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International Digestive Experts Articles

Year I - N. 4, 2019

Special iGLOBE 2019

The international Gastro Liver Oesophagus and Bowel Event

Current developments in endoscopy session

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Editorial

Current developments in endoscopy

by the editorial staff of The IDEA Journal

Endoscopic resection techniques are the preferred modality for management of dysplastic and early cancer lesions throughout the gastrointestinal tract. Both endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) contribute to the successful management of these lesions, and each patient needs to be treated with the most appropriate technique carefully evaluating the case.

ESD is performed by injecting fluid into the submucosa and creating an incision around the perimeter of the lesion, and then carefully dissecting the lesion from the deeper layers. adopted and available to our patients. The technique was developed in Japan because that Country has a high prevalence of gastric cancer. Japanese endoscopists started exploring minimally invasive endoscopic alternatives to EMR. Following the success in the stomach, the use of ESD has expanded to the esophagus and the colorectum, and in Japan this procedure is routinely performed in these areas.

There has been reluctance to adopt ESD in the West because of the lower prevalence of gastric cancer; however, endoscopists have come to the realization that ESD can be a very useful technique throughout the gastrointestinal tract. Over the last few years, there has been great enthusiasm to adopt ESD in the United States as well.

In Japan and Europe, there are guidelines that provide specific recommendations on the appropriate use of ESD. According to those, ESD is endorsed for lesions that have a high likelihood of cancer invading the superficial submucosa and for lesions that cannot be removed by EMR due to fibrosis in the submucosal space or post-EMR recurrences. The main advantage of ESD is that it allows en bloc resection of any type of lesion regardless of size. Removing the entire lesion in a single piece is a basic oncologic principle and carries the benefits of accurate histologic assessment and staging, determination of curative resection, and a very low recurrence rate of less than 1%.

The European Society of Gastrointestinal Endoscopy (ESGE) recommends endoscopic en bloc resection for superficial esophageal squamous cell cancers, excluding those with obvious submucosal involvement. ESD is recommended as the first option, mainly to provide a total resection with accurate pathology staging and to avoid missing important histological features. ESD may also be considered in selected cases in Barrett's esophagus, such as lesions larger than 15mm, poorly lifting tumors, and lesions at risk for submucosal invasion.

Moreover, ESD is recommended as treatment of choice for most gastric superficial neoplastic lesions that possess a very low risk of lymph node metastasis. Finally, ESD can be considered for removal of colonic and rectal lesions with high suspicion of limited submucosal invasion that is based on two main criteria of depressed morphology and irregular or nongranular surface pattern, particularly if the lesions are larger than 20 mm; or for colorectal lesions that otherwise cannot be optimally and radically removed by snare-based techniques.

The use of ESD continues to evolve as the technique improves. In the last decade, a number of advances have made ESD safer and less challenging to perform.

These include:

- The development of a wide variety of dedicated electrosurgical knives suitable for different procedural steps
- Chromoendoscopy or advanced imaging to better characterize the surface of a lesion and demarcate its borders
- Viscous solutions for submucosal injection, including some with autodissection properties
- Novel suturing devices and techniques to close defects or perforations as necessary.

One of the most significant developments is electrosurgical units containing microprocessors that control the current waves, sense changes in electronic current in response to increasing tissue impedance and have the ability to modify the tissue effect accordingly.

These devices provide a good clean cut which makes the procedure much easier, avoiding much bleeding which translates in less time, effort and tissue injury in order to better assess the tissue.

Endoscopic ultrasonography

by the editorial staff of The IDEA Journal

INTRODUCTION

The treatment of gastric cancer includes different options based on preoperative staging tests. Radical surgery can produce curative results, however, new approaches, which comprise endoscopic therapy for early gastric cancer and neoadjuvant therapy for patients with advanced disease, have become the mainstay in the management of these patients (1). In this setting, preoperative staging is essential for the individualized stage-dependent treatment and for the patient's prognosis.

Endoscopic ultrasonography (EUS) is one of the most common technique for the preoperative staging of gastric cancer patients. EUS has shown to be very useful for detecting the depth of gastric cancer invasion, with a T staging accuracy of approximately 80%-90% (2). The advent of EUS-fine-needle aspiration (FNA) has improved the accuracy of EUS for N staging to a promising level, although more data are needed to definitely establish the role of EUS-FNA in this setting (3).

In this article, Thierry Ponchon and Thomas Rösch have tried to answer several relevant questions arising from the practical application of the cancer staging technique.

First question: from the practical point of view, is there any role for endoscopic ultrasound (EUS) for cancer staging?

Cancer staging is fundamental in tailoring treatments on patients' needs and also in stratifying patients in clinical studies. EUS was developed with the aim of providing a better view on the pancreas from inside, since pancreas cannot be seen very well by transabdominal ultrasound. The potential for gastrointestinal wall visualization was realized very soon, since the growth of the cancer in the different layers of the wall and follow a locoregional cancer staging (Figure 1).

During the 1980 many studies were performed and reported a very high initial accuracy in cancer staging (>90%). More recently, in clinical reality accuracy in acer staging is accuracy around 70% or lower with mostly no consequences (4,5). Early stages of

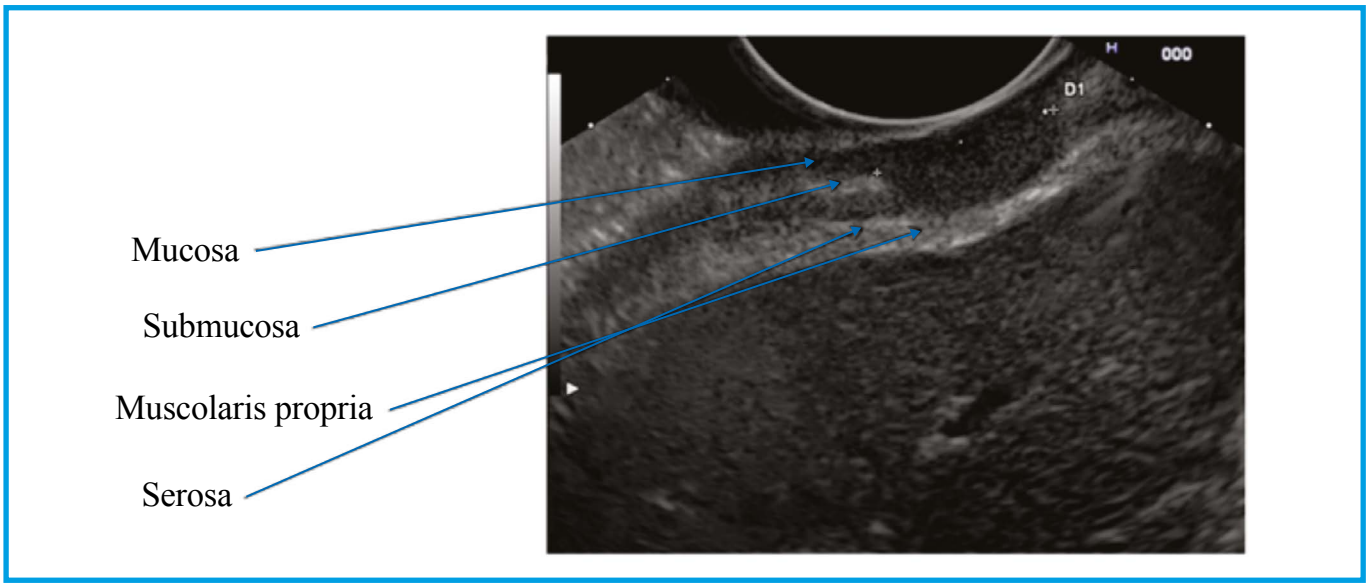

Figure 1. Gastrointestinal wall layers

tumors and results of neoadjuvant chemotherapy are particularly difficult to differentiate. Hence, diagnostic EUS should be improved, optimizing image quality, expanded methods like ultrasound contrast and 3D and, perhaps, artificial intelligence contribution.

Second question: Submucosal tumors - no news for 30 years?

Submucosal tumors are still largely unknown. We know from the studies that images and histology have a weak correlation; also, fine needle aspiration (FNA) has limited yield (generally too rigid) and management is unclear. In a German multicenter study on the performance of EUS in differentiating malignant and benign submucosal lesions on 150 patients followed up for 2 years, sensitivity and specificity were only 64% and 80%, respectively (6). More recently, in a retrospective review on 99 patients diagnosed with gastric subepithelial tumor who underwent EUS with pathologic confirmation, the overall accuracy of EUS was 66.7% (7). A meta-analysis on the use of EUS-guided needle sampling for upper gastrointestinal subepithelial lesions comprising 978 cases reported an accuracy of 59.9% (8). For the future, we can expect a better tissue diagnosis, or, more interestingly, we may have a simple removal technique similar to polypectomy.

Third question: EUS-FNA cytology versus histology

Two options can be considered: one is fine needle aspiration, getting material for cytology, the other is fine needle biopsy (FNB) giving material for histology. When FNA is performed, small needles are used, cytology is done in the room by an experienced cytopathologist and the whole procedure gives high rates of accuracy. On the other side, when FNB is performed, large needles are used, the specimen is collected in formalin and later analyzed by a standard pathologist, with accuracy around 60%, with a wide range of histopathology assessment.

On EUS-FNA, 183 randomized studies and 74 meta-analysis can be found in PubMed. However, it is not clear from all this literature, which technique and which needle should be used. To be correctly performed in daily practice, EUS-FNA should be done with well-defined steps and well-trained professionals.

Fourth question: EUS-FNA any needle preferences?

The Needle tries to get samples for histology by various means. The Standard technique consists in penetrating the tumor with the needle, so that tissue gets in the needle. Suction technique needs to be optimized in order not to destroy the specimen and in the future "freezing" needle will be proposed. However, currently, it is important to get a good penetration and then acting depending on the individual tumor: if the tumor is not particularly hard, suction should not be performed, instead a few pulses should be done. If the lesion is hard, suction should be used since the beginning. If the needle comes out with a large amount of blood, the technique should be done without suction and/or with less pulses.

Available needles are not soundly different and their performance largely depends on the personal technique. In the future, a good histology needle study should be conducted with a large multicenter single arm (no golden standard to compare is available at the moment), with a required histology yield of at least 90%.

Fifth question: EUS for biliary therapy - niche or instead of percutaneous transhepatic bile duct drainage or endoscopic retrograde cholangiopancreatography?

Many techniques exist to get access to the bile duct, from the stomach (transgastric approach), the descending duodenum (transduodenal approach), depending on the obstruction localization. Irrespective of the location punctured, there are two ways to proceed: either to insert a guide wire through the papilla and do a rendezvous, continuing with a endoscopic retrograde cholangiopancreatography (ERCP) or, to perform direct drainage, drain the bile duct into the stomach, with the risk of dislocation. The situation is very complex, depending on many factors:

1. Different indications: biliary or pancreatic, benign or malignant (in case of palliation the stent can be placed in different places since it will not be removed later)
2. Different approaches and techniques (e.g. rendezvous /stent)

3. Different competitors: ERCP, PTCD, enteroscopic approach
4. Failed ERCP (versus PTCD) vs. primary approach
5. Availability and expertise.

A systematic review evaluated the efficacy and safety of EUS-guided biliary drainage and transduodenal and transgastric approaches. Many small, underpowered and biased randomized clinical trials were retrieved and probably technical success (95%) and clinical success (92%) were overrated and adverse events (23%) were quite high (9). A meta-analysis compared the efficacy and safety of EUS-guided biliary drainage and percutaneous transhepatic biliary drainage (PTBD) for biliary obstruction in patients who failed ERCP. Nine studies and 483 cases were reported. The authors observed an equal technical success (OR 1.78) a better clinical success for EUS (OR 0.45) for EUS as well as lower adverse events (0.23, partially due to a very high complications rate in some of the PTCB procedures considered) (10). Also, such observation was derived from trials with different EUS procedures among the several available.

Given all the available techniques (ERCP, enteroscopy, PTCD, EUS), each should have its role in the armamentarium of biliopancreatic intervention in order to offer the most appropriate to patients.

Sixth question: EUS-guided digestive anastomoses: which future?

Other indications for EUS than biliary-duodenum anastomose, are stomach-intestine, intestine-intestine, esophagus-stomach, and vascular.

For stomach-intestine or gastro-entero anastomoses two different options are available, in two different duodenum strictures. The procedure needs to be guided by EUS and begins with the puncture of duodenum with a needle to insert a guide wire. The stent is opened inside the bowel and used to push the bowel to the stomach. Then the stent is opened in the stomach side, the two balls are fixed to each other to quickly create the anastomoses. This procedure is a good alternative to duodenum stenting.

Intestine-intestine anastomoses are considered promising in the treatment of obesity, but probably not sufficient for weight loss as no procedure is applied to the stomach in order to reduce its size.

Esophagus-stomach is used in interesting experiments, but not yet in trials.

Some vascular applications are connected to a device in development for portal pressure gradient measurement (PPGM) through the stomach. PPGM accurately reflects the degree of portal hypertension and it is considered the single best indicator in liver disease. EUS-guided PPG may represent a promising breakthrough for procuring indispensable information in the management of patients with liver disease (11). The technique is under investigation in pigs and permitted the direct EUS-guided portal pressure measurements using a digital pressure wire within minutes (12) (Figure 2).

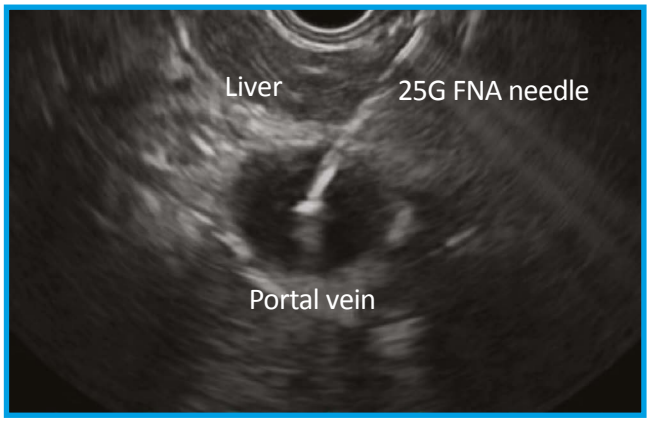

Figure 2. Endoscopic Ultrasound Image of transgastric transhepatic needle puncture into the portal vein with a 25G FNA needle (from Huang 2016)

Seventh question: EUS-guided tumor therapy, anything promising?

There have been many attempts to use EUS in tumor therapy. These include: to locally ablate cystic tumors and neuroendocrine tumors using EUS-guided alcohol ablation, but the topic is still controversial.

Ongoing studies are using radiofrequency ablation in pancreatic tumor and an immune response was observed, but the mechanisms need to be further studied before being translated into clinical practice. Fiducial placement for radiation and sentinel lymph nodes (imaging) might be helpful.

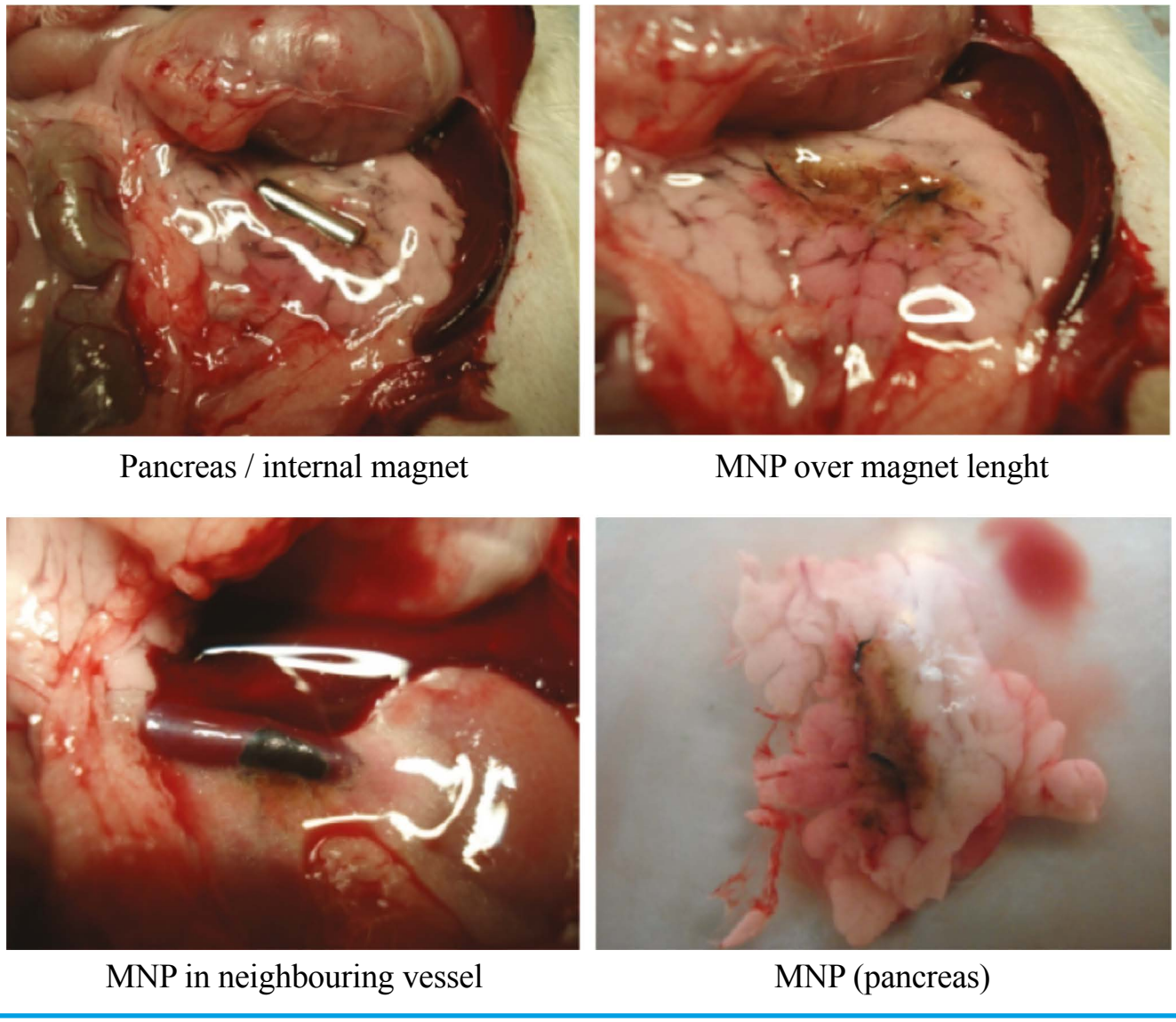

Figure 3. Magnetic nano-particles techniques in tumor therapy

A very promising technique involves magnetic nano-particles (MNP). A small magnet is placed into the pancreas and the MNPs, coupled to a drug injected into the vein. The magnet in the pancreas extracts the whole amount of MNP coupled to the drug in the pancreas. The study is currently running in several centers, and is already demonstrating the efficacy of the technique (Figure 3).

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Endoscopic Submucosal Dissection

by the editorial staff of The IDEA Journal

ABSTRACT

Most of small tumors in the gastrointestinal tract are easily removed by endoscopic mucosal resection (EMR). However, EMR is sometimes not reliable to ensure the complete resection for large tumors. Endoscopic submucosal dissection (ESD) was developed to obviate the limitations of EMR, but it has a higher risk for complications, such as perforation and bleeding. This presentation reviews the techniques and clinical outcomes of EMR and ESD and shows that ESD is more effective for early gastric and esophageal cancer with higher en-bloc resection rate and lower local recurrence in comparison to EMR. Several studies report favorable long-term outcomes of ESD. Piecemeal resection using EMR technique is widely accepted for colorectal large adenomas and results in good clinical outcomes in most patients. However, apparent cancerous lesions need endoscopic en-bloc resection by ESD. Further development of the technique, devices and training systems will promote worldwide standardization of ESD.

INTRODUCTION

Originally, endoscopic resection (ER) of early neoplastic lesions of the gastrointestinal (GI) tract was performed using endoscopic mucosal resection (EMR). This became a widespread procedure around the world in the '80s and is able to remove easily small adenomas and cancers located in every area we can reach endoscopically in the gastroenteric apparatus. However, EMR has important limitations represented mainly by the difficulty of ensuring the complete ablation of large tumors and the association with a certain number of local recurrences. Endoscopic submucosal dissection (ESD) was first developed in Japan in the late 90's in order to overtake the above limitations of EMR and, despite the higher risk of complications, such as bleeding and perforations, the experience accumulated in the last two decades has led it to become more and more popular among the endoscopists of both eastern and western countries. Nowadays, ESD is a well-established technique to treat any kind of early cancer throughout the entire gastrointestinal tract. It is a minimally invasive endoscopic/surgical procedure for curative resection of advanced lesions and, if curative, can obviate surgery (laparoscopic or open).

Naohisa Yahagi, a Japanese expert from the Cancer Center of the Keio University School of Medicine, reviews challenges and methods in the use of ESD and tries to answer several relevant questions arising from the practical application of the technique.

First question: Should ESD replace EMR for high-grade dysplasia on Barrett's esophagus?

The answer is yes, although we should develop more reliable measures to prevent stricture formation after extensive resection.

Barrett esophagus (BE) is a precancerous condition in which the normal squamous epithelium is replaced by a metaplastic columnar one, which represents an increased risk for the development of esophageal adenocarcinoma. Although the modern endoscopes provide excellent image quality, many efforts have been performed to obtain better morphologic details of the mucosa and to detect as early as possible suspicious areas of dysplasia, on which targeted biopsies can be achieved. Chromoendoscopy has been proposed to help

us in identifying both intestinal metaplasia and dysplasia; to perform such procedure, numerous dyes have been used, although methylene blue is the most adopted in patients with BE. The instillation of acetic acid was also proposed as this substance produces reversible intracellular cytoplasmic protein denaturation and allows identification of metaplasia/dysplasia, because the epithelial surface becomes more opaque and looks whiter, as shown in Figure 1.

EMR has been shown to be a valid technique to remove small esophageal cancers and Figure 2 shows an example of EMR performed with band applied to the patch of a nodular mucosa (D) with the image of the site of EMR which demonstrates the complete resection of abnormal mucosa with non-bleeding visible submucosa (E).

Radiofrequency ablation (RFA) is another safe and effective thermal procedure for treating dysplastic BE and, to a lesser extent, non-dysplastic BE. The ease of its performance, along with its efficacy and low rate of adverse events, has established RFA as a reliable technique for the management of esophageal dysplasia. Figure 3 shows an image of RFA being performed with the HALO 360 catheter (B) and the subsequent image of the successful circumferential area of BE.

The use of ER with RFA has shown to be useful in inducing the remission of BE with early neoplasia during a follow-up of 5 years (1), but the occurrence of metachronous lesions is rather frequent.

A recent systematic review and meta-analysis of the literature studies aimed at estimating the accurate recurrence rate risk of intestinal metaplasia/dysplasia after achieving complete remission of esophageal lesions with EMR. It included 41 papers on a total of 4443 patients, showed that the incidence of recurrence is substantial (7% intestinal metaplasia, 1.3% dysplasia and 0.8% high-grade dysplasia/cancer) and therefore continued surveillance of these patients is imperative (see Figure 4).

The reasons for the above findings are that, in long segment BE (LSBE), cancerous lesions sometimes arise multifocally, invisible lesions often exist and diagnosis for lateral extent is sometimes very difficult. Pech et al (2), analyzing retrospectively the acute and long-term results

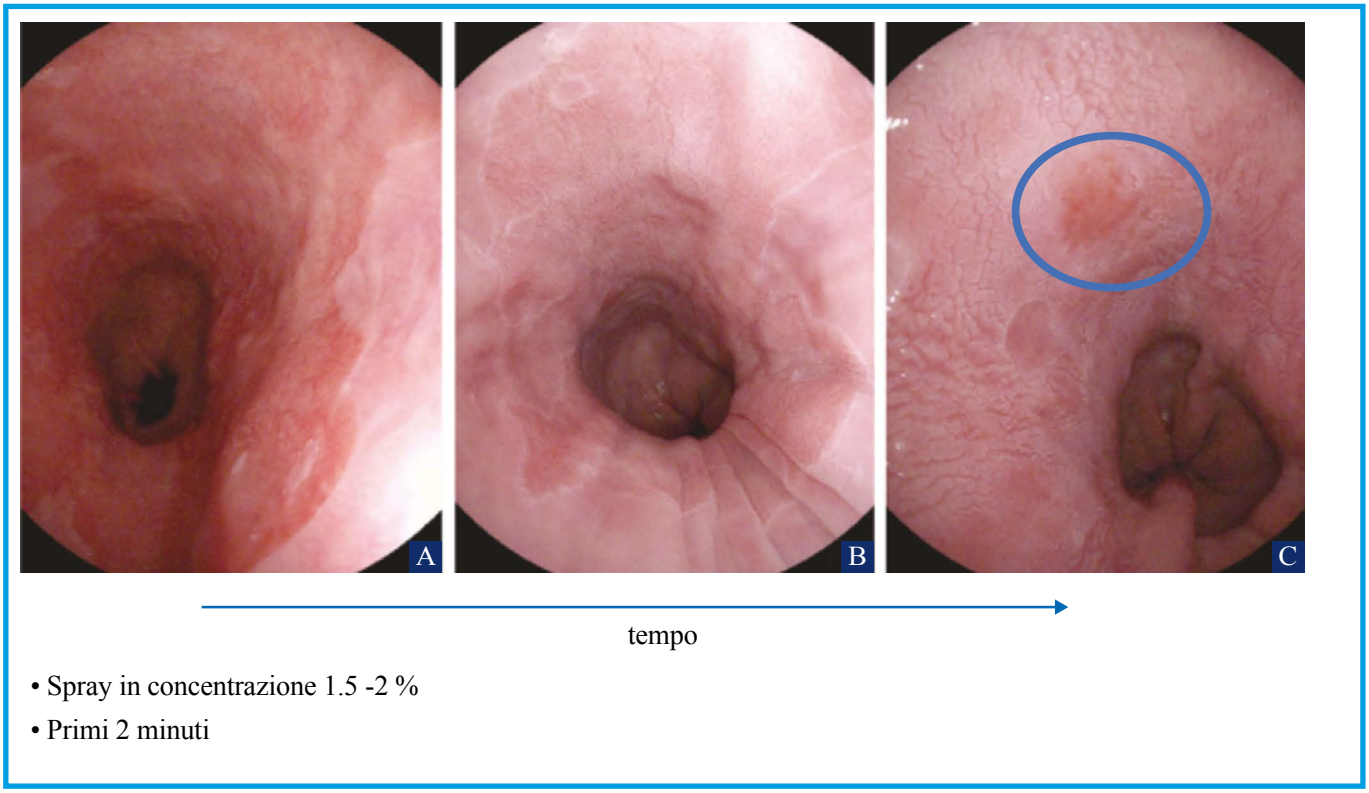
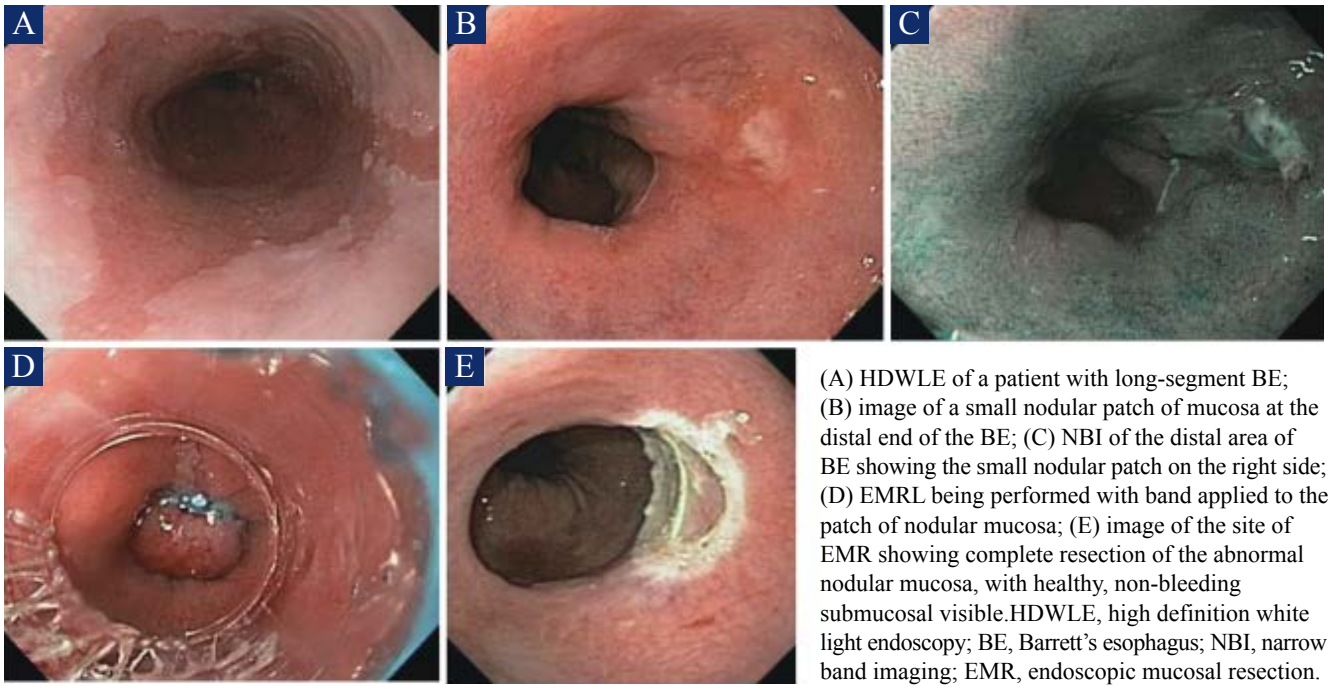


Figure 1. Acetic acid in diagnosis of metaplasia/dysplasia



(A) HDWLE of a patient with long-segment BE; (B) image of a small nodular patch of mucosa at the distal end of the BE; (C) NBI of the distal area of BE showing the small nodular patch on the right side; (D) EMRL being performed with band applied to the patch of nodular mucosa; (E) image of the site of EMR showing complete resection of the abnormal nodular mucosa, with healthy, non-bleeding submucosal visible.HDWLE, high definition white light endoscopy; BE, Barrett's esophagus; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

Figure 2. Endoscopic mucosal resection

(A) HDWLE of a patient with long-segment BE; (B) image of REA being performed with the use of the HAlo 360 catheter; (C) image of successful circumferential ablation of area of BE. HDWLE, high definition white light endoscopy; BE, Barrett's esophagus; RFA, radio frequency ablation

Figure 3. Radiofrequency ablation

of a large sample of 2687 ERs, found 1.5% of major complications and 14.5% of metachronous lesions.

The adoption of RFA after ER is very common, but still unreliable, while the removal of LSBE by ESD is possible. Figure 5 shows an example of ESD in a patient with a large superficial esophageal cancer. The hook knife grasped submucosal fibers (B) and the presence of a flat ulcer without perforation or bleeding is displayed in C. The large resected specimen is visible in D.

However, ESD of widespread superficial esophageal carcinomas may be complicated by the development of severe strictures, which may require serial treatment with endoscopic balloon dilatation. Hashimoto et al (3) studied a total of 41 consecutive patients who had a semi-circumferential mucosal defect that arose after

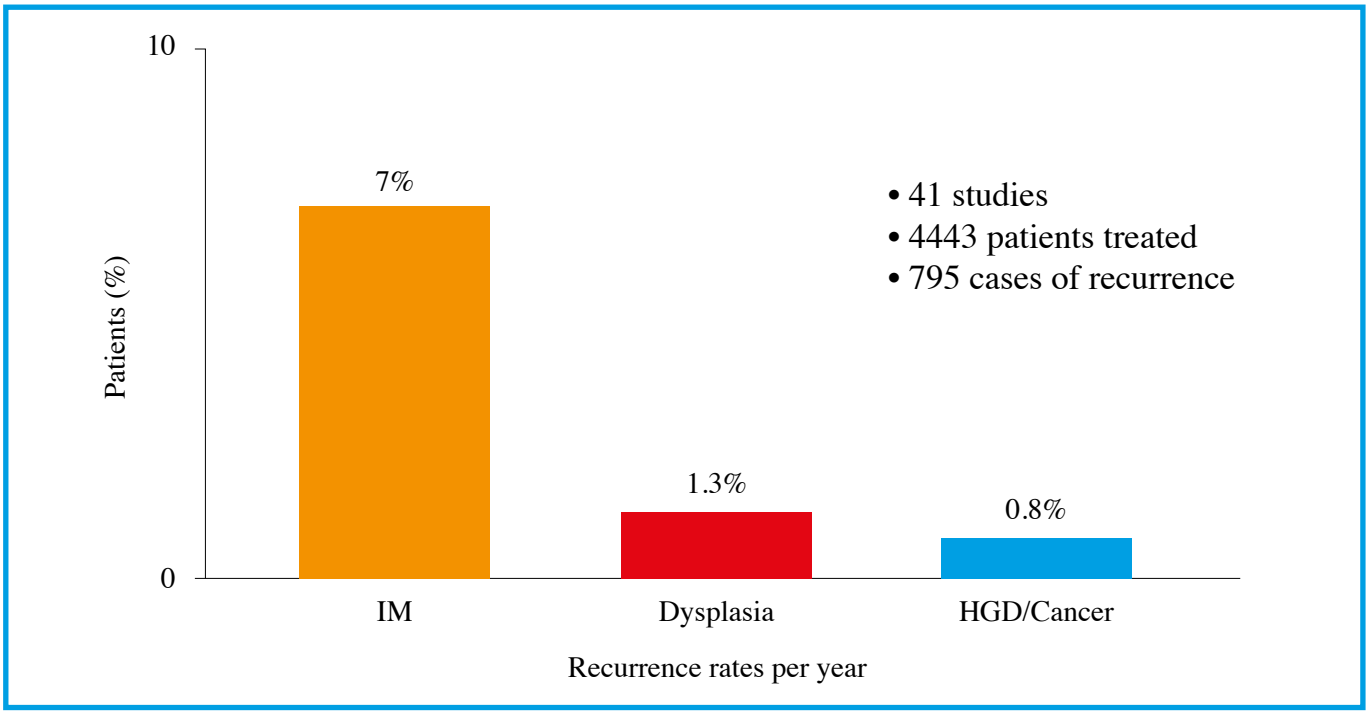
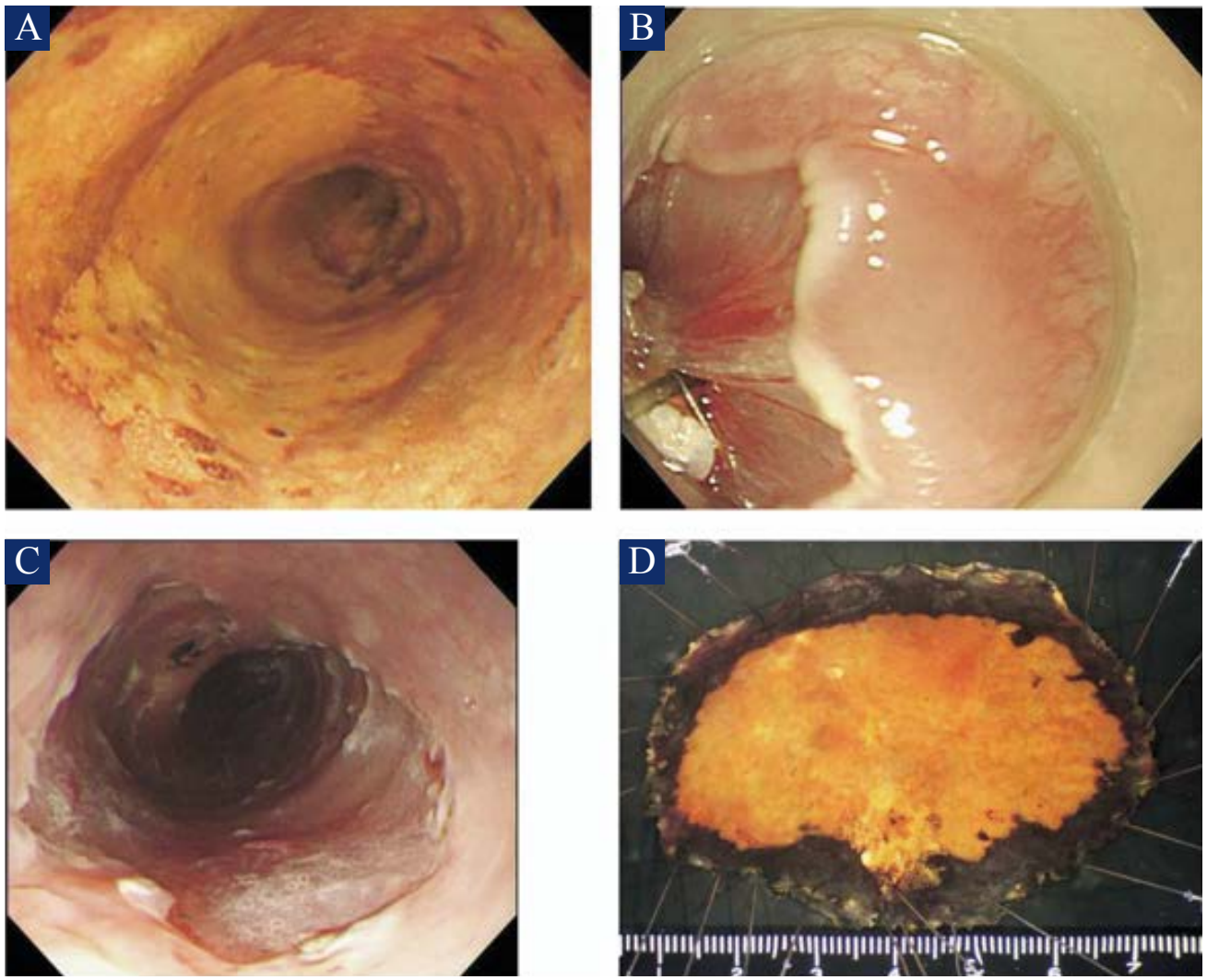


Figure 4. Recurrence rates of Barrett's lesions after endoscopic therapy: a systematic review (mod. from Krishnamoorthi R. Gastrointest Endosc 2016)

ESD for superficial esophageal squamous cell carcinomas in order to assess whether endoscopic triamcinolone injection was able to prevent the above complication. They found that the incidence of stricture was significantly lower in the study group (19.0%) than in the control group (75.0%; P < .001) and concluded that the injection of steroids is safe and effective for the prevention of esophageal stricture in patients undergoing ESD for superficial esophageal squamous cell carcinomas.

Okhi et al (4) approached the same problem by performing an open-label, single-arm, single-institute study, where specimens of oral mucosal tissue from 9 patients with superficial esophageal neoplasms were collected. Epithelial cell sheets were fabricated ex vivo by culturing isolated cells for 16 days on temperature-responsive cell culture surfaces. After a reduction in temperature, these sheets were endoscopically transplanted directly to the ulcer surfaces of patients who had just undergone ESD. All patients were monitored by endoscopy once a week until epithelialization was complete. Autologous cell sheets were successfully transplanted to ulcer surfaces using an endoscope and complete re-epithelialization occurred within a median time of 3.5 weeks. No patients experienced dysphagia, stricture, or other complications following the procedure, except for one patient who had a full circumferential ulceration that expanded to the esophagogastric junction. The Authors concluded that sutureless, endoscopic transplantation of carrier-free cell sheets composed of autologous oral mucosal epithelial cells safely and effectively promotes re-epithelialization of the esophagus after ESD. This procedure might be used to prevent stricture formation following ESD and improve patients' quality of life, but further studies will be needed to show that stricture formation can be prevented. Finally, Sato et al (5) investigated a possible preventive effect of small interfering RNA (siRNA) targeting carbohydrate sulfotransferase 15 (CHST15) on esophageal stricture formation after ESD in 3 pigs. They found that this procedure is able to alleviate esophageal post-ESD stricture formation via repression of fibrosis, revealing a



(A) Esophagoscopy reveals a large superficial esophageal squamos cell carcinoma; (B) The hook knife grasped submucosal fibers; (C) Endoscopic images after ESD show a flat ulcer after ESD. There is neither perforation nor bleeding. (D) The resected specimen showed an iodine-unstained lesion. The cancer was 58x 34 mm and the resected specimen was 65 x 48 mm.

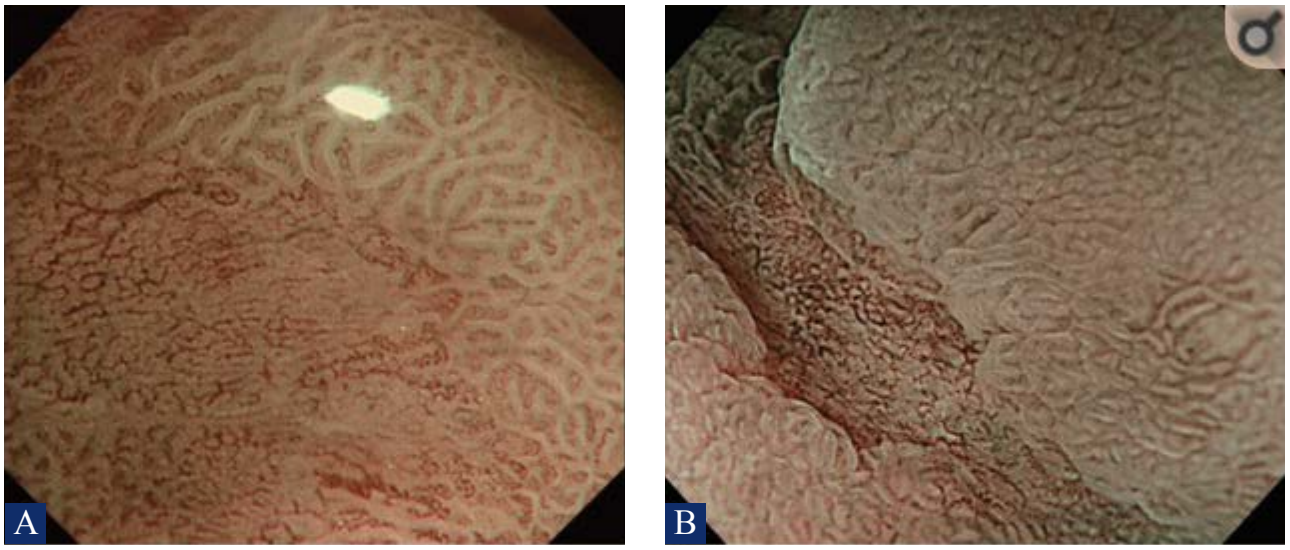
Figure 5. Example of ESD in a patient with a large superficial esophageal cancer

novel therapeutic role for antifibrotic agents in the prevention of post-ESD strictures.

Second question: Which is nowadays the best technique to detect superficial gastric carcinoma: NBI, LCI, white light, indigocarmine, ...?

We should wash the lumen thoroughly before inspection; thereafter numerous techniques for detecting possible dysplastic or cancerous gastric lesions in early phase (EGC) can be adopted. White light (WLI) should be used for initial detection of suspicious lesions in the stomach and magnifying endoscopy with narrow band imaging (NBI) is useful for further evaluation of detected lesions. Figure 6 shows that a demarcation line is clearly revealed between normal and cancerous tissues (A) and the tumor margins are well delineated based on the irregular microvascular patterns in B.

Chromoendoscopy is a further technique which is able to detect EGC, as shown in Figure 7, where you can see a combined flat and elevated lesion with an unclear border at the lower body of the stomach (A), an endoscopic view after acetic acid was sprayed (B), an endoscopic view after indigo carmine was



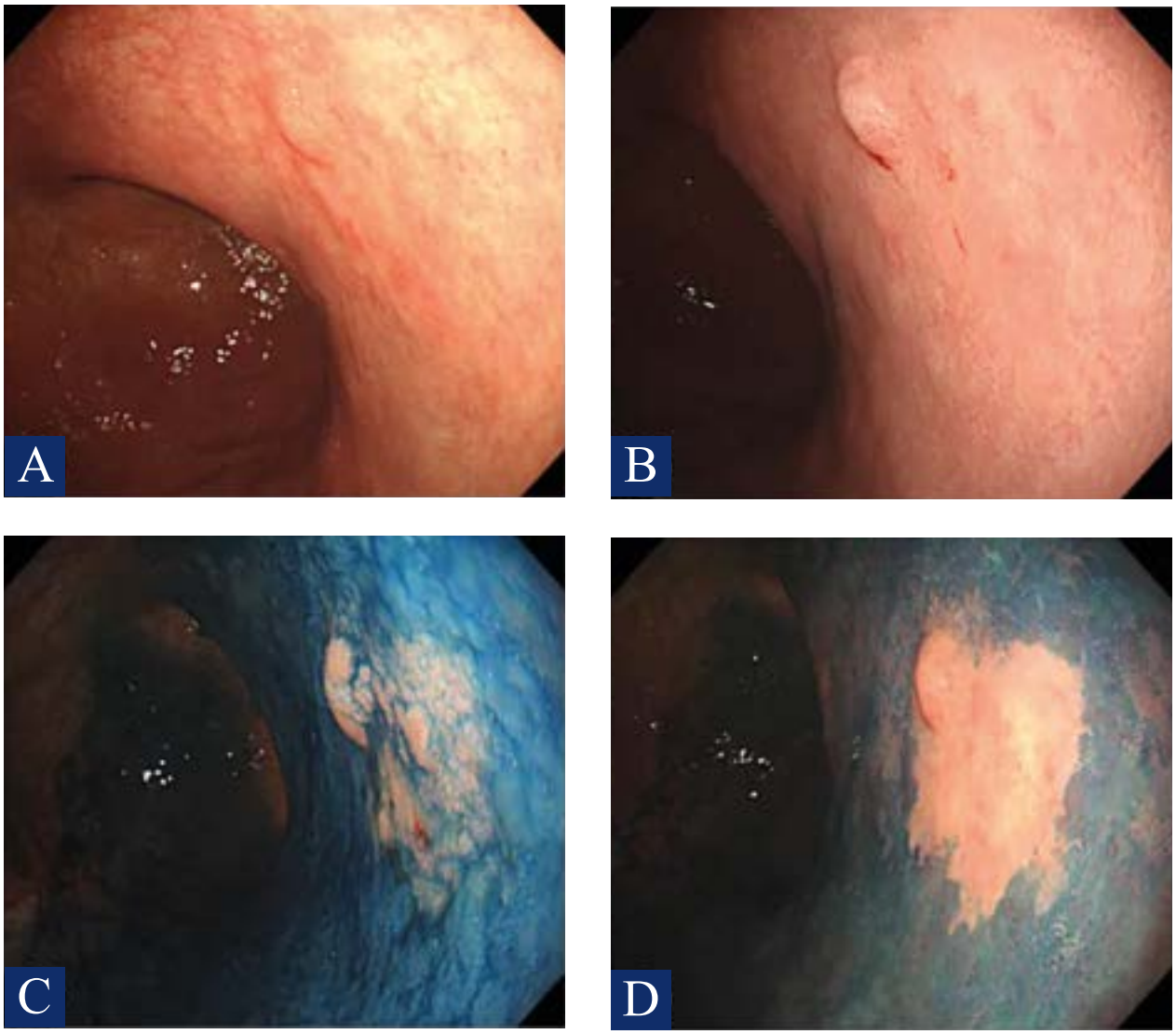
(A) A demarcation line is clearly revealed; (B) The tumor margins are well delineated based on the irregular microvascular pattern

Figure 6. Early gastric cancer observed using magnifying endoscopy with narrow-band imaging

additionally sprinkled (C) and an endoscopic view after the lesion was washed with clean water (D). It is also noteworthy that after chromoendoscopy with indigo carmine dye added to acetic acid, the lesion's borders became distinct and the clarity of image was high.

Linked color imaging (LCI) has a unique character, but there is insufficient clinical data to provide a definite opinion on its reliability and blue laser imaging (BLI) seems to be better than WLI (6). Figure 8 shows an endoscopic image obtained with WLI (a), where you can observe a slight irregular mucosal lesion with unclear margin (arrowhead) and with BLI (b), where there is both an irregular microvascular pattern and an irregular microsurface pattern along with a clear demarcation line (arrows). Dohi et al performed a prospective, randomized, controlled study in 2 Japanese academic centers and investigated 629 patients undergoing follow-up endoscopy for atrophic gastritis with intestinal metaplasia or surveillance after endoscopic resection of early gastric cancer (EGC). Patients were randomly assigned to receive primary WLI followed by BLI-bright or primary BLI-bright followed by WLI. The real-time detection rates of EGC were compared between primary WLI and primary BLI-bright. There were 298 patients in each group. The real-time detection rate of EGC with primary BLI-bright was significantly greater than that with primary WLI (93.1% vs 50.0%; P = .001). Primary BLI-bright had a significantly greater ability to detect EGCs in patients with a history of endoscopic resection for EGC, no Helicobacter pylori infection in the stomach after eradication therapy, lesions with an open-type atrophic border, lesions in the lower third of the stomach, depressed-type lesions, small lesions measuring <10 mm and 10 to 20 mm in diameter, reddish lesions, well-differentiated adenocarcinomas, and lesions with a depth of invasion of T1a. The Authors concluded that BLI-bright has a higher real-time detection rate for EGC than WLI. Therefore, BLI-bright should be performed during surveillance endoscopy in patients at high risk for EGC.

It must be stressed that EGC should be best detected by selecting the high-risk population (history of gastric cancer and presence of H. pylori infection), using the latest endoscopic system that provides good quality images and learning the typical appearance of EGC, like the irregularities of gastric mucosa (Figure 9) and the discoloration of the mucosa (Figure 10).



(A) A combinated flat and elevated lesion with an unclear border at the lower body of the stomachis shown; (B) Endoscopic view after acetic acid was sprinkled; (C) Endoscopic view after indigo carmine was additionally sprinkled; (D) Endoscopic view after the lesion was washed with clean water. After chromoendoscopic with indigo carmine dye added to acetic acid, the lesion's borders became distict and the clarity of the image is high. The lesion was resected by endoscopic submucosal dissection and was shown to be a differentiated adenocarcinoma.

Figure 7. Chromoendoscopy of a differentiated adenocarcinoma

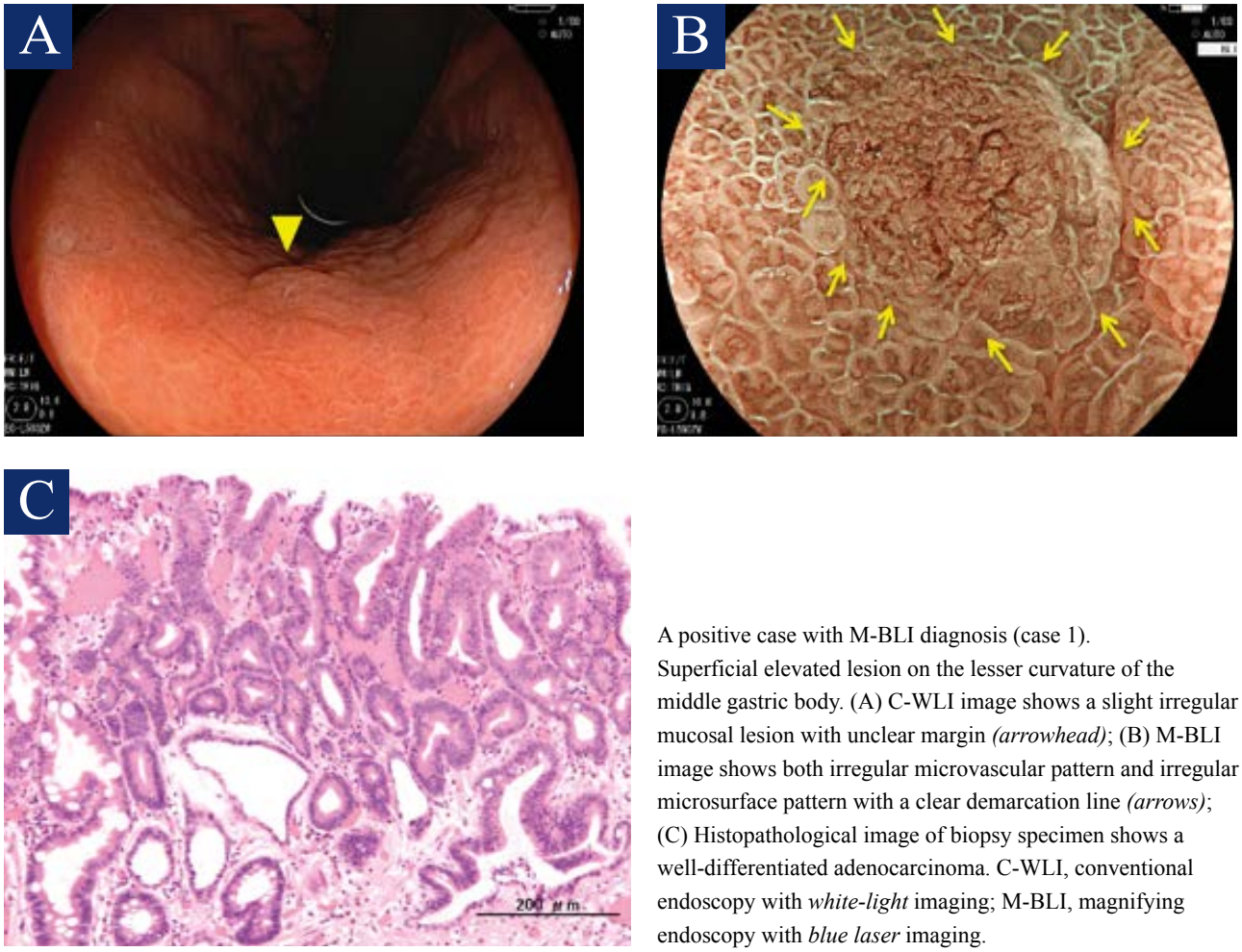
Third question: Can we perform ESD in the duodenum and if yes, when and how?

The answer is yes, but it must be performed by an extremely well experienced expert for malignant lesions. In fact, duodenal ESD is challenging and dangerous. The water pressure method (Figure 11) and the pocket creation method (Figure 12) are very helpful for duodenal ESD.

The large mucosal defects after ESD in the duodenum should be closed in order to avoid serious complications. Figure 13 shows the various steps of an ESD procedure for the removal of a duodenal neuroendocrine tumor.

Fourth question: Which is the best tool and technique for colonic ESD?

The answer is that a short needle type knife with injection capability or a scissors type knife should be used for colorectal ESD. Special techniques or some traction devices can be selected according to



A positive case with M-BLI diagnosis (case 1). Superficial elevated lesion on the lesser curvature of the middle gastric body. (A) C-WLI image shows a slight irregular mucosal lesion with unclear margin *(arrowhead)*; (B) M-BLI image shows both irregular microvascular pattern and irregular microsurface pattern with a clear demarcation line *(arrows)*; (C) Histopathological image of biopsy specimen shows a well-differentiated adenocarcinoma. C-WLI, conventional endoscopy with *white-light* imaging; M-BLI, magnifying endoscopy with *blue laser* imaging.

Figure 8. Diagnostic ability of magnifying endoscopy with blue laser imaging for early gastric cancer

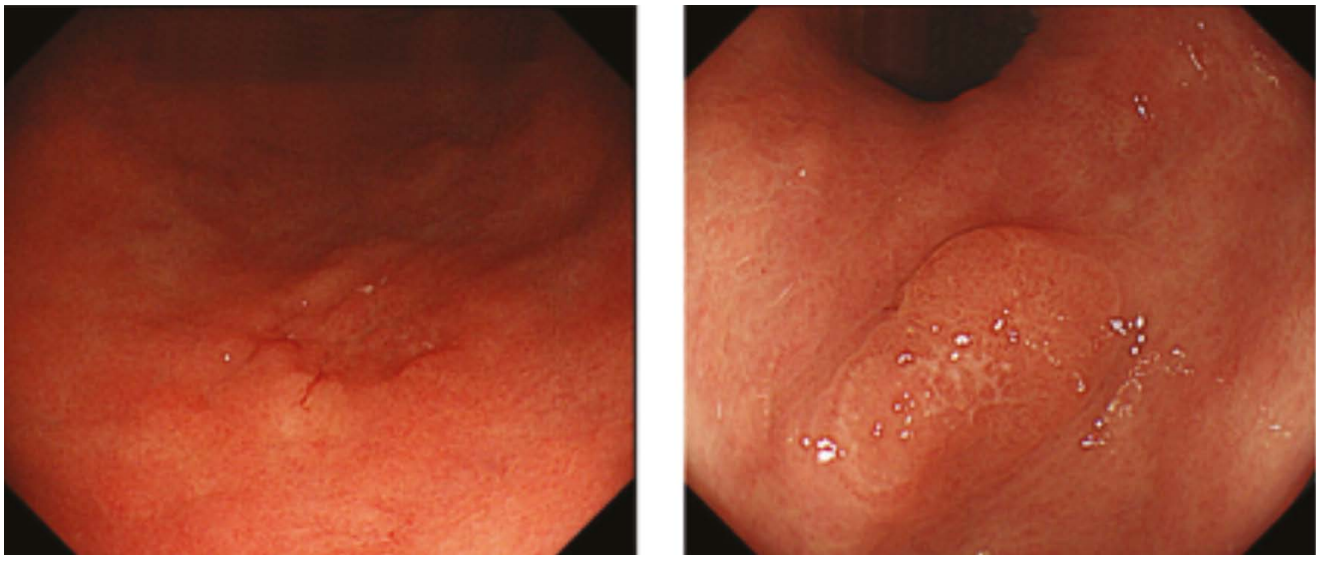


Figure 9. Typical Findings of EGC. Irregularity of the mucosa: shallow depression (0-IIc) and slight elevation (0-IIa)

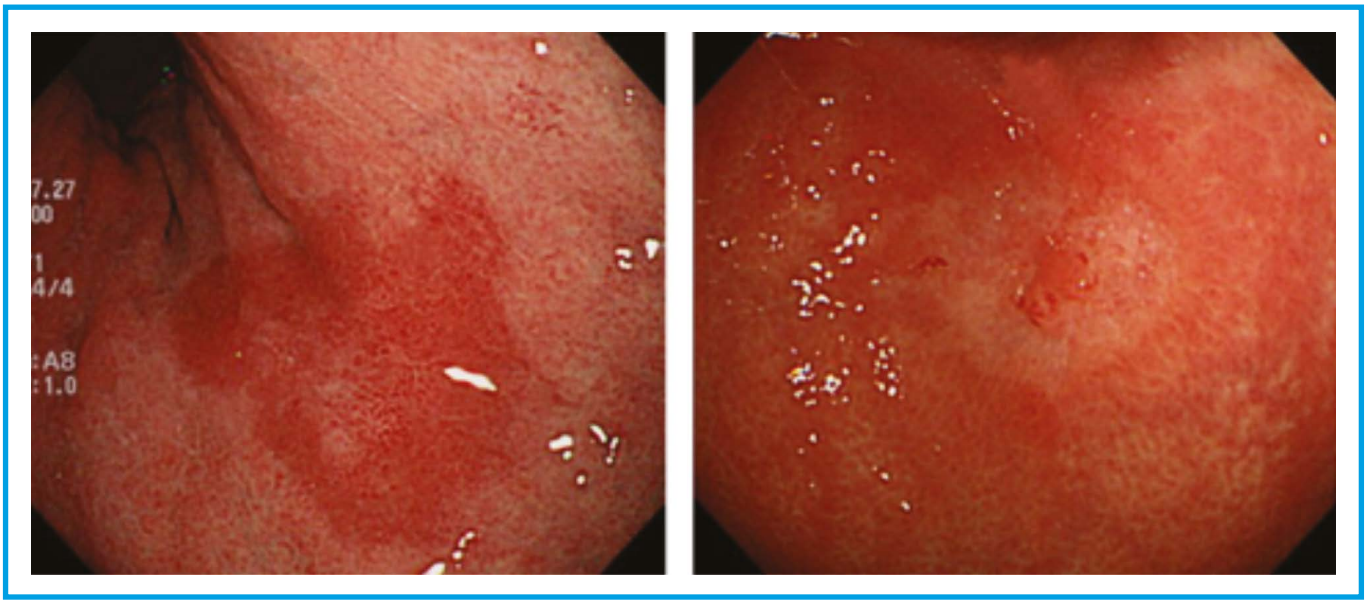


Figure 10. Typical Findings of EGC. Discoloration of the mucosa: reddish (0-IIb) and whitish (0-IIb)

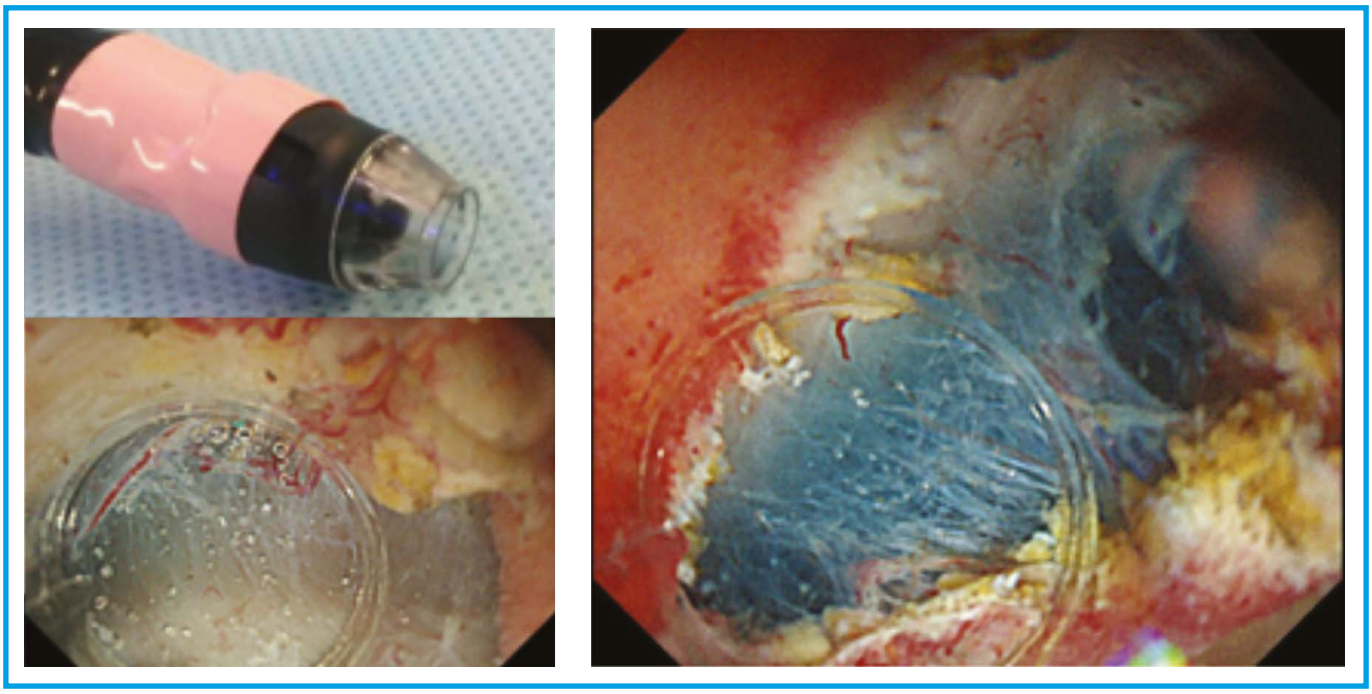


Figure 11. Water Pressure Method

the clinical situation encountered (lesion size, site maneuverability, etc.).

The standard approach for colorectal lesions consists of creating a submucosal pocket at the start of the procedure and opening a submucosal space using transparent hood or gravity (Figure 14).

Fifth question: Colorectum: can traction help and should be systematic?

The answer is yes, because a traction device sometimes helps a lot, even though it is not always necessary. In fact, ESD allows en bloc resection of large GI neoplasms, regardless of their size, but technical difficulties associated with this technique in the colorectum make it less widely applied in the treatment of tumors in this region. To address this difficulty, Sakamoto et al applied a rubber strip-based traction device, called the S-O clip

(Sakamoto-Osada clip) and reported that ESD with this device was effective for complete resection of large, superficial colorectal neoplasms. A further version of the S-O clip (spring S-O clip) was subsequently developed with the aim of improving the facility of clip use during ESD of colorectal tumors and this novel device resulted to be safe and effective for en bloc resection of large superficial

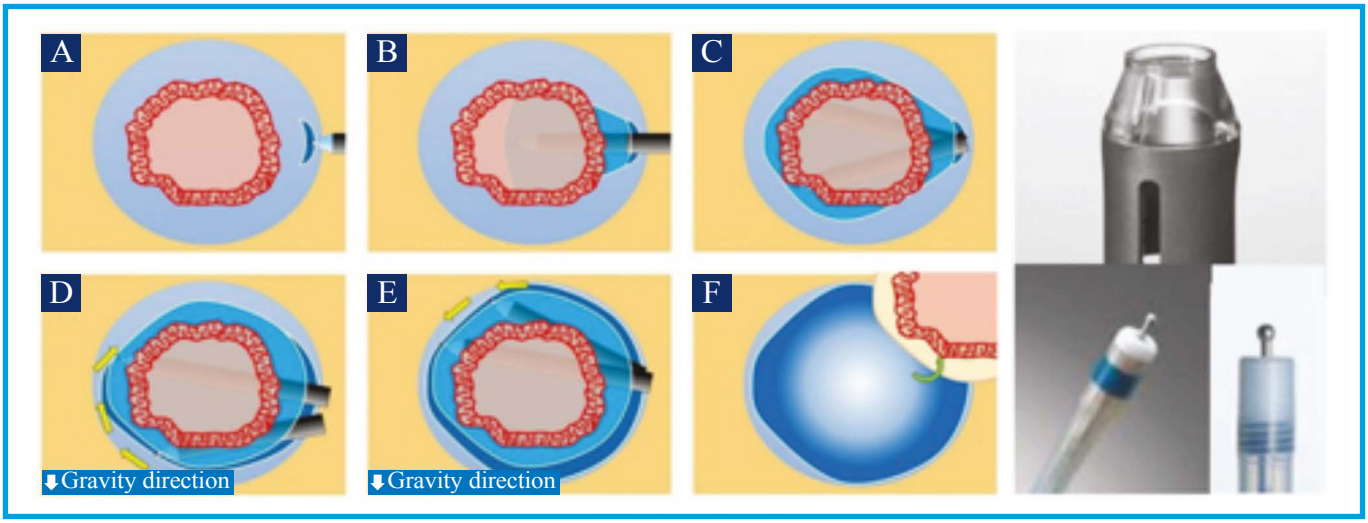
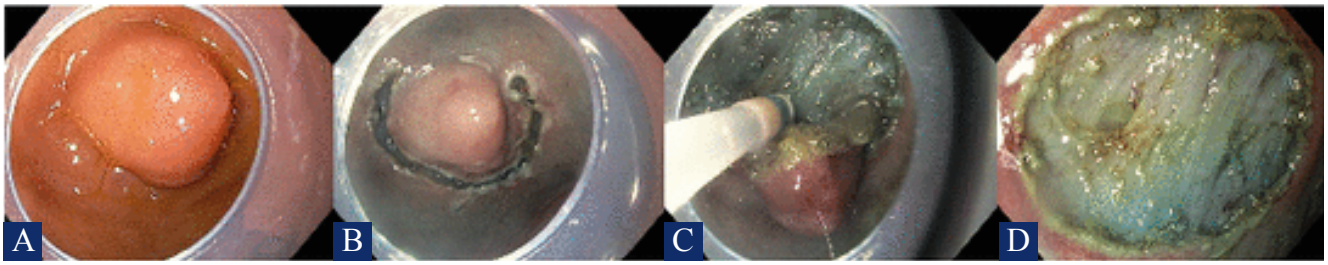


Figure 12. Pocket creation



(A) Visualization of the submucosal lesion in the distal, anterior wall of the duodenal bulb; (B) A submucosal injection was performed using diluite indigo carmine, diluite adrenaline, and succinylated gelatin, followed by a cicumferential mucosal incision; (C) Endoscopic submucosal disection was performed; (D) The lesion was completely exicised en bloc, leaving a clear mucosal defect.

Figure 13. Shows the various steps of an ESD procedure for the removal of a duodenal neuroendocrine tumor

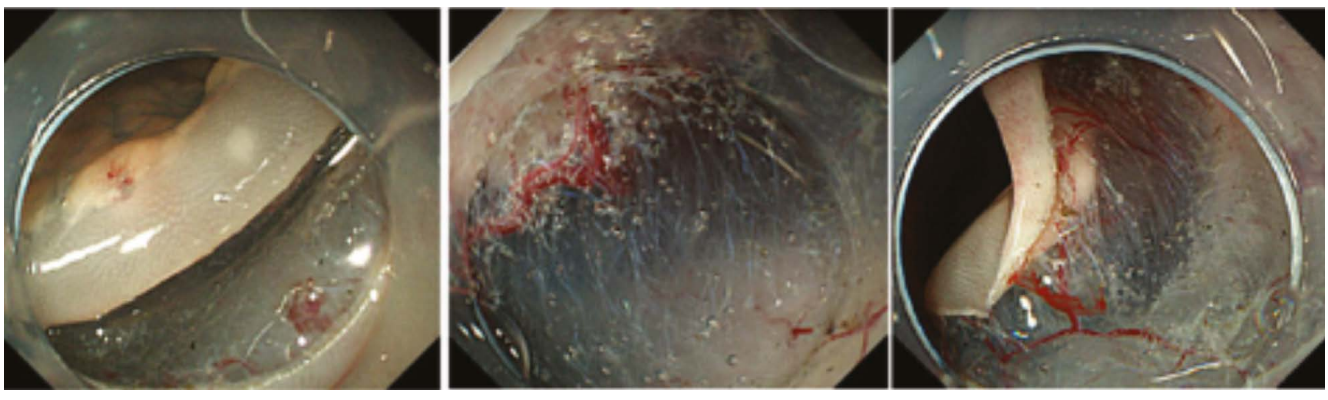


Figure 14. Standard Approach for Colorectal Lesions: create submucosal pocket at the beginning of the procedure and open submucosal space by using transparent hood or gravity

neoplasms in the right side of the colon (7). The same thing can be said for using a balloon assisted overtube. The balloon overtube and a therapeutic colonscope are displayed in Figure 15.

Sixth question: can we still perform a peace-meal EMR in the colon?

The answer is yes, but a peace-meal EMR should be performed only in case of very low-

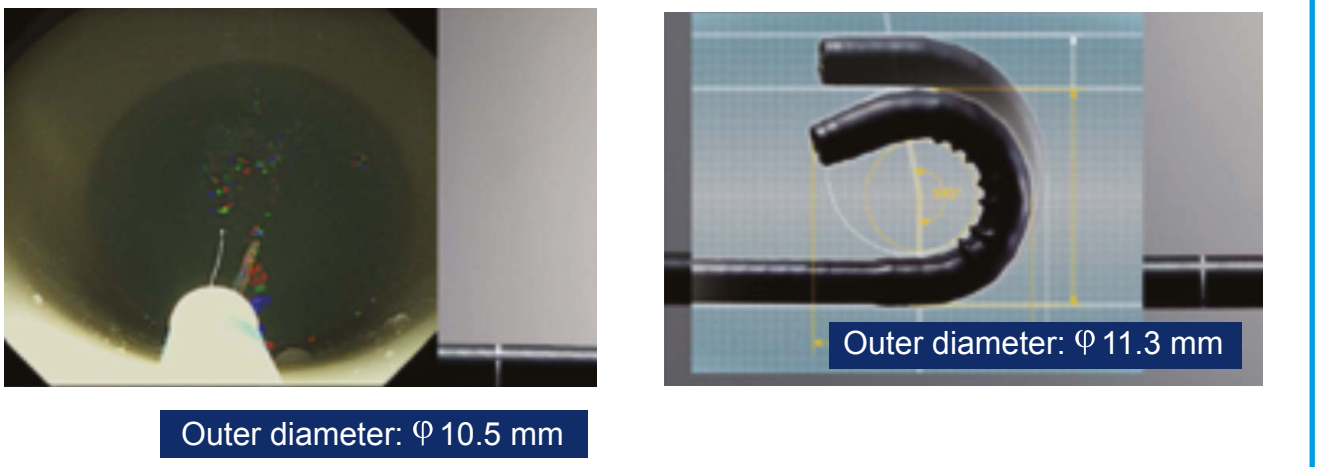
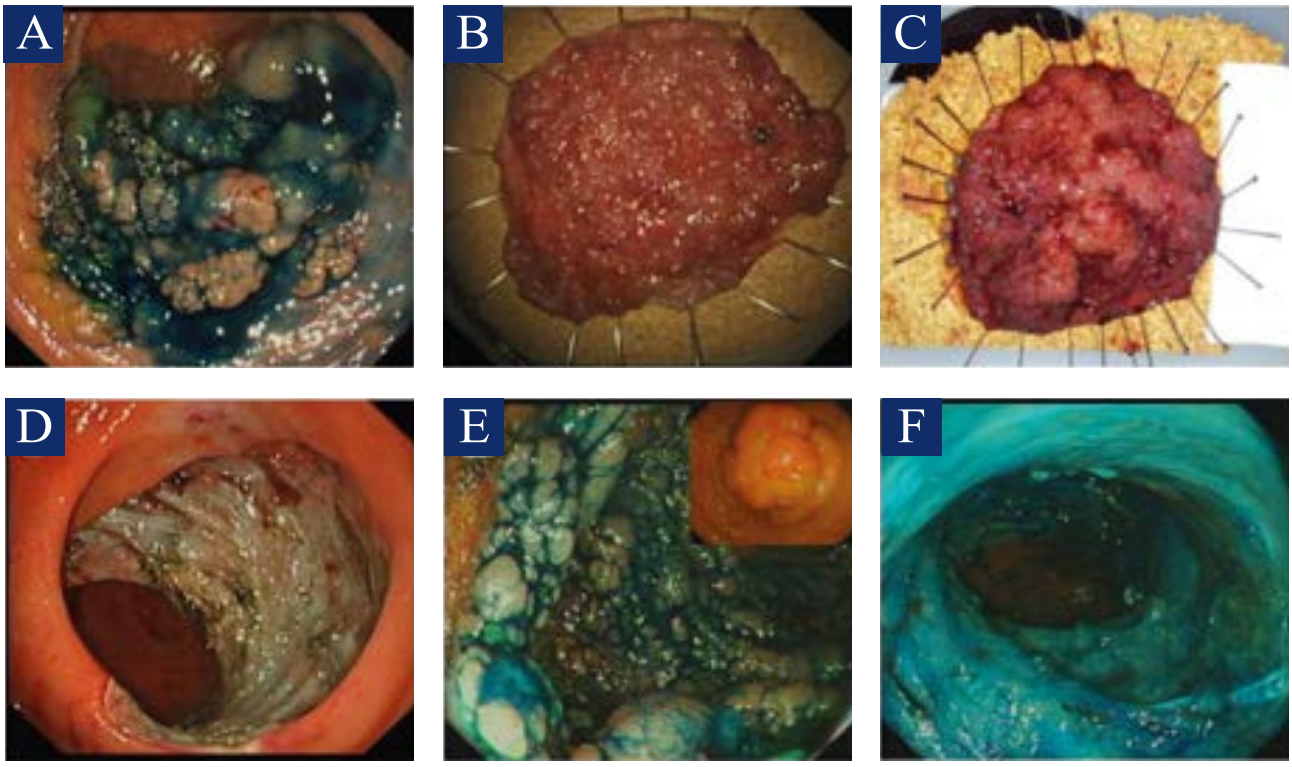


Figure 15. Balloon Overtube



Notes: (A-D) En bloc resection of these 8 and 10 cm LST granular mixed-nodular lesion is the procedure of choice to aid accurate histolopathologic assessment. However, hybrid ESD or pEMR is more aoppropriate for this 16 cm fully circumferential lesion in a 92-year-old patient (E-F) unlikely to tolerate a lengthy ESD. Significant nodular components (E, inset) should be resected in one piece and not sectioned. This was successfully resected as a day case procedure with minimal sedation, with no recurrence at the last follw-up.
Abbreviation: ESD, endoscopic submucosal dissection; LST, laterally spreading tumors; pEMR, piecemeal endoscopic mucosal resection

Figure 16. Example of appropriate selection of resection technique

(A) Endoscopic aspect of a recurrence after piecemeal endoscopic mucosal resection in the ascending colon; (B) The lesion is marked and retracted into the resection cap using a grasping forceps; (C) Resection bed with over the scope clip in situ. Note the periluminal fat within the clip; (D) Resected specimen on cockboard; (E) Histopathology: full-thickness resection specimen with tubulovillous adenoma/low-grade intrapithelial neoplasia (hematoxylin/eosine,magnification 80-fold).

Figure 17. Endoscopic full-thickness resection with the full thickness resection device

risk lesions, such as the homogeneous type of laterally spreading tumors (LST)-G after careful evaluation.

On the contrary, high-risk lesions, like LST-NG, should be resected in an en bloc fashion by ESD. Figure 16 shows the en bloc resection of an 8 cm LST granular mixed-nodular lesion (A) and the large resected specimen (B).

The LST-G greater than 30 mm have a risk of submucosal invasion (SM), while LST-NGs have a risk of SM which remains high regardless of the size, according to data of the Keio University Hospital collected during the time period from 2010 to 2018.

It has been published that the use of peace-meal EMR (pEMR) is associated with a recurrence rate of 23.3%, that is it occurred in 42 out of 180 patients treated (7), while ESD is more reliable. Figure 17 shows the endoscopic aspect of a recurrence after pEMR in the ascending colon (A), the resection bed with over the scope clip in situ after ESD (C) and the resected specimen on corkboard (D).

The merits of ESD are represented by the achievement of a precise diagnosis, a low recurrence rate and a lesser need for surveillance. The ESD demerits are the following: a technically difficult and time-consuming procedure, the need for hospitalization, the high cost and the occurrence of complications.

Seventh question: What is the precise recommendation concerning ESD training?

The answer is that training should start from an animal training model and the trainee should have performed more than 1000 colonoscopies and more than few hundreds of EMR before ESD training.

STEP 1. Clinical observation
STEP 2. Join a procedure as an assistant
STEP 3. Animal model trial
STEP 4. Gastric ESD (easy cases)
STEP 5. Gastric ESD (difficult cases)
STEP 6. Esophageal ESD (SCC → Barrett's ca.)
STEP 7. Colorectal ESD (Rectum → Colon)
STEP 8. Duodenal ESD

Figure 18. Steps of ESD training

The various steps of ESD training are displayed in Figure 18.

CONCLUSIONS

In conclusion, ESD is a mature endoscopic procedure developed in Japan that has spread to the West and is now actively practiced in Europe and in the United States. It has been shown to be better than EMR for the removal of large and difficult tumors located in both the upper and the lower GI tract, such as those which are across the esophago-gastric junction and huge rectal lesions. Therefore, ESD has great potential and the need to learn it continues to grow globally.

However, endoscopists wishing to perform ESD will require specialized training and this procedure should be performed at referral centers with properly trained ancillary staff and surgical back-up.

It is important to emphasize that both training models and e-learning systems have been developed in order to support ESD learning and, obviously, the learning curve has been facilitated and shortened using these training methods.

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