TECHNOLOGY STATUS EVALUATION REPORT

Endoscopic submucosal dissection

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the Committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through April 2014 for relevant articles by using the key words "endoscopic submucosal dissection" and "ESD," combined with other relevant terms such as "gastric," "esophageal," "rectal," "colonic," and "adverse events," among others. Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

BACKGROUND

Endoscopic submucosal dissection (ESD) is a well-established technique of endoscopic resection that allows for en bloc removal of GI epithelial lesions. ESD differs from EMR, the other type of endoscopic resection. Both techniques involve injection of a substance under the targeted lesion to act as a cushion. With EMR, the lesion is then removed with a snare or suctioned into a cap and snared. With ESD, the submucosa is instead dissected under the lesion with a specialized knife. This enables removal of larger and potentially deeper lesions with a curative intent than can be accomplished with EMR. ESD was first described in 1988 as a technique to treat early gastric neoplasia nonoperatively. Over the ensuing decades, procedural techniques and equipment for ESD have evolved significantly, and applications for ESD techniques have expanded to locations throughout the GI tract as well as to the treatment of deeper, nonepithelial lesions. The principles of ESD have also led to the development of procedures with a therapeutic intent other than the resection of neoplasia, including peroral endoscopic myotomy for the treatment of achalasia.

TECHNOLOGY UNDER REVIEW

Proper patient and lesion selection for ESD are essential. Endoscopic resection of neoplastic lesions should only be undertaken when endoscopic and/or endosonographic evaluations predict a curative resection. However, one of the benefits of ESD is that the pathologist is provided with an en bloc specimen, such that noncurative resections can be more easily detected and patients properly referred for further oncologic surgery.

ESD is accomplished in a sequential or stepwise manner, and a variety of devices are available to assist the endoscopist in performing each step. Typically, the ESD steps during resection of a mucosal neoplastic lesion are as follows: (1) the perimeter of the lesion is marked with cautery; (2) a lifting agent is injected into the submucosa around the perimeter of the lesion; (3) the mucosa is incised and then cut circumferentially around the lesion by using an electrosurgical knife; (4) the submucosa beneath the lesion is injected and then dissected in a free-hand manner by using an electrosurgical knife until the specimen has been completely resected; and (5) any intra procedural bleeding that occurs during the mucosal incision or submucosal dissection is managed by using a water jet for washing and hemostatic forceps or an electro surgical knife by using coagulation current for vessel coagulation.

Electrosurgical knives, discussed in the following, are the main devices used in ESD that differentiate it from
other types of endoscopic resection. The other tools used (e.g., endoscope, electrosurgical unit [ESU], and other ancillary devices) are similar to those used for standard endoscopy. However, because of the complexity of the procedure, special considerations in choosing these types of equipment are also necessary.

**Devices for ESD**

The common attribute of all dedicated ESD devices is their ability to perform submucosal dissection. However, some devices are also useful in earlier stages of the procedure, such as marking or initial mucosal incision. The earliest dedicated ESD device simply added an insulated ball-like ceramic tip to an existing needle-knife to prevent inadvertently deep dissection and thus potential perforation. In addition to uncovered and covered (insulated-tip) needle-knife–like devices, a group of forceps-like devices has now been developed. However, although a wide variety of dedicated ESD devices are manufactured worldwide, the number of ESD devices that are approved by the U.S. Food and Drug Administration and available in the United States is limited. Table 1 lists ESD devices approved by the U.S. Food and Drug Administration and their suitability for the different procedural steps in ESD. All ESD devices are designed for single use only. Most ESD devices feature catheter outer diameters that are compatible with a 2.8-mm endoscopic instrument channel. Some ESD devices are available in lengths compatible with use with a colonoscope.

**Knives.** *ITKnife.* The ITKnife and ITKnife2 (Olympus America, Center Valley, Pa) (Table 1, Figs. 1A and 1B) both feature a 2.2-mm ceramic ball mounted on the end of a 4-mm-long cutting knife. The ITKnife2 also has a triangular electrode beneath the ceramic ball that facilitates cutting. The principal applications of the ITKnife and ITKnife2 are for the circumferential incision and submucosal dissection phases of gastric ESD.

The ITKnife nano (Olympus America) (Table 1, Fig. 1C) features a 1.7-mm ceramic ball mounted on the end of a 3.5-mm-long cutting knife. There is a 0.9-mm diameter circular electrode beneath the ceramic ball that is relatively recessed from its lateral margins. The principal applications of the ITKnife nano are for the circumferential incision and submucosal dissection phases of esophageal and colorectal ESD.

**HookKnife.** The tip of the HookKnife (Olympus America) (Table 1, Fig. 1D) is bent at a right angle, creating an L shape. The knife extends to 4.5 mm in length with a 1.3-mm hook. Both the knife length and the direction of the hook are adjustable at the instrument handle. Extending the knife fully locks the direction of the hook. This knife is designed to allow the hooking and retraction of the tissue to be cut. The HookKnife is capable of marking, initial mucosal incision, circumferential incision, and submucosal dissection at any site in the digestive tract, but is particularly useful for dissecting fibrotic tissue.

**Triangle Tip Knife.** The Triangle Tip Knife (Olympus America) (Table 1, Fig. 1E) has a noninsulated triangular electrode at the tip of a 4.5-mm-long cutting knife. The triangular electrode measures 1.6 mm on each side and maximally extends 0.7 mm away from the central cutting knife. Although this knife is useful in multiple steps for ESD, care must be taken with the relatively large distal electrode on the Triangle Tip Knife to avoid perforation. For this reason, it may be used less commonly for ESD than other knives, although it was the knife used in the initial descriptions of peroral endoscopic myotomy.

**DualKnife.** The DualKnife (Olympus America) (Table 1, Fig. 1F) features a very small noninsulated dome-shaped electrode at the tip of the cutting knife, which is 2.0 mm in length for the gastroscopy-length model and 1.5 mm in length for the colonoscopy-length model. For the initial marking phase, full retraction at the knife handle is used. In this position, only 0.3 mm of the knife tip protrudes beyond the catheter tip. The DualKnife is useful for all electrosurgical phases of ESD throughout the digestive tract.

**FlexKnife.** The FlexKnife (Olympus America) (Table 1, Fig. 1G) comprises a braided 0.8-mm diameter cutting knife with a looped tip at the distal aspect that may be extended a variable length from the catheter tip. The FlexKnife is useful for all electrosurgical phases of ESD throughout the digestive tract.

**HybridKnife.** The HybridKnife (ERBE USA, Marietta, Ga) (Table 1, Figs. 1H and 1I) has a central capillary within the cutting knife that can serve as an ultrafine 120-μm water jet when coupled with a foot pedal–activated, computerized jet lavage unit (ERBEJET 2 system; ERBE USA) (Fig. 2). As such, this device can accomplish all phases of ESD including lifting. The pressurized water jet delivered by the HybridKnife can penetrate the mucosa and accrue in the submucosa, thus providing a submucosal lift without requiring needle puncture. The HybridKnife features a 5-mm-long cutting knife with 3 tip configurations: the I type, which is straight with no added tip; the T type, which features a noninsulated, 1.6-mm diameter disk-shaped electrode at the tip; and the O type, which features an insulated, hemispherical, domelike tip. The I-type and T-type knives are approved by the U.S. Food and Drug Administration and available in the United States; the O-type HybridKnife is not yet available in the United States.

**Hemostatic forceps and other devices.** Monopolar and bipolar hemostatic forceps have been developed to treat bleeding with coaptive thermocoagulation. The Coagrasper (Olympus America) is a monopolar hemostatic forceps available in 165-cm and 230-cm lengths designed for gastric and colonic indications and is available in the United States.
United States. The gastric forceps feature serrated jaws with a 5-mm opening width, whereas the colonic forceps have both a smaller opening width (4 mm) and surface area to allow more targeted coagulation within the thinner walled colon (Fig. 3).

As previously mentioned, other forceps-like ESD devices have been developed that are useful for applications beyond hemostasis. The Clutch Cutter (Fujiﬁlm, Saitama, Japan), the SB Knife and SB Knife Jr (Sumitomo Bakelite Co Ltd, Akita, Japan), the Endo-Dissector (Karl Storz, Tuttingen, Germany) and the Endo-Maryland Dissector (Ovesco, Tubingen, Germany) are examples of monopolar forceps-like devices that can grasp and cut or coagulate tissue, depending on the ESU setting. None of these devices are yet available in the United States.

A type of hybrid EMR-ESD technique has been described in which, after circumferential mucosal incision, the targeted epithelial lesion is grasped and retracted toward the lumen and a snare is used to complete the resection. This technique requires a dual-channel endoscope and was the earliest description of ESD. A variety of grasping forceps such as Rat Tooth and Alligator Jaw forceps (PG-42L-1; Olympus America) may be used for retraction. A novel tissue retractor (OTSC Anchor, Ovesco, Tubingen, Germany) is also being marketed in Europe for this purpose. Standard snares (for the hybrid technique) and needle-knives may also be used during ESD.

Ancillary tools for improved visualization and tissue retraction

A transparent distal attachment (cap) applied to the tip of the endoscope is uniformly used in ESD procedures. The cap is particularly useful in maintaining visualization during the dissection phase of the procedure because it serves to keep the resected flap of mucosa off of the endoscope lens, thereby preventing a “red out.” Many caps feature drainage holes that allow egress of water and blood. Caps are disposable and available from many manufacturers and in a variety of diameters that correspond to different endoscope sizes.

Some manufacturers have modified caps to include irrigation ports (eg, KUME hood; Create Medic, Yokohama, Japan), graspers/retractors (eg, EndoLifter, Olympus, Tokyo, Japan), and also integrated cutting wires or snares (eg, KUME cap-knife attachment; Create Medic) to assist in the performance of ESD. However, none of these specialty distal attachments are marketed or sold in the United States at this time.

Although caps do provide some tissue retraction, the effect is suboptimal. As such, several methods and devices have been evaluated for improved tissue retraction during ESD, including weighted (“sinker”) clips that augment gravity retraction, clip(s) with thread external and internal traction methods, external grasping forceps, magnetic anchor retraction systems, spring devices, and dual-endoscope methods. None of these methods have gained widespread adoption, and enhanced tissue retraction remains a targeted area for investigation at this time.

Dyes

Colorants such as indigo carmine, methylene blue, and Lugol’s iodine are useful in several aspects of ESD. In the initial evaluation of mucosal neoplasms, spray chromoendoscopy is used to better characterize the surface of a

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**TABLE 1.** Dedicated endoscopic submucosal dissection devices and their functions, order numbers, and list prices*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Device</th>
<th>Product order no(s.)</th>
<th>Gastroscopy length</th>
<th>Colonoscopy length</th>
<th>Marking</th>
<th>Injection</th>
<th>Precutting</th>
<th>Circumferential incision</th>
<th>Submucosal dissection</th>
<th>Hemostasis</th>
<th>Price, US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olympus</td>
<td>ITKnife (insulated tip knife)</td>
<td>KD-610L</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>709</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITKnife2</td>
<td>KD-611L</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>709</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITKnife nano</td>
<td>KD-612L, KD-612U</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>709</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HookKnife</td>
<td>KD-620LR, KD-620UR</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>709</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FlexKnife</td>
<td>KD-630L</td>
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<td>●</td>
<td>●</td>
<td>●</td>
<td>709</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triangle Tip Electrosurgical Knife</td>
<td>KD-640L</td>
<td>●</td>
<td>●</td>
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<td>●</td>
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</tr>
<tr>
<td></td>
<td>DualKnife</td>
<td>KD-650L, KD-650U</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>709</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Coagrasper</td>
<td>FD-410LR, FD-411UR</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>257-296</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ERBE</td>
<td>HybridKnife T type</td>
<td>20150-060</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>488</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>HybridKnife I type</td>
<td>20150-061</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>488</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Modified from Matsui et al and Draganov et al.

†Olympus America, Inc, Center Valley, Pa.
‡ERBE USA, Marietta, Ga.
lesion and allow clearer demarcation of borders. Dyes are also used to color the injectate used for submucosal lifting in ESD, which may allow better recognition of tissue planes during dissection.

**Injection agents and delivery devices**

Agents for submucosal lifting are first injected around the perimeter of the lesion to provide a margin of safety when incising the mucosa and later are injected beneath the lesion during submucosal dissection for the same reason. Historically, goals for an ideal injection agent included safety, low cost, and provision of a long-lasting submucosal cushion. Various agents have been used for lifting during ESD. Normal saline solution is safe and inexpensive but does not provide a long-lasting cushion. Hypertonic saline solution and dextrose have been noted to cause local tissue damage and thus are not often used.

Use of sodium hyaluronate 0.4% (MucoUp; Johnson and Johnson, Tokyo, Japan) is widely reported in the Asian literature but is expensive. Non-Asian endoscopists have used 0.4% hydroxypropyl methylcellulose, which is relatively inexpensive, for submucosal lifting during EMR and

ESD.\textsuperscript{10,11} Frequently the injectate is colored with a few drops of dye (typically indigo carmine) to help facilitate differentiation of tissue planes. Addition of epinephrine to the injectate has been reported, but its utility has not been clearly established, and adverse events including gastric ischemia and myocardial infarction have been reported.\textsuperscript{12-14} 

Recently, injectates with autodissection properties have been evaluated; the promise of these agents lies in their ability to reduce or eliminate the need for submucosal dissection. Mesna (sodium 2-mercaptoethanesulfonate) is a thiol compound that dissolves disulfide bonds in connective tissue between anatomic planes and has been shown to be useful for chemical dissection in surgical fields.\textsuperscript{15} After showing promise in some animal and pilot human ESD studies,\textsuperscript{16,17} its use was evaluated in a double-blind, randomized, placebo-controlled trial of 101 patients undergoing gastric ESD.\textsuperscript{18} Submucosal dissection time (the primary endpoint) was 18.6 minutes in the mesna group and 24.6 minutes in the placebo group, a difference that did not achieve statistical significance ($P = .13$). However, multivariate regression analysis found use of mesna to be highly correlated with submucosal dissection time. The role of mesna in facilitating ESD requires further evaluation at this time. A proprietary submucosal lifting gel (Cook Medical, Winston-Salem, NC) that is highly viscous and precolored with dye has been evaluated in numerous animal studies and has been shown to have strong submucosal autodissection properties.\textsuperscript{19} Although these agents appear promising, no injectates with autodissection properties are marketed or sold in the United States at this time.

Injectates are typically delivered with a 21- to 25-gauge injection needle catheter. More viscous injectates require a larger bore needle. Some ESD knives have an integrated water jet channel within the device catheter. Of these devices, only the HybridKnife is available in the United States, and it uniquely features an ultrafine 120-μm water jet, powered by a foot pedal–activated, computerized jet lavage unit (ERBEJET 2 system; ERBE USA) that is powerful enough to penetrate the mucosal layer in a needleless fashion for lifting purposes.

**Endoscopes**

A number of considerations may influence the choice of endoscope when performing ESD. Endoscopes with high-definition imaging may allow superior detection and demarcation of mucosal neoplasia compared with endoscopes with standard-definition white-light imaging.\textsuperscript{20} High-magnification endoscopes that feature optical zoom capabilities can magnify images up to 150 times. Although these endoscopes may have a role in improving the diagnosis and characterization of early gastric neoplasia,
Electrosurgical units

Endoscopic submucosal dissection

**TABLE 2. Reported settings for ERBE VIO300D for different stages of ESD**

<table>
<thead>
<tr>
<th>ESD stage</th>
<th>Device</th>
<th>ESU setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marking</td>
<td>Noninsulated tip ESD knife</td>
<td>SOFT COAG, E5, 60-100 W</td>
</tr>
<tr>
<td>Precutting and circumferential incision</td>
<td>Noninsulated tip ESD knife</td>
<td>ENDOCUT I, E2-4, D1-3, II-3</td>
</tr>
<tr>
<td>Submucosal dissection</td>
<td>Any ESD knife&lt;sup&gt;*&lt;/sup&gt;</td>
<td>FORCED COAG, SWIFT COAG, DRY CUT, E2-3, 35-100 W</td>
</tr>
<tr>
<td>Hemostasis</td>
<td>Hemostatic forceps</td>
<td>SOFT COAG, E5, 60-100 W</td>
</tr>
</tbody>
</table>

ESD, endoscopic submucosal dissection; ESU, electrosurgical unit; E, effect; D, cut duration; I, cut interval.

*Devices with a larger cutting surface (and thus decreased current density) may require a power setting at the upper end of the given range.

particularly when coupled with mucosal enhancement technologies (ie, narrow-band imaging),<sup>21</sup> they offer no clear advantage during the performance of ESD. Because bleeding commonly arises during ESD, an auxiliary water channel that may be used in conjunction with a peristaltic flushing pump to produce a water-jet effect is a very useful feature for maintaining visualization and is available with many endoscope models.<sup>22</sup> Although ESD tools may be passed through a 2.8-mm instrument channel, a larger diameter “therapeutic” channel size will allow superior suctioning capabilities, particularly when an instrument is present in the channel. A high-definition therapeutic gastroscope with a single large (3.7 mm) instrument channel (eg, GIF-1TH190; Olympus America) combines the dual advantages of superior optics and suctioning. Endoscopes that feature 2 instrument channels allow dual-instrument use (eg, grasping forceps and an ESD knife), choice of channel with regard to optimal angle of approach for dissection, or an open channel for suctioning if only 1 instrument is being used. To overcome some of the limitations of flexibility inherent with standard endoscopes when approaching anatomically difficult lesions for ESD, a multitubing endoscope has been developed (GIF-2TQ260M; Olympus) but is not marketed or sold in the United States.

ESD devices apply high-frequency electrical current to tissue by using either monopolar or bipolar circuits to achieve a desired effect. An ESU is required to power these devices. Several newer ESUs provide multiple features and functionality that facilitate safe and effective ESD. Newer ESUs contain microprocessors that sense changes in voltage due to increasing tissue impedance during electrosurgery and can responsively keep the voltage constant to attain consistent and safe treatment effects. Newer units also offer a wide array of electrosurgical waveforms that alter duty cycle and maximum peak voltage to produce a range of tissue effects. This flexibility is useful during ESD given the varied needs for marking, mucosal incision, submucosal dissection, and hemostasis as well as different tissue characteristics in different patients (eg, fibrosis associated with a previously treated lesion). Finally, many ESUs are capable of delivering argon plasma coagulation, which may be useful for both marking and hemostasis. ESUs were thoroughly reviewed in a recent ASGE Technology Status Evaluation Report entitled “Electrosurgical Generators.”<sup>23</sup>

Although multiple modern ESUs may be appropriate for safe and effective ESD, specific ESU settings for the various stages of ESD in different anatomic locations in the GI tract while using common ESD devices have been most robustly described for the ERBE VIO300D unit (ERBE USA).<sup>24,25</sup> Some proprietary outputs of the VIO300D that are useful for ESD are briefly discussed in relation to some basic relevant principles of electrosurgery. Specific settings for different phases of ESD are depicted in Table 2; although these settings have been reported, they are not meant to be inclusive of all useful ESD parameters of the ERBE VIO300D unit.<sup>24,25</sup>

**Peak voltage.** The tissue effect of current behaves differently above and below a peak voltage (Vp) of 200 V. Above 200 V, a spark is generated, and an incision effect due to cell bursting can be created even in “coagulation” modes when the current density is high due to a narrow contact area. However, with a Vp of less than 200 V, only dehydration and desiccation of the tissue occurs, without spark generation or cell bursting, thus providing a pure coagulation effect. The SOFT COAG mode of the VIO300D provides continuous current of less than 190 Vp, and this setting is very useful for vessel coagulation with hemostatic forceps (ie, Coagrasper) in the treatment or prevention of bleeding during ESD (Table 2).<sup>24,26</sup>

**Duty cycle.** Duty cycle refers to the percentage of time that the current is actually delivered. Continuously delivered currents with Vp greater than 200 V are effectively pure-cut currents. When the current is delivered in an interrupted manner, the tissue is allowed to cool during these interruptions, producing a greater coagulating effect. As an example, the FORCED COAG mode on the VIO300D has a duty cycle of 8%, whereas the DRY CUT mode has a duty cycle of 30%.<sup>25,26</sup> FORCED COAG, SWIFT COAG, and DRY CUT are commonly used waveforms for the submucosal dissection phase of ESD (Table 2).<sup>24,25</sup>

**ENDOCUT.** ENDOCUT is a proprietary output mode with a 100% duty cycle that alternates a pure cutting current with the SOFT COAG mode. ENDOCUT also supplies a higher power output to assist the successful initiation of a cut, then subsequently modifies the current in response to changing tissue impedance while providing the
specified fractionation (cutting vs coagulation) of the output. Three parameters may be changed by the endoscopist to alter the characteristics of the cut (speed of incision; cut interval; width of incision; cut duration; and hemostatic effect: effect). ENDOCUT is frequently used for the precutting and circumferential incision phases of ESD (Table 2).

Gas insufflation

Although standard air insufflation has been safely used for ESD procedures, luminal insufflation by using CO₂ may hold some advantages. CO₂ is absorbed across the intestines 160 times more rapidly than nitrogen and 13 times more rapidly than oxygen, which are the principal gas components of air. As such, luminal distention with CO₂ insufflation is less prolonged than with air and has been associated with less patient discomfort after longer endoscopic procedures including colonoscopy and fewer postprocedure admissions in a series of patients undergoing resection of large colonic lesions. The safety of CO₂ insufflation during prolonged ESD procedures under moderate and deep sedation is well-established. Further, the rapid reabsorption of CO₂ may theoretically reduce the likelihood of tension pneumoperitoneum developing in the event of a perforation. CO₂ was associated with a reduced rate of radiographically detected pneumomediastinum compared with air insufflation after esophageal ESD in a case-control study. Multiple CO₂ regulators are available in the United States for use in endoscopic procedures.

EFFICACY AND COMPARISON WITH AVAILABLE TECHNOLOGIES

Stomach

In large Asian series of patients with early gastric adenocarcinoma undergoing ESD, the rate of en bloc resection ranged from 86% to 97% and the rate of R0 (negative lateral and vertical margins) resection ranged from 88% to 93%. The rate of local recurrence generally approximates 1%, whereas 5-year overall survival ranges from 96% to 100% and 5-year disease-specific survival ranges from 99% to 100%. Both immediate technical outcomes (eg, R0 resection) and the local recurrence rate are superior for lesions meeting Japanese Gastric Cancer Association criteria (differentiated mucosal cancer, <2 cm, without ulceration) than the expanded National Cancer Center criteria, but there have been no differences in mortality.

Two meta-analyses evaluated ESD versus EMR for the treatment of early gastric cancer. In these analyses, ESD was associated with higher rates of en bloc resection (92% vs 52%) and R0 resection (82%-92% vs 42%-43%) than EMR, as well as a lower rate of local recurrence (0.8% vs 5.0%-6.4%) than EMR. All-cause mortality at mean follow-up durations of 36 to 43 months did not differ between patients treated with ESD versus EMR for early gastric cancer.

There are no data directly comparing modern surgical resections and ESD for early gastric cancer. It was actually a retrospective review of 5265 Japanese patients who had undergone gastrectomy and lymph node dissection that was instrumental in determining the tumor features that were associated with no nodal metastasis and thus appropriate for local (ie, endoscopic) treatment. A Japanese multicenter evaluation of laparoscopic gastrectomy (primarily distal gastrectomy) for early gastric cancer reported 5-year disease-free survival rates of 99.8% for stage T1a disease and 98.7% for stage T1b disease.

Colon and rectum

ESD in the colon has generally been used for laterally spreading tumors larger than 2 cm in diameter. In a systematic review of 22 colorectal ESD studies with more than 2800 patients, the most common lesion site was the rectum (44%) and the median of the mean tumor size was 32 mm. The histologic classification of resected lesions predominantly included adenoma (median rate 43%), intramucosal adenocarcinoma (44%), and submucosal adenocarcinoma (11%). In this review, the summary estimate for an R0 resection rate was 88%. The 2010 guidelines from the Japanese Society for Cancer of the Colon and Rectum define R0 resections as curative when none of the following are present: depth of submucosal invasion greater than 1000 μm, lymphovascular invasion, poor differentiation, or higher grade (2 or 3) tumor budding at the site of deepest invasion. However, a meta-analysis reported that the incidence of lymphatic metastasis is 1.9% even when these criteria are satisfied and also highlighted the limited quality and quantity of the source data.

In 4 large retrospective series that compared conventional endoscopic resection (including lift polypectomy and cap-based EMR [cEMR]) with ESD for colorectal neoplasms larger than 2 cm, the lesions in the ESD group were generally larger (29-37 mm vs 22-28 mm) and ESD was associated with a higher rate of en bloc resection (84%-95% vs 33%-57%). Data regarding the curative resection rate for ESD versus conventional polypectomy/EMR are mixed, with important caveats being that larger lesions were being resected in the ESD groups in these studies and that lateral margins cannot be accurately assessed with piecemeal polypectomy/EMR. Over mean follow-up durations ranging from 17 to 26 months, the local recurrence rate for conventional polypectomy/EMR ranged from 12% to 26% compared with 0% to 2% for ESD.

With regard to nonepithelial colorectal neoplasia, ESD has been evaluated for the endoscopic treatment of rectal carcinoid tumors. Although ESD is effective in this setting,
data are mixed as to whether it provides any benefit over faster procedures such as cEMR or cap-and-band ligation. EMR, particularly as the mean lesion diameter in many series is less than 10 mm.51-53

The data comparing ESD with surgical treatments for colorectal neoplasia are also retrospective and limited. A single-center South Korean retrospective series compared 63 patients who underwent either ESD or transanal endoscopic microsurgery (TEM) for Tis or T1 rectal cancers.54 Patients treated with ESD (n = 30) and TEM (n = 33) had similar rates of R0 resections (97%) and curative resections (77% and 79%, respectively). ESD was associated with a shorter procedure duration and hospital stay than TEM. Of patients who had a curative resection, there were no cases of local recurrence or distant metastasis in either group in approximately 2 years of follow-up. A meta-analysis combined data from 21 single-arm case series (11 ESD and 10 TEM) evaluating outcomes in the treatment of rectal neoplasms larger than 2 cm.55 In this analysis, TEM was associated with higher rates of en bloc resection (99% vs 88%, P < .001) and R0 resection (89% vs 75%, P < .001) than ESD. However, a greater proportion of lesions in the ESD group were cancers compared with the TEM group, which comprised mostly adenomas. Last, there was a trend toward fewer local recurrences in the ESD group than in the TEM group (2.6% vs 5.2%, P = .07), but this likely reflects the standard practice of referral for further oncologic surgery after noncurative ESD.

A large retrospective series from the National Cancer Center in Tokyo compared outcomes in 589 patients with T1 colorectal cancers who underwent either ESD (n = 297) for endoscopically predicted mucosal or superficial submucosal neoplasms or laparoscopy-assisted colorectal surgery including lymphadenectomy ([LAC], n = 292) for predicted deep submucosal cancers.56 Importantly, this study included a large number of patients with colonic (nonrectal) lesions, including 185 who underwent ESD and 243 who underwent LAC, although unfortunately most outcomes data are reported for all colorectal patients and not separately for the colon-only subgroups. In this study, ESD was associated with a shorter procedure time and hospital stay than LAC. The en bloc and curative resection rates with ESD were 87% and 80%, respectively, with surgical referral for patients with noncurative ESD resections. The 3-year overall survival rate exceeded 99% in both the ESD and LAC groups.

Esophagus

Early adenocarcinoma of the gastroesophageal junction represented a logical extension of gastric ESD techniques in a more technically challenging anatomic site. In 4 series that retrospectively evaluated ESD for non-Barrett’s gastroesophageal junction adenocarcinoma, the rate of en bloc resection was 100%, with curative resection rates (defined similarly to criteria for colonic lesions [see previously], except >500 μm of submucosal invasion deemed noncurative) of 68% to 79%.57-60 Patients with noncurative resections were typically managed with esophagectomy and LAC, and patients with curative ESD resections had no local recurrences or metastatic cancer detected in mean follow-up durations of 15 to 30 months in 2 of the series.57,58 The other 2 series had longer follow-up available, and both reported a 5-year disease-specific survival rate of 100% for those with curative resections.59,60

A German study prospectively enrolled 30 patients with Barrett’s esophagus featuring either intramuscular cancer or high-grade dysplasia for treatment with ESD.61 Although a 90% en bloc resection rate was attained, an R0 resection was achieved in only 38% of patients. The authors specified that any degree of mucosal dysplasia at a lateral margin precluded R0 classification, and this was the predominant reason for the low R0 resection rate. However, over a median follow-up duration of 17 months that included surveillance endoscopies with biopsies, 96% of patients were found to be free of any neoplasia, suggesting that the rim of coagulation necrosis resulting from ESD may have eradicated marginal dysplasia in many of these patients.

Several studies evaluating esophageal ESD for early squamous cell carcinoma (SCC) have included a comparator EMR arm. A retrospective cohort study of 300 patients undergoing ESD or EMR for early SCC excluded all patients found to have histologic evidence of submucosal invasion.62 In this study, the rate of en bloc resection for ESD was 100% (mean lesion size 30 mm) compared with 53% for EMR (mean lesion size 20 mm), and the rate of local recurrence was 1% in the ESD group and 10% in the EMR group. However, there was no difference in survival in more than 4 years follow-up. Similarly, a retrospective series of 70 patients with SCCs 2 cm or larger treated with cEMR or ESD reported local recurrence rates of 0 of 34 (0%) for lesions resected en bloc, 4 of 27 (15%) for piecemeal resections with 2 to 4 pieces, and 8 of 17 (47%) for resections with 5 or more pieces.63 However, in a retrospective study with 171 SCCs 2 cm or smaller stratified by size, for lesions smaller than 15 mm in diameter treated with cEMR or ESD, there were equivalent rates of en bloc resection (100%) and no local recurrences, with a significantly shorter mean procedure time in the cEMR group (21 minutes vs 64 minutes, P < .01).64

T1a SCC that involves the muscularis mucosa poses a substantial risk (~9%) for lymph node metastasis that appears to be greater than esophageal adenocarcinoma of the same depth.62,65,66 In a large single-operator series, patients undergoing ESD resection of T1a SCCs not involving the muscularis mucosa (confined to the epithelium and lamina propria) had a 5-year overall survival rate of 82%.67 There are no data directly comparing ESD with surgical resection for early esophageal cancer. In a large German registry, the 5-year survival rate for patients with surgically resected T1a cancer was 78%, with notable differences between adenocarcinoma (91%) and SCC (62%).68

Endoscopic submucosal dissection
Duodenum

The use of ESD in the duodenum for sessile adenomas, early carcinomas, and carcinoid tumors has been described, but available data comprise only case reports and small case series.69-71

SAFETY

Bleeding

Intraprocedural bleeding is a common and expected event during ESD. Typically, minor oozing from small vessels can be treated with coagulation current delivered through the ESD knife, whereas more significant active bleeding is treated with hemostatic forceps. Efforts are also made to identify larger nonbleeding submucosal vessels during the dissection for prophylactic coagulation with hemostatic forceps.26 Although rare, severe intraprocedural bleeding that cannot be managed endoscopically has been described. In a large South Korean series of 1244 patients with early gastric cancer, 6 severe bleeding events occurred that required urgent surgery (wedge resection or laparoscopic gastrectomy).35

Delayed bleeding after ESD is more common in gastric ESD than colorectal or esophageal sites. Although a meta-analysis of gastric ESD studies reported a 4.5% delayed bleeding rate, many individual studies from experienced centers have described higher rates, as high as 15.6%.34 Lesion size larger than 40 mm and resumption of oral antithrombotic therapy have been identified as risk factors for delayed bleeding after gastric ESD.72 Antisecretory therapy is routinely used to promote healing of ESD-related ulcers, and a meta-analysis of 6 studies reported a reduced incidence of delayed bleeding after gastric ESD in patients treated with a proton pump inhibitor compared with an H2 receptor antagonist (5.4% vs 10.5%; odds ratio 0.41; 95% confidence interval, 0.20–0.85).73 Further, several randomized, controlled trials have demonstrated that the combination of a mucosal protective agent and a proton pump inhibitor results in faster healing of gastric ESD ulcers than a proton pump inhibitor alone, although an impact on delayed bleeding has not been shown.74-76 In 1 series, 76% of delayed bleeds occurred within 24 hours of ESD, whereas the remaining 24% occurred 2 to 15 days after the procedure.77 Given this, the practice of performing a next-day “second look” endoscopy is common, but has not been clearly shown to improve outcomes including delayed bleeding.78 Delayed bleeding after non-gastric ESD is less common and has been reported in 0% to 5.2% of patients in series of esophageal ESD79 and 2% of patients in a meta-analysis of colorectal ESD.44

Perforation

The rate of perforation in meta-analyses of gastric ESD is approximately 4.5%,40,41 and in a meta-analysis of colorectal ESD, it was 4.8%.44 In a review of esophageal ESD adverse events, perforation rates of 0% to 10% are reported; a review of the data in these series suggests a pooled perforation rate of 19 of 816 (2.3%).79 Fortunately, almost all perforations are recognized intraprocedurally and are amenable to clip closure. A report on 117 consecutive EMR/ESD gastric perforations between 1994 and 2004 at a large Japanese cancer center described successful clip closure and nonoperative management in 115 of 117 patients (98%), with the remaining 2 patients needing urgent surgery.80 Primary clip closure was used for defects 1 cm and smaller, and an “omentum patch” method was used for larger defects, whereby the greater or lesser omentum is suctioned into the defect, and multiple clips are used to secure the omentum to the gastric wall circumferentially around the perforation. Patients in this series were initially managed with nasogastric suction for 3 days, total parenteral nutrition for 9 days, and a second-generation cephalosporin; a water-soluble contrast study was used to guide the timing of return to oral intake. Later in the authors’ experience, these timelines were shortened with no compromise in outcomes. Use of other devices for successful closure of ESD-associated perforations including over-the-scope clip(s) has also been reported.81

High rates of successful clip closure and conservative management of colorectal ESD perforations have also been reported. In a large series of 816 ESD resections of colorectal lesions, 16 perforations occurred (2%), 14 of which were managed nonoperatively and 2 (0.2%) which required urgent surgery.47 Although the majority of esophageal perforations can also be managed with endoscopic closure and conservative measures, in some patients life-threatening mediastinitis can develop, requiring urgent surgery.62,79,82 In a small subset of patients, mediastinal emphysema will develop in the absence of a recognized perforation, and conservative management also appears to benefit these patients.62

A small subset of patients with perforations present in a delayed manner and have a less favorable clinical course. A Japanese group reported 6 delayed perforations in 1159 patients (0.5%) after ESD for early gastric cancer.83 All presented 10 to 24 hours after the procedure with clinical signs and symptoms of peritonitis, and 5 of 6 required emergency surgery.

Stricture

Post-ESD esophageal stricture is generally defined as a narrowing through which a standard gastroscope cannot be advanced. Strictures develop in 12% to 17% of patients after esophageal ESD, with risk factors including the circumference and length of the resection.62,84-86 ESD resections encompassing more than 75% of the circumference of the esophagus are at highest risk of stricture development.62 Due to the relatively high frequency of this adverse event, a number of strategies aimed at preventing and/or treating post-ESD esophageal stricture have been used, including prophylactic serial dilation,
intralesional steroid injection or topical steroid gel application, radial electroincision, and prophylactic placement of fully covered self-expandable metal stents. Endoscopic transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets and resected gastric mucosa have also been reported for prophylaxis of post-ESD esophageal stricture, but remain experimental. Stricture development after gastric ESD is uncommon and anatomically limited to sites of relative luminal narrowing. In a review of 2011 gastric ESDs at a single Japanese center, strictures occurred in just 15 patients (0.7%) overall, exclusively in resections involving the cardia (7/41, 17%) or prepyloric antrum (8/115, 7%). Stricture development after colorectal ESD has not been reported.

**EASE OF USE**

**Need for specialized training**

ESD is a technically demanding procedure that requires substantial training to achieve competence; inadequate training compromises both patient safety and technical outcomes. Two series reported on the outcomes of participants attending 2- to 3-day ESD courses that featured hands-on stations in which live pigs were used. In both series, participant demographics indicated a mean of more than 10 years of clinical endoscopic experience, with some participants having limited previous experience with ESD. However, perforation rates of 22% to 63% were observed during gastric and esophageal ESD even with these experienced endoscopists, suggesting that ESD poses significant risk when undertaken by an operator inadequately trained in ESD.

**Training models**

In Japan, the training model is relatively established: after obtaining initial didactic training in ESD, learners observe experts for a variable number of procedures, then assist in a variable number of procedures before finally undertaking ESD on less technically challenging lesions (generally in the distal stomach) under expert supervision. In a survey of Japanese experts, observation of 10-20 procedures and acting as an assistant in 5 procedures were the most common responses for the minimum experience needed before beginning ESD. However, this model is difficult to establish in Western countries, where both early gastric cancer and ESD experts are rare. As a result, the best training paradigm for Western learners is likely to differ. Although animal models are suggested but optional for learners in Japan, they are essentially mandatory for Western learners and represent the next step after initial didactic learning.

Ex vivo and in vivo porcine models for gastric ESD are well studied and closely resemble human anatomy. In contrast, the porcine colon is difficult to cleanse and is thinner walled and more mobile than the human colon; as such, the utility of the porcine colon model for ESD training is unclear. It has been suggested that 10 resections in an ex vivo porcine gastric model represent an adequate experience to justify a transition to a live pig model, which provides a more realistic experience including the presence of peristalsis, intraluminal secretions, and bleeding.

In a study of 2 novice learners who each performed gastric ESD on 60 lesions each in an ex vivo porcine model, the total resection time, en bloc resection rate, and perforation rate all improved for both endoscopists when the last 30 resections were compared with the first 30 resections. The authors calculated that the cost to train an endoscopist with 30 ex vivo gastric porcine procedures (assuming 6 lesions per stomach) would be US$8410, given the cost of the simulator used, the gastric specimens, and the disposable devices used. In comparison, the authors calculated that the cost to train an endoscopist with 30 in vivo gastric porcine procedures (also assuming 6 lesions per stomach) would be about US$16,000.

Although observerships can be logistically challenging, some Western endoscopists have undertaken observerships in high-volume ESD centers in Asia, typically for 2 to 5 weeks. One American endoscopist had performed 29 resections in an ex vivo gastric porcine model before observing 43 ESDs over 5 weeks at an expert center in Japan. The endoscopist’s next 9 resections in the gastric porcine model took 32.7 ± 15.0 minutes to complete, which was significantly shorter than the mean duration of his last 9 resections before the observership (61.0 ± 7.4 minutes, P = .001). As with other technically demanding procedures, once the skill set for ESD is learned, it must be maintained over time by performing an ample volume of cases and/or attending courses.

Lesion selection is important to maximize the chance of a successful outcome in human patients early in the endoscopist’s ESD experience. Gastric antral lesions are easily accessible, have a favorable wall thickness, and allow a stable endoscope position both forward-viewing and in retroflexion; for these reasons, smaller antral lesions are optimal for ESD learners. In 2 studies that each evaluated the outcomes of the first 20 to 30 gastric ESDs performed by Japanese trainees, risk factors for nonself-completion included size larger than 3 cm and location other than the antrum. Similarly, experts suggest that rectal ESD is anatomically favorable compared with colonic ESD and that smaller rectal lesions may be a reasonable early target for Western endoscopists. Indeed, in some series of colorectal ESD performed by novice/trainee endoscopists, all perforations occurred in colonic (nonrectal) cases.

**Learning curves**

There is no single “learning curve” for ESD, but rather multiple learning curves that vary based on lesion characteristics (eg, anatomic site, size) and outcome of interest (eg, total procedure time, R0 resection rate, adverse event
rate). Further, learners with abundant experience assisting in human procedures and/or performing resections in animal models will enter at a higher point on most learning curves and thus experience measurable improvements at a less rapid pace than more novice operators. Finally, as endoscopists become more comfortable with ESD, they tend to accept more challenging cases with regard to lesion size and location, and this may distort the upper end of a learning curve. With these caveats stated, many studies reflect a breakpoint that occurs between 20 and 50 human procedures, during which significant improvements across multiple outcomes can be demonstrated, irrespective of anatomic site. In centers with ESD expertise, this level of experience may also correspond to graduating to performing unsupervised ESD. However, most ESD training studies incorporate fewer than 50 procedures per endoscopist, and outcomes at the conclusion of these studies for the most critical endpoints (ie, R0 resection) still fall short of results achieved by providers at expert Japanese centers, indicating that further improvement in operator skill occurs far out on the learning curve.

Logistical issues

**Procedure duration.** Although high-volume Asian centers have reported mean procedure times for gastric ESD as short as 25 minutes, it should be recognized that ESD is a lengthy procedure for nonexperts. In a French multicenter survey, 188 ESD procedures (primarily gastric and rectal) from 16 centers were self-reported; the median procedure duration was 105 minutes. In 2 European series of 60 and 76 colorectal ESDs procedures performed early in these studies averaged more than 3 hours in duration, whereas median procedure durations near the end of the studies varied from 70 to 136 minutes. Finally, a relatively experienced German group reported a median procedure duration of 74 minutes for 29 gastric ESDs. As such, adequate time and resources must be allotted before undertaking an ESD.

**Sedation.** Safe sedation for patients undergoing upper GI ESD has been described by using a range of levels including moderate sedation (eg, by using midazolam), deep sedation (eg, by using propofol or dexmedetomidine), or general anesthesia. Retrospective data on gastric ESD in South Korea demonstrated higher en bloc resection rates and shorter procedure durations in patients cared for by an anesthesiologist. Given the duration of the procedure, need for fine-motor maneuvers, and potential for reflux and aspiration of secretions or blood, strong consideration should be given to using general anesthesia for upper GI lesions, particularly for endoscopists who have limited experience in performing ESD. In contrast, moderate or deep sedation is generally sufficient for colorectal ESD; conscious sedation may facilitate changes in patient position that beneficially use gravity for countertraction on the lesion.

**FINANCIAL CONSIDERATIONS**

**Reimbursement**

Despite clinical benefits for patients, ESD remains time-consuming and is not adequately reimbursed at the present time. There is no unique Current Procedural Terminology (CPT) code for ESD. In 2014, new codes for esophagoscopy with EMR (43211) and EGD with EMR (43254) were introduced, and in 2015, there will be counterpart codes for colonoscopy. However, the several modalities that are bundled in the EMR code (submucosal injection, snare resection, biopsy if performed, control of bleeding if performed) are not the key aspects of ESD, and CPT instructs that codes that are only approximate are not appropriate to report. The best 2 choices at present would be to report a snare polypectomy service (eg, 43251 during EGD or 45385 during colonoscopy) and to report an unlisted code to describe the remainder of the work or just to report an unlisted procedure code (43499 for gastric, 45999 rectum, 44799 small intestine, 45399 new code for unlisted procedure, colon) with supporting documentation to seek appropriate reimbursement. In this case, a cover letter submitted with the claim that explains the nature of the procedure, equipment required (equipment invoice copies are helpful), estimated practice cost, and a comparison of physician work (time, intensity, risk) with other endoscopic services for which the payer has an established value should be included to the payer. A center performing this procedure frequently might find it worthwhile to arrange a personal discussion between an endoscopist and the medical director of larger payers to facilitate coverage and appropriate pricing. The dedicated ESD devices do add to the facility cost of the procedure largely without added reimbursement.

**Device and equipment costs**

List prices for dedicated ESD devices are shown in Table 1. The cost of a transparent distal attachment (cap) is approximately $30. The cost for several ESUs appropriate for use during ESD is available in the ASGE Technology Status Evaluation report entitled “Electrosurgical Generators.” The list price for the ERBEJET 2 system is US$45,500.

**AREAS FOR FUTURE RESEARCH**

A key deficit that future studies should address is the lack of high-quality, randomized, controlled trial–level data comparing ESD with competing procedures such as EMR, TEM, and laparoscopic surgical resections. Studies should also address device-specific outcomes data. Although they are emerging, additional outcomes data from Western endoscopists would be useful. Human data on newer autodissecting injectates are needed. If an agent could be developed that markedly reduces the need for
submucosal dissection, this would have the potential to significantly modify both the technical difficulty and the risk of ESD. Early pilot studies are ongoing to develop techniques that reduce the risks of postoperative adverse events after ESD (eg, delayed bleeding, perforation) including endoscopic sutting of ESD defects and the use of polyglycolic acid sheets and fibrin glue to “shield” defects. ESD techniques have been applied to the endoscopic resection of neoplasia arising in the submucosa and muscularis propria, including full-thickness resections. In some series, these deeper resections have been facilitated by the variant technique of endoscopic submucosal tunnel dissection. These techniques remain in development and require further study.

SUMMARY

ESD is an established effective treatment modality for premalignant and early-stage malignant lesions of the stomach, esophagus, and colorectum. Compared with EMR, ESD is generally associated with higher rates of en bloc, R0, and curative resections and a lower rate of local recurrence. Oncologic outcomes with ESD compare favorably with competing surgical interventions, and ESD also serves as an excellent T-staging tool to identify noncurative resections that will require further treatment. ESD is technically demanding and has a higher rate of adverse events than most endoscopic procedures including EMR. As such, sufficient training is critical to ensure safe conduct and high-quality resections. A standardized training model for Western endoscopists has not been clearly established, but will be self-directed and include courses, animal model training, and optimally an observership at an expert center. Numerous dedicated ESD devices are now available in the United States from different manufacturers. Although the use of ESD in the United States is increasing, issues related to technical difficulty, limited training opportunities and mentors, risk of adverse events, long procedure duration, and suboptimal reimbursement may limit ESD adoption in the United States to a modest number of academic referral centers for the foreseeable future.

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Abbreviations: cEMR, cap-based EMR; ESD, endoscopic submucosal dissection; ESU, electrocautery unit; LAG, laparoscopic gastrectomy; SCC, squamous cell carcinoma; TEM, transanal endoscopic microsurgery; Vp, peak voltage.

REFERENCES

Endoscopic submucosal dissection


