

Endoscopic submucosal dissection

Carlos Robles-Medranda

Endoscopy and Gastroenterology
Division, Ecuadorian Institute of
Digestive Diseases (IECED), University
Hospital OMNI, Universidad de
Especialidades Espiritu Santo (UEES),
Ecuador

Abstract

Endoscopic submucosal dissection (ESD) is a minimally invasive technique developed by Japanese endoscopists that allows one-piece endoscopic removal of early malignant lesions in the gastrointestinal tract. There is now a large and ever-increasing number of reports worldwide, and in the West use of this technique is on the increase. New materials and techniques have been developed to improve the technical aspects of ESD. Recent reports show successful clinical outcomes and improved overall 5-year survival rates for this technique. This review aims to offer an update of ESD based on the latest reports in the literature.

Introduction

Endoscopic submucosal dissection (ESD) is an innovative technique that has improved the rate of successful en bloc resection of large early gastrointestinal neoplasia. Since its introduction,^{1,2} new devices and techniques have been developed to improve the outcomes of ESD. Nowadays, these improvements have allowed ESD resections to be extended from stomach to other gastrointestinal mucosal areas, such as esophagus, duodenum, colon and rectum.^{3,4} Moreover, when comparing endoscopic mucosal resection (EMR) with ESD for superficial neoplastic lesions, ESD is currently considered the best endoscopic resection method for lesions with diameters over 20 mm³ due to the higher curative resection rates, less risk of recurrence, and better histological assessment obtained by this technique. In spite of the better results obtained and the experience gained over time, this technique remains technically difficult, demanding particular endoscopic skills from operators. It also involves a longer procedure time with associated risks of complications such as bleeding and perforation. This article is a summary and update review of ESD based on new reports found in the literature.

Technical aspects

After endoscopic detection and histological diagnosis of an intramucosal neoplasia, ESD is performed using a standard single accessory channel endoscope. Marking dots are placed by electrocautery to delimitate the margins of the lesion to be resected. Using an injection needle, a submucosal fluid cushion is created to lift the mucosa from the submucosa layer, isolate the lesion and protect the muscularis propria from thermal and mechanical injury, reducing the risk of perforation. A circumferential incision is performed around the lesion using special electrocautery knives, and a submucosal dissection is finally performed with special knives to remove the specimen (Figures 1 and 2).

Finally, the removed specimen is pinned on a corkboard, oriented and placed in formalin for correct analysis with standard histological techniques.

Materials and Methods

Many types of endoscopic electrocautery knives have been developed to perform ESD (Figure 3): a needle knife,⁵ an insulation-tipped (IT) knife 1 and 2,⁶⁻¹² a hook knife,¹³ a flex knife,¹⁴ a flush knife,¹⁵ a triangular-tipped (TT) knife,¹⁶ a fork knife,¹⁷ and the recently introduced dual knife,¹⁸ hybrid knife¹⁹ and the splash needle.²⁰ Each knife has its own characteristic regarding its design: diameter, length and the form of the tip, as well as rigidity (in the case of the flex knife). These characteristics mean there are both some advantages and disadvantages in its use regarding the direction of the incision, depth of the incision and coagulation properties. In some cases, additional characteristics such as multiple materials, injectors, or snares are presented in the same knife. This is the case of the flush, hybrid, dual and fork knives. The characteristics of each knife are summarized in Table 1.

The use of an electrosurgical unit with endocut properties is required to perform the cut and promote coagulation during ESD. For these purposes, generators, such as the ERBOTOM ICC 200, the VIO 300D (ERBE, Tübingen, Germany), or the recently introduced ESG-100 (Olympus Medical System Co. Ltd., Tokyo, Japan) (Figure 4), are available.

Submucosal injection solution

Injection-assisted endoscopic resection has been traditionally used to remove sessile or flat neoplastic lesions from the gastrointestinal tract. As has been proposed, an ideal solution for ESD should be inexpensive, easily available, non-toxic, easy to inject and able to provide a long-lasting submucosal cushion.^{21,22}

Correspondence: Carlos Robles-Medranda, Instituto Ecuatoriano de Enfermedades Digestivas – IECED, Hospital Universitario OMNI, Universidad de Especialidades Espiritu Santo, Torre Vitalis, Mezanine 1. Av. Abel Romeo Castillo y Av. Juan Tanca Marengo, Guayaquil, Ecuador.
Tel. +593.42109180- Fax: +593.52633265.
E-mail: carlosoakm@yahoo.es

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Saline solution (NaCl 0.9%) has been largely used for endoscopic mucosal resection either alone or in combination with epinephrine.²³ However, in spite of it being a seemingly ideal solution, the duration of the normal saline solution is short and, therefore, not ideal for the purposes of ESD.

Other solutions have been demonstrated to be superior to NaCl 0.9% in creating a long-lasting submucosal fluid cushion (SFC) such as a hypertonic solution of sodium chloride (3.0%), glycerol, dextrose (20%, 30%, 50%), albumin, fibrinogen, autologous blood, hyaluronic acid and the hydroxypropyl methylcellulose.²⁴⁻³⁰ The advantages and disadvantages of each solution include its availability in the endoscopy units, its price (how expensive it is), and whether or not it can produce tissue damage or local inflammation. Today, the best cushion duration available is obtained with substances such as hyaluronic acid, hydroxypropyl methylcellulose, fibrinogen and autologous blood. Recently, other substances such as polyvinyl alcohol 1.4%, hydroxyethyl starch 6% and polyethylene glycol have been demonstrated to be superior to normal saline solution and to perform equally as well as sodium hyaluronate in an ex vivo study.³⁰

Drawbacks and new developments

Many studies have demonstrated the feasibility and efficacy of ESD for treating gastrointestinal lesions. The drawback of ESD is that it

is technically difficult to perform and is, therefore, associated with long operating time and higher rates of complications.^{8,12,31} In addition, ESD requires advanced endoscopic techniques.³¹ Imagawa *et al.* show that the difficulty of ESD depends on: location, size (>20 mm) and characteristics of the lesion (ulcerated lesions) as well as the endoscopist's experience.³²

There are important technical aspects to be considered during ESD: the placement of the endoscope under the submucosal layer to obtain direct visibility during dissection and the long-lasting SFC required to reduce the time needed for the procedure and to avoid complications. As far as long-lasting SFC is concerned, many substances have been tested for ESD (see above) and have shown good results. Adaptable caps on the tip of the endoscope can be used to facilitate the positioning of the endoscope under the submucosal layer.

Recently, other materials and techniques have been developed for the same purpose, such as the use of clips for peroral traction-assisted ESD,³³ clips for internal counter-traction spring devices³⁴ and a peralloy tissue anchor for external magnetic force-assisted ESD³⁵ all of which demonstrate the feasibility of the technique. However, some of these materials are not always available and cost issues sometimes limit their use for routine application in real clinical conditions.

Water-jet technology

Water-jet (WJ) technology was first introduced in flexible endoscopes to assist mucosal resections during bleedings, by washing

the bleeding field with the WJ. The bleeding source can then be immediately identified and coagulated, avoiding the use of the syringe over the forceps channel of the endoscope.³⁶

WJ technology is under investigation as a

medical tool in many other surgical areas. It has demonstrated a clear technical advantage over the conventional surgical dissection modalities. It allows: i) a selective dissection of fibrous and connective tissues, preserving blood vessels for delayed ligation;³⁷⁻³⁹ ii)

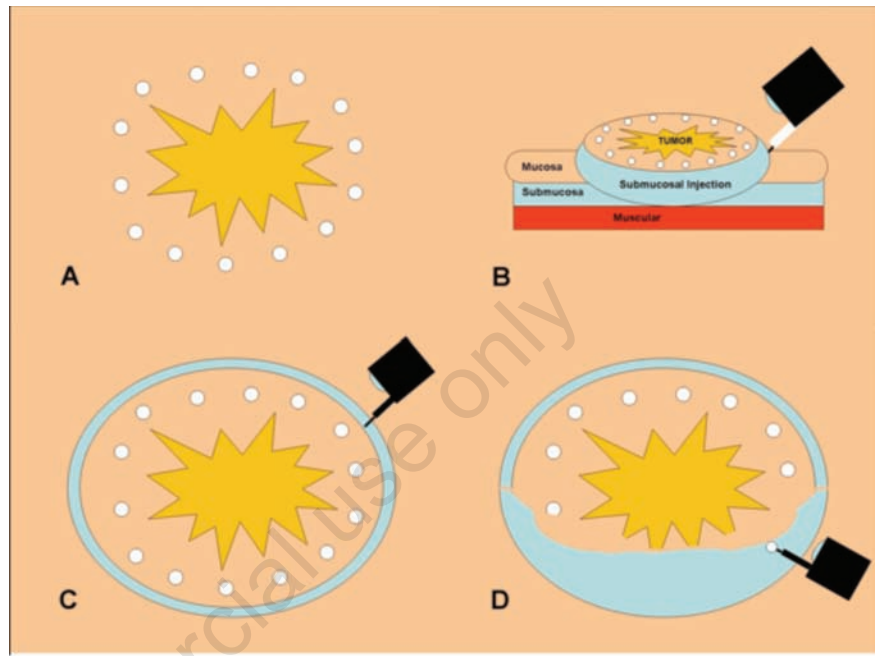


Figure 1. Endoscopic submucosal dissection schematic steps. A) Marking dots to delimitate the lesion; B) Submucosal injection; C) Circumferential incision; D) Submucosal dissection.

Table 1. Characteristics of endoscopic submucosal dissection knives.

Name (Manufacturer)	Characteristics
Needle knife (Olympus®, Boston®, Cook®)	Needle tip with adjustable length. High risk of perforation
Insulation Tipped knife 1: IT-knife 1 (Olympus®)	Small ceramic ball on the tip of a needle knife. Prevents perforations. Can not operate in any direction, does not permits coagulation. Can not be used for injection
Insulation Tipped knife 2: IT-knife 2 (Olympus®)	Small ceramic ball on the tip of a triangle tip knife. Prevents perforation, it permits to cut and to coagulate. Can not be used for injection
Flex knife (Olympus®)	Soft and flexible cutting, rounded tip with a twisted wire. Flexible tip that prevents perforations, permits to cut and to coagulate. Can not be used for injection
Flush knife (Fujinon®)	Water jet fine needle knife with regulated length. Avoid exchange between knife and the injection needle. Allows washout of blood
Triangle Tip knife: TT-knife (Olympus®)	Triangle form at the tip. It permits to cut and to coagulate. It can operate in any direction. Risk of perforation
Fork knife (Endo FS®)	Two knives: a forked knife, fixed flexible snare and an inlet for material injection. Avoid exchange between knife and the injection needle. Single working unit
Dual knife (Olympus®)	Water jet with a rounded needle knife with regulated length. Avoid exchange between knife and the injection needle. Allows washout of blood
Hook knife (Olympus®)	Right angle bend of the needle knife tip. The tip is rotatable and can pull dissect the tissue. It permits to cut and to coagulate. It can operate in any direction. High risk of perforation
Splash needle (Pentax®)	Water jet fine needle knife with regulated length. Avoid exchange between knife and the injection needle. Allows washout of blood
Hybrid knife (ERBE®)	Water jet fine needle knife. Avoid exchange between knife and the injection needle. Allows washout of blood.

reduction in dissection-related complications,^{38,40} iii) reduction in tissue injury,⁴⁰ and iv) reduction in dissection time compared with conventional techniques.⁴¹ Based on these observations, in 2007 two reports described the application of water-jet technology as a technique used together with ESD.^{42,43} Lepilliez *et al.*⁴² describe the use of WJ as two techniques in a porcine model: i) as an injection technique; and ii) as a dissection method with a catheter prototype and using the water as a dissection method. In this report, the feasibility and possible applications of WJ technology for stomach and esophageal ESD were demonstrated. At the same time, Toyonaga *et al.*⁴³ also demonstrated use of WJ technology in ESD as an injection method with the flush knife, facilitating the dissection by thermal coagulation. WJ technology seems to facilitate ESD. This could be due to the speed and quality of injection using provided by the WJ that allows a longer lasting SFC. Kaehler *et al.*⁴⁴ demonstrated that submucosal injection of a saline solution using WJ provides a selective long-lasting SFC for over 20 min. These results were confirmed by the same team in a study on humans obtaining long-lasting SFC for over 40 min using other solutions such as plasma expanders.⁴⁵ Today, the number of clinical trials using the WJ technology is on the increase as are the devices developed for its use.^{19,36,46}

Learning curves

Japanese physicians have suggested some criteria that they consider should be required before performing ESD,⁴⁷ such as: i) attendance at ESD pre- and post-treatment conferences; ii) initial experience as an assistant physician during ESD procedures for at least one year; iii) skillful recognition of the extent and depth of the tumors; and iv) expertise in hemostasis.

Previous studies have investigated the learning curves for ESD.⁴⁸⁻⁵⁰ Choi *et al.*⁴⁸ have found an increase in the en bloc resection rate from 45-85% after an experience of 40 cases. Gotoda *et al.*⁴⁹ reported that experience of at least 30 cases is required for a beginner to gain early proficiency in ESD. Kakushima *et al.*⁵⁰ have indicated that a change in en bloc complete resection and complication rates did not represent operator proficiency with ESD under supervision, but that a reduction in operation time is a marker of proficiency. According to them, this is only acquired with time and a minimum number of cases.

Recently, an interesting and well-designed report from Yamamoto *et al.*⁴⁷ showed that experience of more than 30 cases is necessary in order to become proficient.

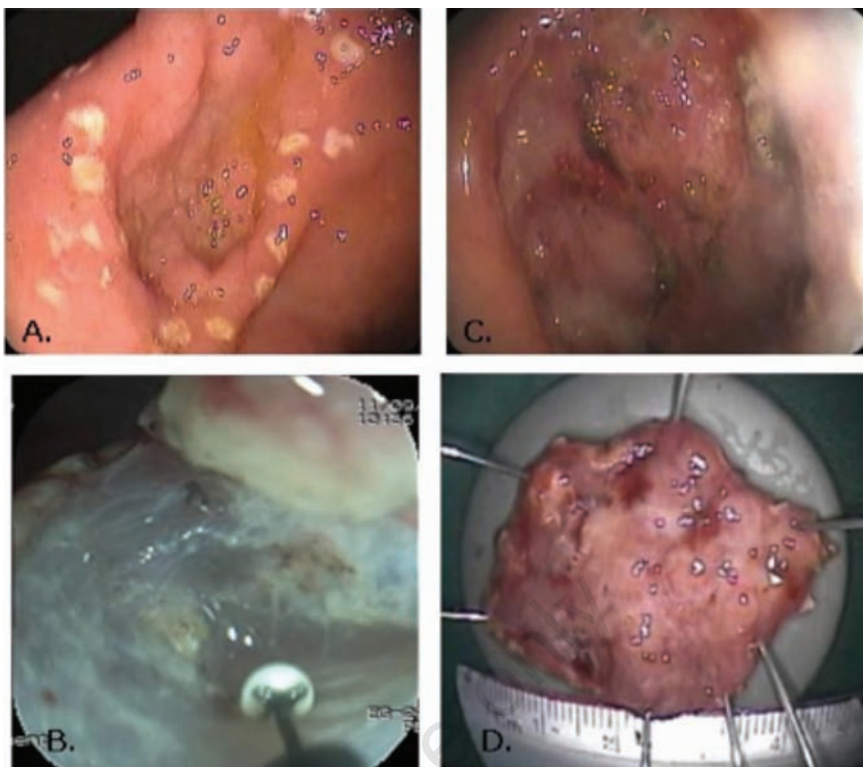


Figure 2. Endoscopic submucosal dissection of an early gastric cancer type 0-IIa from the antrum. A) Marking dots around the lesion; B) Submucosal dissection using IT-knife 2; C) The mucosal ulcer after complete resection of the lesion; D) The mucosal tumor of 40 mm of diameter resected in one piece.



Figure 3. Electrocautery knives for Endoscopic submucosal dissection. A) Insulation-tipped knife (IT-knife 2); B) triangle-tip knife (TT-knife); C) flex knife; D) hook knife (pictures courtesy from Olympus Latinamerica).

Clinical applications and efficacy at follow up

ESD is generally indicated for resections of intramucosal neoplastic lesions of more than 20 mm. Initially, it was created to treat early gastric cancers but the development of new materials, as well as the performance of the endoscopists, have allowed this method to be extended to other parts of the gastrointestinal tract, such as the esophagus, duodenum, colon and rectum. It is very important to have a good staging of the lesions with complementary studies before performing ESD. It is also important that the extent of the lesion is appropriate. For this purpose, the use of magnifying endoscopy, chromoendoscopy and new endoscopy technology, such as narrow band imaging (NBI) (Olympus Optical Co., Tokyo, Japan), and/or the intelligent-scan system (i-Scan) (Pentax Corporation, Tokyo, Japan) (Figure 5) could be of help.^{51,52}

Endoscopic submucosal dissection for upper gastrointestinal tumors

Esophagus

In the esophagus, ESD is indicated for the treatment of moderated and well-differentiated epidermoid cancer and recently it has also been proposed as a therapeutic approach in high-grade dysplasia in Barrett's esophagus and the adenocarcinoma.⁵³⁻⁵⁵ The lesions should be located in the mucosal layer and there should be no lymph node involvement (T1N0). The absolute indication for endoscopic resection in cases of epidermoid cancer is defined as m1 (restricted to the propel mucosa) -m2 (adjacent or invading but not beyond the muscularis mucosa) esophageal cancer plus no more than two-thirds extension of the circumference.⁵⁴ In a recent report, Higuchi *et al.*⁵⁶ showed that an extension of these indications could be achieved for lesions involving m3-sm1 esophageal cancer, without lymphatic invasion, larger surface dimensions, and wider lamina muscularis mucosae invasion. On the other hand, m3 or sm1 lesions accompanied by lymphatic invasion confirmed after endoscopic resection should be treated as a systemic disease with high risk of lymph-node metastasis.⁵³ A 5-year survival rate for lesions limited to the lamina propria mucosa has been reported in 100% of such cases and 86% for lesions deeper than the lamina propria mucosa.⁵⁷ Barrett's esophagus often has double muscularis mucosae, therefore the depth of invasion should be subdivided into m1-m4.⁵⁵ In these cases, endoscopic resection is indicated for lesions limited to the mucosa and in



Figure 4. The electrosurgical unit with endocut properties ESG-100 (picture courtesy from Olympus Latinamerica).

lesions with high-grade dysplasia where the risk of lymph-node metastases or micrometastases is often absent.^{55,58} A 5-year survival rate of 98% has been reported after endoscopic treatment of these lesions.⁵⁹

Stomach

The first application of ESD was in gastric cancer. The literature reports that more than 10,000 of these types of lesions have been treated. ESD is indicated for differentiated type intramucosal cancer without ulcer, differentiated type intramucosal cancer no larger than 3 cm in diameter with ulcer, and differentiated type minute invasive submucosal cancer (<500 micrometers below the muscularis mucosa). Cancerous lesions no larger than 3 cm in diameter are now considered as indications for endoscopic resection.⁶⁰ A 5-year survival rate for lesions limited to the lamina propria mucosa has been reported in around of 96 to 100% of cases.⁶¹ ESD has also been reported in submucosal lesions specifically when the tumors display a submucosal layer or muscularis mucosa origin,⁶² as well as for the treatment of neoplasms arising from the remnant stomach after gastrectomy or esophagectomy.⁶³ But these results are limited to a case series.

Duodenum

Recent reports have shown the use of ESD for duodenal lesions. Honda *et al.*⁶⁴ described the feasibility of ESD for duodenal neoplasm in a series of cases. The authors concluded that duodenal ESD remains a technique demanding time-consuming procedures, and is associated with a high risk of complications. Fukushima *et al.* reported the first en bloc resection of a large ampullary adenoma with focal adenocarcinoma by using ESD.⁶⁵ However, these experiences are restricted to a case series and follow-up results remain unclear.

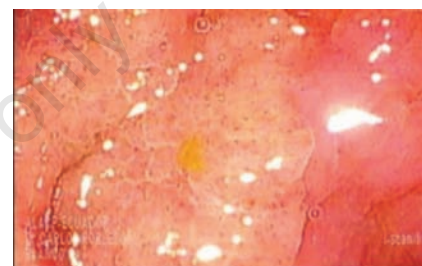


Figure 5. Macroscopic aspect of a segment of an early gastric cancer: meshed capillary vessels are observed with the *i-scan* system and magnification (Pentax Corporation, Tokyo, Japan).

Endoscopic submucosal dissection for lower gastrointestinal tumors

Ileum, colon and rectum

Endoscopic resection is indicated for the treatment of adenoma and intramucosal or submucosal superficial (sm1: less than 1000 μ m from the muscularis mucosae) colorectal cancer because of its minimal invasiveness, negligible risk of lymph-node (LN) metastasis 1 and excellent results in terms of clinical outcome.⁶⁶⁻⁶⁸

In colorectal mucosal cancer, endoscopic piecemeal mucosal resection (EPMR) can treat many LSTs over 20 mm with only a few cases requiring surgery.⁶⁹ Recently, an increasing number of colorectal ESDs have been reported from Japan showing the feasibility of the technique, especially in lateral spread tumors of the non-granular type.⁷⁰⁻⁷² Furthermore, a case series study of colorectal ESD, published by Niimi *et al.* shows that the 5-year survival rate is as high as 95.3%.⁷³

Table 2. Rates of bleeding and perforation in endoscopic submucosal dissection in accordance to the location of the mucosal resection reported by some authors.

Location	Total Cases	Bleeding %	Perforation %
Esophageal ⁷⁴	58	0	6.9
Stomach ⁷⁵	1033	4	1
Colorectal ⁷⁷	292	0.7	8.2

Finally, a case report of ESD in the terminal ileum by Japanese endoscopists⁷⁴ shows the feasibility of this technique in this area.

Complications

The great majority of complications arising from ESD are bleeding and perforation.⁷⁵⁻⁷⁸ Most are, however, solved during the procedure. In an interesting study, Takizawa *et al.*⁷⁷ show that the experience of the operators does not influence delayed bleeding after gastric ESD. However, the tumor location and post-ESD coagulation are important factors in post-ESD bleeding risk, which indicates that preventive coagulation should be routinely performed. Isomoto *et al.*⁷⁸ reported that the clinicopathological factors associated with colorectal ESD are essentially large tumor size and presence of fibrosis. Hemostasis is required as well as a good visibility when performing ESD. For hemostasis, the use of a thermal coagulation grasper, hemoclips, esclerotherapy needles, and an argon plasma coagulator are used. To maintain good visibility during bleeding, water-jet irrigation endoscopes and/or irrigation pumps are available. To treat perforation, endoscopy clips have been used with good results.⁷⁸

The rates of bleeding and perforation related to the esophagus, stomach and colon are summarized in Table 2. Other types of complications have been described. These concern pain, stricture and bacteremia.⁷⁹⁻⁸¹ In cases of stricture, it has been proposed that large circumferential resections should be avoided.⁷⁹ The use of cellular therapy, such as extracellular matrix scaffold or autologous buccal keratinocyte implantation, has shown promising results in the prevention of esophageal strictures after circumferential mucosal resection.^{82,83} Finally, when there is post-ESD stricture, the use of repeated balloon dilations might constitute a useful option.⁷⁹ Nevertheless, we still need to develop low-cost and low-risk techniques that are readily available. Mention should also be made of post-procedural discomfort after ESD. This is observed in some patients and often attributed to air insufflations during the procedure. This problem is largely controlled nowadays by the use of CO₂ pumps, as suggested by Saito *et al.*⁸⁴ in a recent study.

Endoscopic submucosal dissection in Western countries

To acquire the necessary expertise in ESD, operators need to carry out a minimum number of procedures and methodology in training is important. In the West, experience of ESD is limited to reference centers with a low number of cases reported.⁸⁵ This limitation could be due to several conditions,⁸⁶ which include screening systems to detect early gastrointestinal cancers, the relative infrequency of early gastric cancer in many Western countries, the differences in the evaluation criteria between Japanese and Western pathologists, and the low number of structured training courses.

Summary and perspectives

Nowadays, ESD is without doubt an efficient technique for the treatment of early gastrointestinal tumors with good results at follow up. Early detection of gastrointestinal tumors, accurate pre-operative diagnosis, and familiarity with the correct indications for ESD are indispensable to ensure successful treatment.

Despite the excellent results achieved so far, more progress could be made in reducing time-consuming or risky procedures and perfecting general techniques. Western experience and expertise in advanced techniques is still far behind that of Japan. In the West, improved techniques and early screening, as well as better training of endoscopists, are still required in order to achieve positive results.

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