5 (10-57)
$\leq 20$ mm : $> 20$ mm	7:13
Growth pattern	
Intraluminal	16
Extraluminal	4
Histological diagnosis	
Gastrointestinal stromal tumor	7
Leiomyoma	6
Schwannoma	2
Aberrant pancreas	2
Glomus tumor	1
Metastatic hepatocellular carcinoma	1
Not diagnosed	1

( $n = 7$ ), leiomyoma ( $n = 6$ ), schwannoma ( $n = 2$ ), aberrant pancreas ( $n = 2$ ), glomus tumor ( $n = 1$ ), metastatic hepatocellular carcinoma (HCC,  $n = 1$ ), and nondiagnostic ( $n = 1$ ).

Of the three cases that could not be diagnosed by either method, two were treated surgically and diagnosed histologically as a schwannoma and a glomus tumor, respectively, and the third case is being followed closely without treatment. The tumors were located at the lesser curvature of the middle corpus in the schwannoma, at the greater curvature of the fornix

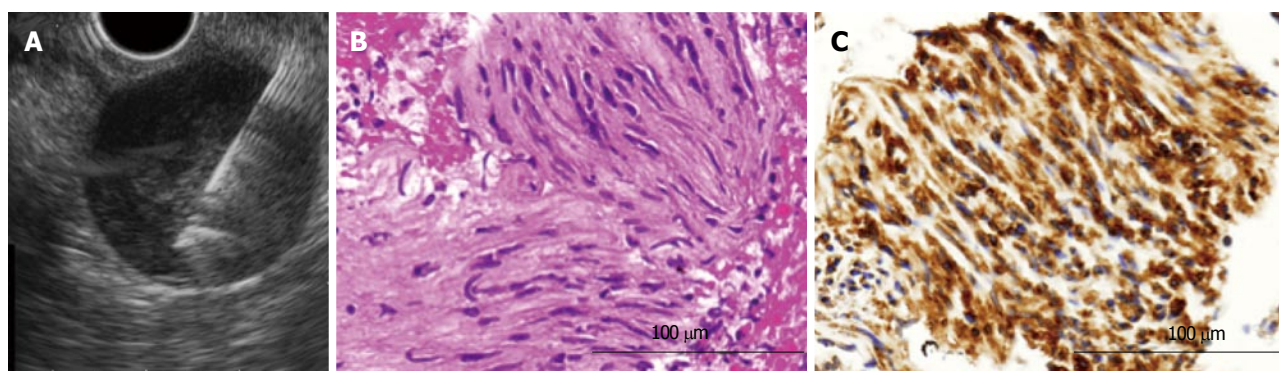
for the glomus tumor, and at the greater curvature of the antrum in the nondiagnostic case. All seven GIST cases diagnosed by EUS-FNAB or MCB were surgically resected and confirmed histologically as GISTs.

#### Diagnostic yields of EUS-FNAB and MCB

The median values 3.0 [interquartile range (IQR): 2.0, 4.0] for the EUS-FNAB samples and 3.0 (IQR: 1.5, 4.5) for the MCB samples were obtained per patient. All 15 cases of GIST, leiomyoma and schwannoma were diagnosed by IHC. The rates of histological definitive diagnosis were 65.0% (13 of 20) by EUS-FNAB and 60.0% (12 of 20) by MCB, a nonsignificant difference. The concordance rate of the histological diagnosis between the two methods was 100%. There were also no significant differences in the diagnostic yield regarding tumor location or tumor size between the EUS-FNAB and MCB methods (Table 2). However, diagnostic specimens were significantly more frequently obtained in lesions with intraluminal growth than in those with extraluminal growth in the MCB method ( $P = 0.01$ ). All four of the SMTs that showed extraluminal growth, including three GISTs and the single HCC, were correctly diagnosed only by EUS-FNAB (Figure 2), and not by MCB ( $P = 0.03$ ). Seventeen of the SMTs (85.0%) were histologically diagnosed by both methods.

#### Complications in both procedures

Two cases showed mild bleeding during the MCB procedure, but both were successfully managed by



**Figure 2** Endoscopic ultrasonography-guided fine-needle aspiration biopsy of a gastrointestinal stromal tumor with extraluminal growth. A: EUS-FNAB of a hypoechoic lesion in the muscularis propria layer showing extraluminal growth; B: Histological finding showing spindle cells in the EUS-FNAB specimen (HE); C: Immunohistochemical staining is positive for c-kit. EUS-FNAB: Endoscopic ultrasonography-guided fine-needle aspiration biopsy.

**Table 2** Diagnostic yields obtained with endoscopic ultrasonography-guided fine-needle aspiration biopsy and mucosal cutting biopsy

	EUS-FNAB				P value	MCB				P value
	Diagnosed (%) (n = 13)		Not diagnosed (%) (n = 7)			Diagnosed (%) (n = 12)		Not diagnosed (%) (n = 8)		
Histological diagnosis	13 (65.0)					12 (60.0)				> 0.99
Location 1										
Upper	7	(63.6)	4	(36.4)	0.33	8	(72.7)	3	(27.3)	0.28
Middle	6	(75.0)	2	(25.0)		4	(50.0)	4	(50.0)	
Lower	0	(0)	1	(100)		0	(0)	1	(100)	
Location 2										
Lesser curvature	4	(66.7)	2	(33.3)	0.81	3	(50.0)	3	(50.0)	0.27
Greater curvature	2	(50.0)	2	(50.0)		1	(25.0)	3	(75.0)	
Anterior wall	4	(80.0)	1	(20.0)		4	(80.0)	1	(20.0)	
Posterior wall	3	(60.0)	2	(40.0)		4	(80.0)	1	(20.0)	
Tumor size										
≤ 20 mm	7	(58.3) <sup>a</sup>	5	(41.7)	0.64 <sup>1</sup>	9	(75.0) <sup>a</sup>	3	(25.0)	0.17 <sup>1</sup>
> 20 mm	6	(75.0) <sup>c</sup>	2	(25.0)		3	(37.5) <sup>c</sup>	5	(62.5)	
Growth pattern										
Intraluminal	9	(56.3) <sup>e</sup>	7	(43.8)	0.10 <sup>1</sup>	12	(75.0) <sup>e</sup>	4	(25.0)	0.01 <sup>1</sup>
Extraluminal	4	(100) <sup>b</sup>	0	(0)		0	(0) <sup>b</sup>	4	(100)	
Median number of samples to the diagnosis (IQR)	1	(1.0, 1.0)				1	(1.0, 1.75)			
Median number of samples (IQR)	3	(2.5, 3.5)	3	(3.0, 3.0)	0.93	5	(3.0, 6.0)	2.5	(1.0, 5.75)	0.17

<sup>1</sup>P values were calculated using Fisher's exact test; <sup>a</sup>P = 0.67 between EUS-FNA and MCB in tumor size ≤ 20 mm; Fisher's exact test; <sup>c</sup>P = 0.31 between EUS-FNA and MCB in tumor size > 20 mm; Fisher's exact test; <sup>e</sup>P = 0.46 between EUS-FNA and MCB in intraluminal growth pattern; Fisher's exact test; <sup>b</sup>P = 0.03 between EUS-FNA and MCB in extraluminal growth pattern. EUS-FNAB: Endoscopic ultrasonography-guided fine-needle aspiration biopsy; IQR: Interquartile range; MCB: Mucosal cutting biopsy.

hemoclips. The mean number of hemoclips for closing the incised mucosa was 3.4 (range: 1-6 clips). No post-procedural hemorrhage, fever, or peritonitis was seen following either procedure.

## DISCUSSION

To date, there are many reports on the methods of tissue acquisition from SMTs: EMR, MCB and EUS-FNAB. Histological diagnosis by a standard biopsy or EMR may be confined to SMTs that arise from the muscularis mucosa or submucosa, which corresponds to second- or third-layer lesions on EUS. In contrast, it may be impossible to make a histologic diagnosis of

the lesions located in the muscularis propria by these methods. Therefore, EUS-FNAB was suggested to play an important role in histological diagnoses such as gastric SMTs, although the results can be quite variable<sup>[10]</sup>. However, although the use of EUS-FNAB is quite prevalent, only a limited number of patients undergo this procedure - even in hospitals specializing in gastroenterology - because an expensive dedicated endoscopic system is needed to conduct an EUS-FNAB. For example, the price of the needle for EUS-FNAB is approximately \$300 United States dollars (USD), and the total prices of devices such as the needle knife, injection needle and EZ Clip™ for MCB are also approximately \$100 USD, and thus the cost may be



significantly cheaper in the MCB method than in the EUS-FNAB method. Additionally, the needle knife used in the MCB method is reusable. The EUS-FNAB system comprised of an echoendoscope and its observing system is very expensive, over \$100000 USD. Therefore, MCB may be the less expensive procedure compared to EUS-FNAB.

Generally, the accuracy rates of EUS-FNAB in the histological diagnosis of gastric SMTs vary from approximately 60% to 80%<sup>[9,11]</sup>. It was noted that the sensitivity of EUS-FNAB for the diagnosis of GIST, especially in cases of small GISTs, is relatively low compared to that for other types of SMTs<sup>[21,22]</sup>, indicating that the diagnostic yield may be influenced by the lesion's size<sup>[11,21-24]</sup>, because technical expertise is required to diagnose smaller lesions by EUS-FNAB. Several studies showed that the diagnostic rate increased with the increase of tumor size<sup>[22-24]</sup>, but another study did not observe this association<sup>[11]</sup>. A recent report by Sekine *et al.*<sup>[25]</sup> showed that cytological or histological specimens obtained by EUS-FNAB met the diagnostic criteria of GIST in 81.3% of the cases, even among small GISTs (< 20 mm). In their procedure, the samples obtained by EUS-FNAB were examined immediately with a rapid staining method to verify the adequacy of the specimen and to provide a presumptive diagnosis. It was reported that when an on-site cytopathologist immediately reviewed the adequacy of the samples, the sensitivity of EUS-FNAB was > 90%<sup>[23,26]</sup>. It was also suggested that the sensitivity of EUS-FNAB drops by 10%-15% in the absence of an on-site pathologist to evaluate the cellular adequacy of the samples<sup>[27]</sup>. However, this diagnostic procedure for cytology during an EUS-FNAB may be troublesome for not only endoscopists but also cytology technicians in daily medical practice. For this reason, an easy and useful diagnostic tool for SMT regardless of the tumor size is needed.

In the present study, the histological diagnosis rate of MCB was significantly higher than that of EUS-FNAB in the lesions with intraluminal growth ( $P = 0.01$ ). In addition, all four extraluminal-growth tumors could be histologically diagnosed only by EUS-FNAB. The diagnostic capability of MCB was thus increased from 60% to 75% when the four cases with extraluminal growth were excluded. Additionally, when we examined the histological diagnosis for both methods together, the accurate histological diagnosis increased to 85%. In previous studies, the accurate histological diagnosis of MCB ranged from 85% to 100%<sup>[16-18]</sup>, which is relatively higher than that of our study. One of the reasons for the differences in diagnostic yield may be that the numbers of cases in those studies were relatively small, and they were retrospective studies. To date, there are two studies that compared the diagnostic yield between the jumbo biopsy "unroofing" technique and EUS-FNAB<sup>[28,29]</sup>. The results of both studies indicated a lower diagnostic yield than ours. In those studies, the diagnostic procedures (*i.e.*, jumbo biopsy vs EUS-FNAB) were not performed during the same session

in the same patients, as was done in our study. In addition, both studies<sup>[28,29]</sup> included many cases of lipoma (16.6%-22.1%), which is considered to be easily diagnosed by the jumbo biopsy unroofing technique or only by EUS.

The diagnostic yield of the EUS-FNAB method in the present study was relatively lower compared to previous reports<sup>[26,30]</sup>. One of the reasons might be an effect of the difference in the FNA needle size used for the EUS-FNABs. The larger-bore 19-gauge needle may actually show a higher diagnostic yield compared to the 22-gauge needle used in the present study<sup>[24,31]</sup>, but the exact difference in diagnostic yield between 19- and 22-gauge FNA needles remains unclear<sup>[24,30]</sup>. We did not adequately assess procedural factors such as the needle gauge and the number of needle passes in the present study. More passes or the use of a larger-bore needle would provide more tissue. However, Sepe *et al.*<sup>[23]</sup> reported that the number of passes did not significantly affect the diagnostic capability of EUS-FNAB. In their study, as is standard practice, this decision regarding the number of passes was made at the discretion of the individual endosonographer and was based on a real-time assessment of presumed tissue adequacy, as in our study, and our finding is in agreement with their result<sup>[23]</sup>.

No major complications were caused by either the EUS-FNAB or MCB method in the present study, although mild bleeding occurred in two cases during the MCB; both were successfully managed by hemoclips. Perforation did not occur in any of the 20 patients during MCB, but extra care should be taken to prevent perforation in cases with extraluminal growth<sup>[17]</sup>. A laparoscopic and endoscopic cooperative surgery (LECS) is now being performed for the treatment of gastrointestinal SMTs<sup>[32,33]</sup>. However, the MCB method is unlikely to preclude LECS for the treatment of SMTs.

The present study had some potential limitations. First, the sample size of this study was small and drawn from a single institution. When the diagnostic yield is assumed to be approximately 70% for the EUS-FNAB without cytology method and approximately 90% for the MCB method, 62 patients with SMT are needed in each group in order to have a power of 80% to detect a difference at the level significance of  $\alpha = 0.05$  (two-sided).

Second, there is the issue of EUS-FNAB- and MCB-related dissemination as a late complication, but this has not been reported to date. It is important to close the mucosal incisions appropriately with endoclips after tissue sampling to prevent post-procedure complications in MCB<sup>[17]</sup>. Third, if the diagnostic yield of the combination of EUS-FNAB and MCB is assessed, the histological diagnosis by the two methods should be compared to that of a surgically resected whole specimen as a "golden standard."

In conclusion, although EUS-FNAB is the widely used gold standard for the histological and cytological diagnoses of gastric SMTs, MCB may be chosen as an alternative diagnostic modality in tumors showing the



intraluminal growth pattern. A randomized controlled trial to compare the capability of MCB with that of EUS-FNAB is needed.

## COMMENTS

### Background

As gastric submucosal tumors (SMTs) comprise both benign and malignant lesions, histological diagnosis is needed. Endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) is a useful method for the histological evaluation of SMTs. However, EUS-FNAB systems are very expensive and require experienced pathologists and cytology technicians, and thus this procedure may be unavailable in hospitals not specializing in gastroenterology.

### Research frontiers

Although the diagnostic yields of EUS-FNAB and mucosal cutting biopsy (MCB) have been reported, there are no studies comparing the diagnostic capabilities of EUS-FNAB and MCB based on endoscopic submucosal resection in the same patients. The authors prospectively compared the diagnostic yield, feasibility, and safety of these two methods.

### Innovations and breakthroughs

In this prospective study, no significant difference in histological diagnosis was found between EUS-FNAB and MCB regardless of tumor location and tumor size. However, diagnostic specimens were significantly more frequently obtained in the lesions with intraluminal growth compared to those with extraluminal growth by the MCB method. All SMTs with extraluminal growth were diagnosed only by EUS-FNAB, not by MCB. No complications were produced by either method.

### Applications

MCB may be chosen as an alternative diagnostic modality in tumors showing an intraluminal growth pattern regardless of tumor size, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

### Terminology

EUS-FNAB: This method is a needle biopsy procedure considered to be a reliable and accurate method for the evaluation of SMTs in the gastrointestinal tract; gastrointestinal stromal tumor (GIST): GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract.

### Peer-review

The authors present an interesting result regarding the efficacy of MCB in the histological diagnosis of SMTs. This procedure will be accepted widely even in hospitals not specializing in gastroenterology.

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**P- Reviewer:** Amorniyotin S, Pauli E, Yan SL **S- Editor:** Tian YL  
**L- Editor:** A **E- Editor:** Wu HL



## Laparoscopic endoscopic cooperative surgery as a minimally invasive treatment for gastric submucosal tumor

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**Author contributions:** Namikawa T drafted the manuscript, prepared the figures and tables; Hanazaki K made critical revisions.

**Institutional review board statement:** This study was considered exempt by the Kochi Medical School Institutional Review Board.

**Informed consent statement:** Informed consent was obtained from the patients for publication in this case report.

**Conflict-of-interest statement:** We declare that there is no conflict of interest associated with any of the authors contributed their efforts in this manuscript.

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Received: June 30, 2015

Peer-review started: July 4, 2015

First decision: July 29, 2015

Revised: August 5, 2015

Accepted: September 7, 2015

Article in press: September 8, 2015

Published online: October 10, 2015

### Abstract

Laparoscopic wedge resection is a useful procedure for

treating patients with submucosal tumor (SMT) including gastrointestinal stromal tumor (GIST) of the stomach. However, resection of intragastric-type SMTs can be problematic due to the difficulty in accurately judging the location of endoluminal tumor growth, and often excessive amounts of healthy mucosa are removed; thus, full-thickness local excision using laparoscopic and endoscopic cooperative surgery (LECS) is a promising procedure for these cases. Our experience with LECS has confirmed this procedure to be a safe, feasible, and minimally invasive treatment method for gastric GISTs less than 5 cm in diameter, with outcomes similar to conventional laparoscopic wedge resection. The important advantage of LECS is the reduction in the resected area of the gastric wall compared to that in conventional laparoscopic wedge resection using a linear stapler. Early gastric cancer fits the criteria for endoscopic resection; however, if performing endoscopic submucosal dissection is difficult, the LECS procedure might be a good alternative. In the future, LECS is also likely to be indicated for duodenal tumors, as well as gastric tumors. Furthermore, developments in endoscopic and laparoscopic technology have generated various modified LECS techniques, leading to even less invasive surgery.

**Key words:** Cooperative surgery; Endoscopy; Gastrointestinal tumor; Laparoscopy; Submucosal tumor

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**Core tip:** Resection of intragastric-type submucosal tumor can be problematic due to the difficulty in accurately judging the location of endoluminal tumor growth, and often excessive amounts of healthy mucosa are removed; thus, full-thickness local excision using laparoscopic and endoscopic cooperative surgery (LECS) is a promising procedure for these cases. The important advantage of LECS is the reduction in the resected area of the gastric wall compared to that in conventional laparoscopic wedge resection using a linear

stapler. Developments in endoscopic and laparoscopic technology have generated various modified LECS techniques, leading to even less invasive surgery.

Namikawa T, Hanazaki K. Laparoscopic endoscopic cooperative surgery as a minimally invasive treatment for gastric submucosal tumor. *World J Gastrointest Endosc* 2015; 7(14): 1150-1156 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i14/1150.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i14.1150>

## INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumors among submucosal tumors (SMTs) of the gastrointestinal tract. Complete resection of GISTs is recommended because of their malignant potential, such as risk of tumor recurrence and progression to metastatic disease<sup>[1,2]</sup>. Lymphadenectomy is not recommended as lymph node involvement is rare. Laparoscopic surgery for GISTs is safe and effective and provides a minimally invasive approach for tumors less than 5 cm in diameter<sup>[3-5]</sup>.

Extragastic-type SMTs can be treated relatively easily using a conventional laparoscopic wedge resection with adequate margins. However, resection of intragastric-type SMTs can be more problematic due to the difficulty of accurately judging the tumor's location under laparoscopic examination. This results in the necessity of removing relatively large sections of healthy stomach to remove the tumor, which sometimes leads to postoperative deformity of the stomach<sup>[6]</sup>.

Laparoscopic endoscopic cooperative surgery (LECS) was first reported by Hiki *et al.*<sup>[7,8]</sup> in 2008, and is a minimally invasive surgical technique designed to resect SMTs originating in the gastrointestinal tract. In recent years we have performed LECS in patients presenting with gastric SMT with mainly intraluminal growth. In the present study, we reviewed a number of clinical reports describing LECS, including our own series, to evaluate the procedure and its clinical outcomes.

## CASE REPORT

LECS requires the participation of experienced laparoscopic surgeons and experienced endoscopists<sup>[7,8]</sup>. After inducing general anesthesia, a port for a camera is inserted through the umbilicus using an open technique, and a pneumoperitoneum is established by insufflation of carbon dioxide to 8-10 mmHg abdominal pressure. Four additional ports, two 5-mm ports and two 12-mm ports, are inserted into the upper left and right and lower left and right quadrants, respectively. The proximal jejunum near the ligament of Treitz is clamped using detachable forceps to avoid air inflating the distal intestine during endoscopic manipulation. When confirmation of the tumor location from the serosal side is difficult, it is confirmed by an intraluminal

approach using endoscopy (Figure 1A). Blood vessels in the excision area around the tumor are then prepared using ultrasonically activated laparoscopic coagulating shears (Figure 1B).

The location of the tumor is first confirmed endoscopically, followed by submucosal dissection using intraluminal endoscopy to determine an appropriate resection line (Figure 1C). Endoscopic submucosal dissection (ESD) is widely accepted as the standard treatment for early gastric cancer without lymph node metastasis and enables a clinician to resect a target lesion *en bloc*<sup>[9]</sup>. This technique is applied to LECS using various endoscopic devices such as a needle knife to mark the mucosal resection line and an insulation-tipped diathermic electrosurgical (IT) knife to dissect the submucosal layer. After circumferential dissection of the mucosal to submucosal layers, a full-thickness incision into the serosal layer around the lesion is made using the needle knife to connect the endoscopic and laparoscopic approaches.

Subsequently, an ultrasonic coagulation incision device is inserted into the artificial perforation under laparoscopic view, and the seromuscular layer is dissected along the incision line made by ESD (Figure 1D). After circumferential full-thickness resection (Figure 1E), the resected specimen is put into a plastic bag, which is then removed through the umbilical incision. The edges of the incision line are then lifted up by an assistant using forceps, and the incision line is closed using laparoscopic stapling devices (Figure 1F). After completing the full-thickness closure, the endoscope can be inserted into the stomach to confirm that there is no air leakage, despite insufflation of the stomach. Gross examination of the resected specimen reveal that the resection margin of healthy gastric wall is limited to the minimum necessary (Figure 2).

Table 1 details the clinicopathological results of 19 patients who underwent laparoscopic resection for SMT in the stomach at the Kochi Medical School Hospital. Conventional laparoscopic resection of the tumor was undertaken in 11 patients, and LECS was performed in 8 patients. Basically, the indications of laparoscopic surgery including LECS for gastric SMT include the tumors less than 5 cm detected on esophagogastroduodenoscopy, computed tomography or upper gastrointestinal barium study. We performed LECS for gastric SMT when the main tumor location was intragastric type. Until the advent of LECS, we performed conventional laparoscopic resection for the gastric SMT less than 5 cm in diameter even if the main tumor location was intragastric type.

The median age of patients was 72 years (range, 35-86 years), and there was a female predominance, with a male-to-female ratio of 5:14. The tumor was located in the upper third of the stomach in 9 patients, in the middle third in 6 patients, and in the lower third in 4 patients. The tumor circumference included the lesser curvature in 7 patients, greater curvature in 7 patients, posterior wall in 4 patients, and anterior wall in 1



**Table 1 Characteristics of patients who underwent laparoscopic surgery for a gastric submucosal tumor**

Patient	Age	Gender	Tumor location	Main location of tumor	Operation method	Operating time (min)	Estimated blood loss (mL)	Tumor size (cm)	Histology
1	78	M	M, Less	Extragastric	Conventional	145	20	4.0 × 3.5	GIST (low risk)
2	60	F	U, Gre	Intragastric	laparoscopic approach	175	20	1.7 × 1.7	GIST (very low risk)
3	66	F	U, Post	Intragastric	Conventional	85	30	5.5 × 4.5	GIST (high risk)
4	42	M	L, Gre	Mixed	laparoscopic approach	155	5	3.0 × 2.7	Schwannoma
5	86	F	M, Less	Extragastric	Conventional	190	40	3.5 × 2.5	GIST (low risk)
6	35	F	U, Gre	Extragastric	laparoscopic approach	115	5	3.8 × 3.0	GIST (intermediate risk)
7	84	F	U, Gre	Intragastric	Conventional	235	130	4.0 × 3.3	GIST (intermediate risk)
8	78	F	M, Less	Extragastric	laparoscopic approach	145	5	4.5 × 4.0	GIST (low risk)
9	61	F	U, Post	Intragastric	LECS	130	5	4.4 × 2.2	GIST (low risk)
10	64	F	U, Post	Intragastric	LECS	250	5	3.1 × 3.0	GIST (low risk)
11	43	F	L, Less	Intragastric	LECS	155	5	2.0 × 1.7	GIST (very low risk)
12	72	M	M, Less	Extragastric	Conventional	165	70	5.0 × 3.5	GIST (low risk)
13	77	M	U, Gre	Mixed	laparoscopic approach	230	5	3.0 × 1.5	GIST (low risk)
14	63	F	L, Gre	Intragastric	LECS	202	0	3.0 × 2.0	Schwannoma
15	73	M	U, Ant	Intragastric	Conventional	226	0	3.0 × 2.0	GIST (low risk)
16	36	F	M, Less	Mixed	laparoscopic approach	214	0	4.0 × 2.5	GIST (low risk)
17	82	F	L, Gre	Mixed	LECS	212	10	2.8 × 2.0 × 1.8	GIST (low risk)
18	81	F	U, Post	Extragastric	Conventional	130	0	4.5 × 3.0	GIST (low risk)
19	81	F	M, Less	Intragastric	laparoscopic approach	221	0	3.2 × 3.0	GIST (low risk)

U: Upper third; M: Middle third; L: Lower third; Less: Lesser curvature; Gre: Greater curvature; Ant: Anterior wall; Post: Posterior wall; LECS: Laparoscopic endoscopic cooperative surgery; GIST: Gastrointestinal stromal tumor.

**Table 2 Clinicopathological characteristics of patients with gastric submucosal tumor who underwent either conventional laparoscopic surgery or laparoscopic endoscopic cooperative surgery**

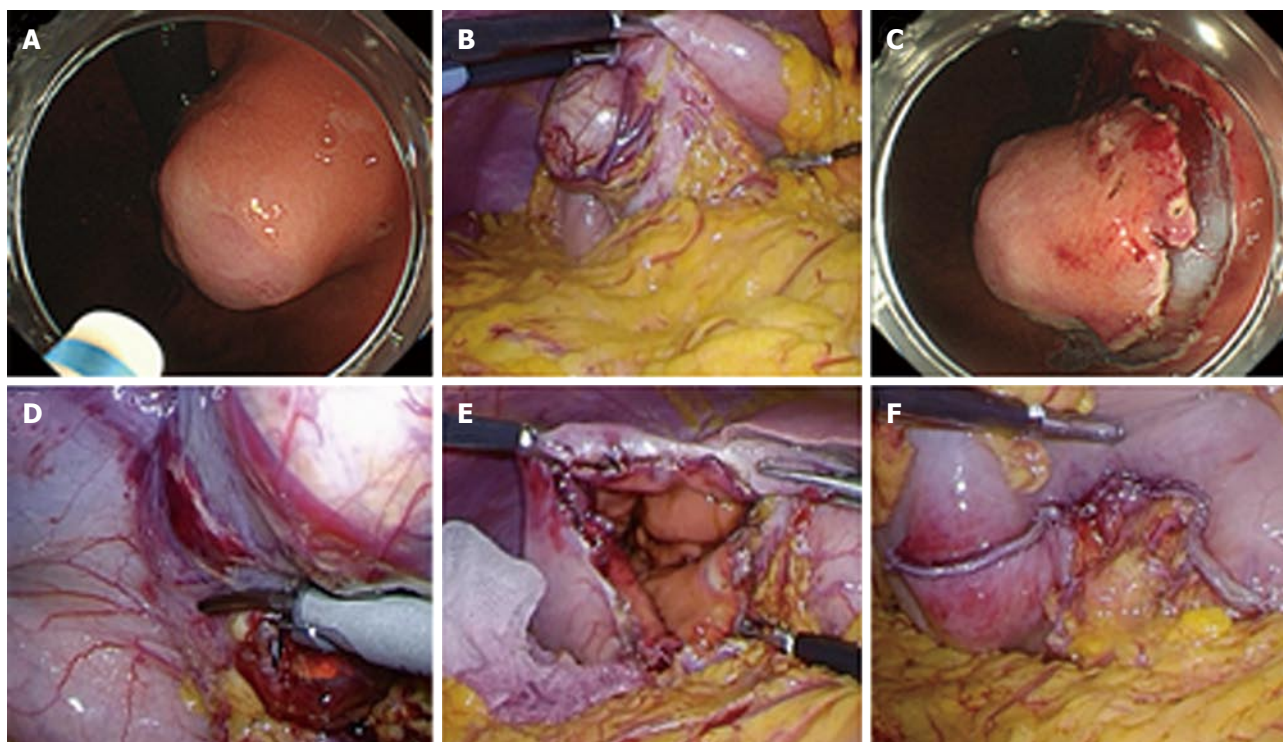
	LECS ( <i>n</i> = 8)	Conventional laparoscopic approach ( <i>n</i> = 11)	<i>P</i> value
Age, median (range), yr	64 (36-82)	73 (35-86)	0.51
Gender			0.52
Male	1	4	
Female	7	7	
Tumor location			0.7
Upper third	3	6	
Middle third	2	4	
Lower third	3	1	
Tumor size, median (range), cm	3.1 (2.0-4.4)	4.0 (1.7-5.5)	0.12
Estimated blood loss, median (range), mL	5 (0-10)	20 (0-130)	0.06
Operating time, median (range), min	213 (130-250)	155 (85-235)	0.05

LECS: Laparoscopic endoscopic cooperative surgery.

patient. The median tumor diameter was 3.5 cm (range, 1.7-5.5 cm), the median operating time was 175 min (range, 85-250 min), and the median estimated blood

loss was 5 mL (range, 0-130 mL). The main location of the tumor was intragastric in 9 patients, extragastric in 6, and mixed (both intragastric and extragastric) in 4. The histological diagnosis was GIST in 17 patients, and schwannoma in 2 patients. Of the patients with GISTs, 2 were classified as very low risk, 12 as low risk, 2 as intermediate risk, and 1 patient as high risk, according to the modified Fletcher classification<sup>[10,11]</sup>. There were no remarkable postoperative complications including mortality, leakage or surgical site infection.

Table 2 compares the clinicopathological characteristics of the 19 patients in our current series who underwent either conventional laparoscopic surgery (*n* = 11) or LECS (*n* = 8) for gastric SMT. The clinicopathological characteristics included the tumor location, major axis of the tumor, estimated blood loss, and operating time. The median estimated blood loss in patients who underwent LECS tended to be smaller than in those who underwent conventional laparoscopic surgery (5 mL vs 20 mL, respectively; *P* = 0.06). The median operating time of patients who underwent LECS also tended to be longer than those who underwent conventional laparoscopic surgery (213 min vs 155 min, respectively; *P* = 0.05). There were no significant differences in the median age, gender, tumor location,



**Figure 1** Laparoscopic endoscopic cooperative surgery for gastric submucosal tumor. A: The tumor is located in the lesser curvature of the middle third of the stomach; B: The stomach was mobilized by dividing the gastrocolic omentum and the lesser curvature vessels near the tumor by laparoscopic dissection; C: A circumferential incision was made around the tumor by an endoscopic submucosal dissection technique using an insulation-tipped diathermic electrosurgical knife; D: The seromuscular layer of the stomach was dissected along the incision line using the laparoscopic coagulating shears; E, F: The post-excisional hole in the stomach was closed using a laparoscopic linear stapling device.



**Figure 2** Gross appearance of the resected specimen. The tumor is a mixed-type, with a predominant intragastric component. The resection margin of healthy gastric wall is limited to the minimum necessary. The pathological diagnosis confirmed a gastrointestinal stromal tumor, classified as low risk.

or median tumor size in patients who underwent conventional laparoscopic surgery compared to LECS.

## DISCUSSION

Conventional surgical operations may be excessively invasive for the treatment of gastrointestinal SMT. Successful laparoscopic wedge resection has been reported for 2-5 cm gastric GISTs, and confirmed by studies examining long-term surgical outcomes<sup>[3,12,13]</sup>. However, it is sometimes difficult to determine the

appropriate resection line from the outside of the stomach when tumors are located intragastrically. There have been several reports on the use of LECS for SMT of the stomach including GISTs, leiomyomas, and schwannomas<sup>[6,7,14-19]</sup>. Table 3 summarizes the clinical variables of patients from a number of studies who underwent LECS, including our own series.

Kawahira *et al.*<sup>[14]</sup> reported that the median ratio of the longest diameter of the tumor divided by the longest diameter of the surgical specimen was significantly greater in LECS compared to laparoscopic wedge resection (0.86 vs 0.69, respectively;  $P = 0.02$ ). This means that LECS results in the resection of a smaller area of healthy gastric wall, which is an important advantage of LECS over conventional laparoscopic wedge resection using linear staplers. Therefore, LECS has good prospects for the treatment of GISTs, applying the modern concept of minimally invasive surgery, regardless of the location of the tumor even if it is adjacent to the esophagogastric junction or pyloric ring<sup>[16]</sup>.

In our series, there was a tendency for the estimated blood loss to be lower in the LECS group than in the conventional laparoscopic resection group, with the difference just failing to reach significance. A major reason for this lower blood loss is that in the case of intragastric-type SMT, division of the extended gastric vessels or the omentum in the excision area around the tumor is needed to maintain a safe margin from the

**Table 3** Previous clinical reports of laparoscopic endoscopic cooperative surgery for gastric submucosal tumor

Ref.	Year	Number of patients	Median tumor size (cm)	Median operating time (min)	Median estimated blood loss (mL)	Conversion to open surgery
Hiki <i>et al</i> <sup>[7]</sup>	2008	7	4.6	169	7	0
Kawahira <i>et al</i> <sup>[14]</sup>	2012	16	2.8	172	5	0
Tsujimoto <i>et al</i> <sup>[6]</sup>	2012	20	3.8	157	3.5	0
Dong <i>et al</i> <sup>[15]</sup>	2013	6	3.5	83.3	NA	0
Qiu <i>et al</i> <sup>[16]</sup>	2013	69	2.8	81.6	29.8	0
Hoteya <i>et al</i> <sup>[17]</sup>	2014	25	NA	156.3	NA	0
Waseda <i>et al</i> <sup>[18]</sup>	2014	27	3.6	167.5	5	0
Mori <i>et al</i> <sup>[19]</sup>	2014	12	3.9	146.3	NA	0
Our case	2015	8	3.1	213	5	0

NA: Not available.

tumor. There was also a tendency for longer operation times in the LECS group than in the conventional laparoscopic resection group, although this difference was not significant. This longer operation time for LECS is not surprising since time is required for both the ESD and laparoscopic procedures. Previous studies have not shown any difference in perioperative outcomes between LECS and the conventional approach, and a larger sample size would be useful to clarify this issue.

Developments in endoscopic and laparoscopic technology have yielded various modified LECS techniques aimed at further minimizing invasiveness. Examples of these improved techniques include the laparoscopy-assisted endoscopic full-thickness resection, a full-thickness resection method using the non-exposure technique (CLEAN-NET), and non-exposed endoscopic wall-inversion surgery (NEWS)<sup>[20-22]</sup>. Because LECS has an inherent risk of peritoneal infection due to the necessity for gastric perforation, CLEAN-NET and NEWS have been developed to prevent the risk of cancer cells seeding during open gastrectomy. These procedures might thus have potential minimally invasive resections of gastric tumors, even those in an ulcerated state<sup>[22]</sup>.

Single-port LECS, which is a single-incision laparoscopic surgery combined with an endoscopic approach, might provide an alternative to gastric wedge resection with minimal transformation of the stomach<sup>[23]</sup>. It may contribute to reduced pain, faster recovery, and improved cosmesis for patients. However, careful selection of patients based on the tumor location and growth morphology is needed to clearly identify the risks and benefits of this new approach, also taking into account the need for needlescopic instruments.

Initially, the indication criteria for LECS was limited to SMT of the stomach measuring up to 5 cm in diameter without ulceration of the mucosa<sup>[7]</sup>. In the future, it is likely that LECS will also be indicated for tumors of the duodenum<sup>[24,25]</sup>. Although ESD is widely accepted as the standard treatment for gastric lesions including early gastric cancer, the duodenal wall is generally thinner than that of the stomach and ESD for duodenal tumors is associated with an increased risk of perforation<sup>[25]</sup>. Furthermore, maneuvering a flexible endoscope is technically difficult in the tiny duodenal lumen. In these cases, LECS might be a useful therapeutic modality

not only for avoiding perforation of the duodenal wall by ESD, but also for achieving a more precise incision line<sup>[24]</sup>.

Moreover, Nunobe *et al*<sup>[26]</sup> reported the successful use of LECS for a large spreading mucosal cancer in the stomach that would have been difficult to treat with ESD because of the high likelihood of complications and the long surgical time required for ESD. Thus, early gastric cancer that fits the criteria for endoscopic resection, but presents difficulties for ESD, is likely to be a candidate for the LECS procedure<sup>[26]</sup>.

In conclusion, recent advances in endoscopic and laparoscopic techniques have facilitated several variations of endoscopic procedures derived from ESD, and created a fusion of endoscopy and laparoscopy technologies suitable for upper gastrointestinal SMTs. LECS is a useful and safe procedure for SMT that avoids excessive resection of healthy gastric wall. Further investigations, including a prospective randomized controlled trial and a study exploring long-term consequences, are needed to verify the usefulness of the LECS for gastrointestinal SMT.

## COMMENTS

### Case characteristics

The authors demonstrated the patients with gastric submucosal tumor treated by laparoscopic surgery.

### Clinical diagnosis

The subjects were the gastric submucosal tumors including intragastric and extragastric type.

### Differential diagnosis

Histopathological diagnosis of submucosal tumors includes gastrointestinal stromal tumor and schwannoma.

### Laboratory diagnosis

Laboratory findings were within the normal range.

### Imaging diagnosis

The gastric submucosal tumors were diagnosed by computed tomography and esophagogastrroduodenoscopy.

### Pathological diagnosis

Pathological findings of gastrointestinal stromal tumor were characterized by



interlacing bundles of elongated cells with c-KIT expression.

### Treatment

The patients were treated by conventional laparoscopic wedge resection or laparoscopic endoscopic cooperative surgery.

### Related reports

The authors summarized the clinical variables of patients from a number of studies who underwent laparoscopic endoscopic cooperative surgery, including their own series.

### Term explanation

Laparoscopic surgery for submucosal tumors effective and provides a minimally invasive approach for tumors less than 5 cm in diameter.

### Experiences and lessons

Laparoscopic endoscopic cooperative surgery is a useful and safe procedure for submucosal tumor that avoids excessive resection of healthy gastric wall.

### Peer-review

Further investigations, including a prospective randomized controlled trial and a study exploring long-term consequences, are needed to verify the usefulness of the laparoscopic endoscopic cooperative surgery for gastrointestinal submucosal tumors.

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**P- Reviewer:** Tomizawa M **S- Editor:** Tian YL

**L- Editor:** A **E- Editor:** Wu HL





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