

Endoscopic mucosal resection and 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 methods are used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications 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. For this review the MEDLINE database was searched through September 2007 by using the key words “endoscopic lesion removal,” “endoscopic mucosal resection,” “EMR,” “endoscopic submucosal dissection,” and “ESD.”

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BACKGROUND

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) were developed for minimally

invasive, organ-sparing endoscopic removal of benign and early malignant lesions in the GI tract. For removal of larger lesions, ESD is usually required. This report focuses on instruments, injection solutions, and techniques currently used during EMR and ESD.

TECHNOLOGY UNDER REVIEW

EMR

EMR is an endoscopic technique developed for removal of sessile or flat neoplasms confined to the superficial layers (mucosa and submucosa) of the GI tract. EMR is typically used for removal of lesions smaller than 2 cm or piecemeal removal of larger lesions. Most commonly used techniques can be subdivided as injection-, cap-, and ligation-assisted EMR. Before the start of any EMR technique, it may be helpful to mark the margins of a targeted lesion with superficial cautery marks.

Injection-assisted EMR, also often called “saline-assisted” polypectomy, is frequently used for large flat colon polyps. This technique was introduced in 1955 for rigid sigmoidoscopy¹ and then in 1973 for flexible colonoscopy.² The procedure starts with injection of a solution into the submucosal space under the lesion, creating a “safety cushion.” The cushion lifts the lesion to facilitate its removal and minimizes mechanical or electrocautery damage to the deep layers of the GI tract wall. Injection-assisted EMR can be further subdivided into the “inject-and-cut” technique (using an electrocautery snare through a single-channel endoscope) or the “inject-lift-and-cut” technique (using a grasping forceps to lift the lesion and an electrocautery snare through 2 separate channels of a double-channel endoscope).³ As a variation of the latter technique, EMR of large gastric lesions may be assisted by countertraction of the lesion with a grasping forceps placed through a percutaneous endoscopic gastrostomy tract.⁴ To facilitate the basic processes of injection and snare excision with 1 instrument, a device combining these 2 functions has recently been developed (Table 1).

Cap-assisted EMR also uses submucosal injection to lift the target lesion. Dedicated mucosectomy devices that use a cap affixed to the tip of the endoscope have been developed (Table 1).⁵ These single-use devices come equipped with a specially designed crescent-shaped electrocautery snare that must be opened and positioned on the internal circumferential ridge at the tip of the cap.

TABLE 1. Commercially available devices for EMR

Needle/snare device	Gauge/snare size	Manufacturer	Cost (\$US)	Minimum working channel required (mm)
iSnare (combination injection needle and snare)	25-gauge needle 2.5 × 4 cm snare	US Endoscopy, Mentor, Ohio	125	3.2
Tissue collection devices				
	Net size			
Roth Net	3 × 6 cm	US Endoscopy, Mentor, Ohio	75	2.8
Polyp-Pak, combination rotatable snare and retrieval net	3 × 6 cm 25 mm snare	US Endoscopy, Mentor, Ohio	85	2.8
Standard Nakao Spider-Net	3 × 6 cm	ConMed Endoscopic Technologies, Billerica, Mass	75	2.8
Mucosectomy devices				
	Endoscope tip diameter (mm)			
EMR Kits (includes cap, needle, and 25-mm crescent snare)	9.3-10	Olympus America Inc, Center Valley, Pa	191	2.0
Hard straight 13.9 mm cap	10-11			
Hard straight 14.9 mm cap	9.3-10			
Hard wide oblique 16.1 mm cap	10-11			
Hard wide oblique 16.1 mm cap	8.6-9.2			
Hard straight 12.9 mm cap	8.6-9.2			
Hard wide oblique 16.1 mm cap	8.6-9			
Soft oblique 18 mm cap	9.1-9.8 mm			
Soft oblique 18 mm cap	9.8-10.4			
Soft oblique 18 mm cap	10.3-11.3			
Soft oblique 18 mm cap	11.2-11.8			
Soft oblique 18 mm cap				
Duette Multi-Band Mucosectomy device		Cook Medical Inc, Winston-Salem, NC	271	
DT-6	9.5-13			3.7
DT-6-5F	9.5-13			2.8
DT-6-XL	11-14			3.7

The endoscope is then positioned immediately over the target lesion, suction is used to retract the mucosa into the cap, and the snare is closed to capture the lesion. The lesion is then resected with a standard snare excision technique. The available cap-assisted mucosectomy devices differ primarily in the characteristics of the cap. Caps are composed of clear plastic that may be soft or hard. The caps are cylindrical and available with flat circular (straight) or oblique-shaped tips both with outer diameters ranging from 12.9 to 18 mm. The oblique caps are usually used for resection of esophageal lesions (to compensate for the parallel position of the endoscope relative to the esophageal wall), whereas the straight caps are most commonly used in the stomach and colon. The

size of the lesion will determine the optimal size of the cap. The largest caps (18 mm) are made from a soft material to allow passage through the narrow portions of the GI tract (esophagus, pharyngoesophageal, and esophago-gastric junctions).

In ligation-assisted EMR, a standard variceal band ligation device is positioned over the target lesion with or without prior submucosal injection. Suction is applied to retract the lesion into the banding device, and a band is deployed to capture the lesion. The band has enough contractile force to squeeze the mucosal and submucosal layers, but it is not strong enough to capture the muscularis propria layer. The banding device is then removed and a standard electrocautery snare is used to resect the lesion above or

below the band.^{6,7} A recently introduced single-use banding device for mucosectomy (Table 1) uses a specially designed 6-band ligator similar in design to variceal ligation devices. This ligator's handle has a larger diameter at the connection with the accessory channel of the endoscope permitting insertion of a snare device without removal of the banding apparatus. It comes equipped with a 1.5 by 2.5 cm hexagonal braided electrocautery snare available with a 5F or 7F insertion sheath. Two sizes of ligating caps are available to fit endoscopes with outer diameters of 9.5 to 13 mm and 11 to 14 mm.

ESD

ESD has been developed for en bloc removal of large (usually more than 2 cm), flat GI tract lesions.⁸⁻¹¹ The procedure is usually done in several steps. First, the margins of the lesion are marked by electrocautery, and submucosal injection is used to lift the lesion. Then, a circumferential incision into the submucosa is performed around the lesion with specialized endoscopic electrocautery knives (Table 2). Finally, the lesion is dissected from underlying deep layers of GI tract wall with the electrocautery knife and removed. After removal, the en bloc pathologic specimen should be mounted and oriented to facilitate histologic examination. Multiple cutting devices and accessories have been developed specifically for ESD. These devices are not yet commercially available in the United States.

Submucosal injection solutions

For the submucosal injection used in all these techniques, the volume of injected fluid varies from 5 to 50 mL depending on the size of the lesion. Repeated injections can be required if the cushion dissipates before complete removal of the lesion. The addition of staining dye (ie, 0.004% indigo carmine or methylene blue) to the injection solution is frequently used to assist in identifying the deep margin during the resection process.¹²

Various solutions are currently used for submucosal injection (Table 3). The ideal agent should be inexpensive, readily available, nontoxic, and easy to inject and provide a long-lasting submucosal cushion.^{13,14} Normal saline solution is widely available and often used for injection-assisted EMR. However, even with the addition of epinephrine, a cushion made with normal saline solution often dissipates within minutes. Multiple studies have demonstrated long-lasting effects of cushions made with hyaluronic acid, hydroxypropyl methylcellulose (a semisynthetic viscous ophthalmic solution used for artificial tears), glycerol, and a fibrinogen solution.¹⁵⁻¹⁹ Hyaluronic acid is expensive and not readily available in most endoscopy units.^{15,20,21} Hyaluronic acid and hydroxypropyl methylcellulose are very viscous and must be diluted to facilitate injection. In addition, tissue damage and local inflammatory reactions have been reported at the injection sites of hydroxypropyl methylcellulose, hypertonic sodium chloride (3.75%), and hypertonic dextrose ($\geq 20\%$).^{20,22} Several studies report

encouraging results when autologous blood is used for submucosal injection.^{13,22} The cushion created with autologous blood does not appear to interfere with visualization during EMR and lasts up to 7 times longer than a 0.9% saline solution cushion.¹³

Retrieval of resected tissue

Several options are available for collection of resected tissue. After the cap-assisted EMR, the resected pieces can be collected into the cap and retrieved from the patient. The tissue resected during EMR or ESD can also be collected by specially designed retrieval devices (Table 1): Roth Net (US Endoscopy, Mentor, Ohio), Spider-Net (ConMed Endoscopic Technologies, Billerica, Mass), and a combination of polypectomy snare and a retrieval net (Polyp-Pak, US Endoscopy).

CLINICAL APPLICATIONS

EMR and ESD may be used for definitive therapy of premalignant and early stage (T1mN0) malignant lesions of the digestive tract. EUS is often used for locoregional staging before endoscopic resection to ensure that there is no tumor involvement of deeper wall layers or lymph nodes.²³⁻²⁶ EMR and ESD also can be used to obtain larger histologic specimens (compared with standard endoscopic tissue sampling techniques) and can provide an accurate histologic T stage for these superficial malignancies.²⁷ These techniques also can be used to sample or resect layers deep to the mucosa and hence obtain a histologic diagnosis of subepithelial lesions in the GI tract located in the muscularis mucosa or superficial submucosa.^{3,28,29} EMR and ESD should not be attempted for lesions that do not "rise" during the submucosal injection because nonlifting of the tumor after submucosal injection is a predictor of deep invasion and that the lesion is not amenable to endoscopic removal.³⁰⁻³²

The role of ESD for colon lesions is less established. Multiple factors make colon ESD more difficult compared with gastric ESD, including difficulties in maintaining the endoscope position, the thin colon wall with multiple folds, luminal angulations, and peristalsis.³³ In addition, colon perforation with fecal spillage is generally more morbid than gastric perforation.³³

EASE OF USE

EMR can be considered a variation of standard polypectomy with specialized devices, whereas ESD typically is performed by endoscopists with experience in advanced procedures and familiarity with mucosal dissection techniques. Both EMR and ESD are technically difficult and time-consuming procedures.³⁴⁻³⁶ For large gastric lesions, the reported time to complete EMR is 25.8 ± 25.9 minutes, whereas ESD lesion removal averages 84.0 ± 54.6 minutes.³⁷ For colon lesions the average time required

TABLE 2. Specialized endoscopic equipment used during ESD

Type	Manufacturer	Description	Advantages	Disadvantages	Marketed in United States
Needle-knives	Olympus, Boston Scientific, Cook Medical	Fine tip with regulated length	Small contact area with high cutting power	Perforation can be easily caused by the needle knife's tip	Yes
Insulated tip (IT) knife	KD-610L, KD-611L, Olympus	Ceramic ball on top of needle knife	Insulated tip prevents perforation		No
Hook knife	KD-620LR, Olympus	Right angle bend of the tip of needle knife	Rotatable tip can pull dissected tissue		No
Flex knife	KD-630L, Olympus	Soft cutting tip	Flexible tip to prevent perforations		No
Triangle tip knife	KD-640L, Olympus	Triangle tip at the distal end	Can be used for any step of procedure		No
Flush knife	DK2618JN 10-30, Fujinon	Water jet from the tip of short needle-knife	Allows instant washout of blood for clear view		No
Transparent hood	DH-15CR, DH-16CR Fujinon	Attached to tip of endoscope	Improve visualization by pushing tissues away from endoscope	Need to front load before procedure	No

to complete ESD is reported as high as 70.5 ± 45.9 minutes, largely because of the difficulties mentioned above.³³ The positioning of the snare in the cap-assisted mucosectomy device before tissue capture may be challenging and a relatively unfamiliar maneuver for endoscopists and assistants. Ligation-assisted EMR does not require special repositioning of the snare, and the concept of tissue capture is an extension of commonly used variceal band ligation.

EFFICACY

Esophagus. EMR and ESD are indicated for early (T1mN0) moderately and well-differentiated squamous cell esophageal cancer.³⁸ Endoscopic therapy for superficial esophageal squamous neoplasms has a low complication rate and a disease-specific 5-year survival rate of 95%.³⁹⁻⁴¹ EMR and ESD are also gaining popularity for high-grade dysplasia arising from Barrett's esophagus and superficial esophageal adenocarcinoma.⁴² In observational studies Barrett's epithelium is reported to be completely replaced in 76.6% and resection for high-grade dysplasia or early invasive cancer (T1N0) resulted in remission-free survival with a median follow-up of 34.9 months. In these series, postprocedure complications occurred in 10.3% to 14.3% of patients.^{42,43} In a large prospective study of 100 patients with low-risk lesions (less than 20 mm, limited to mucosa on the basis of EUS, well or moderately differentiated, and no lymph or venous invasion), treated with either cap-assisted or ligation-assisted EMR, there was an 11% recurrence rate at a mean follow-up of 36 months

with minor bleeding (hemoglobin decline <2 g/dL) as the only complication.⁴⁴

Stomach. The largest experience in endoscopic treatment of early gastric cancer is accumulated in Japan where approximately 50% of gastric cancers (10,000 cases yearly) are now discovered at an early stage.^{4,25,45-47} A summary of endoscopic therapy outcomes for 1832 Japanese patients with early gastric cancer treated with EMR and ESD demonstrated complete resection in 73.9% and a combined complication rate of 1.9% (1.4% bleeding, 0.5% perforation).⁴⁸

Duodenum. Benign periampullary lesions are usually removed with a standard polypectomy snare without the submucosal injection techniques described for EMR.⁴⁹ In a review of 13 observational reports of papillectomy, some using saline solution injection, the technical success rate ranged from 50% to 100% with an adenoma recurrence rate of 0% to 33%.⁵⁰ There is 1 preliminary report of 3 patients undergoing cap-assisted EMR as a follow-up therapy to successfully remove all residual adenoma tissue after standard snare ampullectomy.⁵¹ Endoscopic removal of malignant ampullary tumors is usually inadequate, and these patients should be referred for surgical resection.^{49,52,53}

Duodenal adenomas located outside of the major duodenal papilla are usually flat and can be removed with the simple inject-and-cut technique or with cap-assisted or ligation-assisted EMR. The majority of published reports on endoscopic removal of duodenal polyps are limited by the small number of patients and their retrospective design.^{49,50} Reported success rates vary from 74% to 93% for ampullary and 62% for nonampullary duodenal lesions.^{49,50,54,55}

TABLE 3. Solutions for submucosal injection during EMR and ESD

	Cushion duration	Advantages	Disadvantages
Normal saline solution (0.9%)	+	Easy to inject, cheap, readily available	Quickly dissipates (short duration of cushion)
Hypertonic solution of sodium chloride (3.0%)	++	Easy to inject, cheap, readily available	Tissue damage, local inflammation at sites of injection
Hyaluronic acid	+++	Longest lasting cushion	Expensive, not available in most endoscopy units, special requirements for storage, might stimulate growth of residual tumor cells
Hydroxypropyl methylcellulose	+++	Long-lasting cushion, relatively inexpensive	Tissue damage, local inflammation at sites of injection
Glycerol	++		
Dextrose (20%, 30%, 50%)	++	Cheap, readily available	Tissue damage, local inflammation at sites of injection
Albumin	++	Easy to inject, available in most endoscopy units	Expensive
Fibrinogen	+++	Easy to inject, long-lasting cushion	Expensive, not readily available
Autologous blood	+++	Clotting in syringe if injection delayed	Religious beliefs may preclude; limited human data

Colon. EMR is widely used for resection of flat benign colon lesions, although this is typically done with a simple inject-and-cut technique as opposed to the ligation or cap-assisted techniques. Although even large benign colon polyps can be removed endoscopically, the reported recurrence rates range as high as 21.4% to 46%, which justifies aggressive surveillance for detection and removal of recurrent or residual lesions.^{34,56-59} Although several studies have reported no recurrence after endoscopic removal of malignant colon polyps, the effectiveness of EMR for treatment of these lesions has been questioned and EMR should not be attempted for indurated, ulcerated, or “nonlifting” colon lesions.^{34,60-62}

SAFETY

Bleeding is the most common complication of EMR and ESD, with rates reported ranging from 1% to 45% with average rates of 10% in larger series.^{60,63-68} Most bleeding is observed during the procedure or within the first 24 hours.¹² Delayed bleeding has been reported in up to 13.9% of patients.^{69,70}

Reported perforation rates during ESD (4%-10%) are much higher compared with EMR (0.3%-0.5%).^{33,35,71-77} Small perforations recognized during the procedure can be successfully sealed with endoscopic clips.^{18,78,79} Large perforations require urgent salvage surgery to prevent peritonitis.¹²

Stenosis has been reported in 6% to 26% of patients after endoscopic removal of esophageal lesions and in 3.3% after

removal of gastric (prepyloric) lesions.^{27,72,80-82} These strictures are more common after removal of large lesions occupying more than 75% of the esophageal circumference and usually can be successfully treated by endoscopic dilation.⁸³

Endoscopic removal of lesions affecting the major duodenal papilla is associated with an increased risk of postprocedure pancreatitis, which may be reduced by prophylactic stenting of the pancreatic duct.^{84,85} Postpapillectomy bleeding is another frequent complication and argon plasma coagulation can be used to control bleeding and may be helpful as an adjunctive therapy to destroy residual adenomatous tissue.^{49,86}

FINANCIAL CONSIDERATIONS

Although EMR and ESD have obvious benefits for patients with benign and early malignant lesions of the GI tract, these endoscopic techniques are both technically demanding, time consuming, and are not adequately reimbursed at the present time.^{34,35,87} There are no unique Current Procedural Terminology (CPT)* codes for EMR

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or ESD.⁸⁷ The most applicable identifiers are 43236 (submucosal injection during EGD), 45381 (submucosal injection during colonoscopy), 43251 (snare polypectomy during EGD), and 45385 (snare polypectomy during colonoscopy). If adjunctive mucosal ablation of lesion margins is used, an additional code 43258 (ablation during EGD) and 45383 (ablation during colonoscopy) can be attached to the primary procedure code. Ordinarily the polypectomy (highest reimbursed of existing CPT codes) would be listed first, and -59 modifier attached to other reported codes. Use of the modifier 22 (unusual procedural services) can increase the reimbursement for the procedure, but the details of how the services were more extensive than the standard procedure must be documented in a cover letter or within the report. An alternative to the -22 modifier is to code an unlisted 47999 code appended to the polypectomy code adding the -59 modifier billed at a fee judged appropriate for the EMR. In this last case a cover letter submitted with the claim that explains the nature of the procedure, equipment required, 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 EMR and ESD devices do add to the facility cost of the procedure largely without added reimbursement.

AREAS FOR FUTURE RESEARCH

The search for an ideal injection solution for EMR and ESD is continuing. Development of new endoscopic tools and simplification of ESD techniques are necessary to enhance safety and facilitate its further dissemination into clinical practice. There is a consensus in the literature that, after endoscopic removal of large premalignant and early malignant lesions, patients should have endoscopic surveillance but that studies defining optimal follow-up intervals are needed. Studies comparing EMR and ESD with other ablative techniques will help establish the optimal role of these therapies.

SUMMARY

EMR and ESD have emerged as important therapeutic options for premalignant and early stage GI malignancies. These techniques also aid in the diagnosis and therapy of subepithelial lesions localized to the muscularis mucosa or submucosa. Several dedicated EMR and ESD devices are available to facilitate these procedures. Complication rates are higher after EMR and ESD relative to other basic endoscopic interventions. Further research on long-term out-

comes and development of devices to enhance safety are needed.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CPT, Current Procedural Terminology; ESD, endoscopic submucosal dissection; MAUDE, Food and Drug Administration Center for Devices and Radiological Health.

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