Endoscopic Submucosal Dissection in the Esophagus

Indications, Techniques, and Outcomes

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KEYWORDS

- Esophageal squamous cell carcinoma • Barrett's-related neoplasm
- Early esophageal adenocarcinoma • Endoscopic resection
- Endoscopic submucosal dissection • Endoscopic mucosal resection

KEY POINTS

- Knowledge and experience with endoscopic evaluation of lesions with chromoendoscopy or advanced imaging modality are paramount in choosing treatment modality for the best outcomes.
- Primary endoscopic resection with curative intent is beneficial for superficial squamous neoplasm without suggestive changes for deep submucosal invasion, and it does not affect survival outcomes.
- Visible Barrett's dysplasia requires endoscopic resection. Endoscopic submucosal dissection (ESD) offers potential benefit over endoscopic mucosal resection (EMR) for larger lesions, multifocal high grade dysplasia (HGD) or cancer, or with significant nodularity.
- Postresection specimen processing is one of the most important steps of ESD.
- Stricture prevention should be considered after large circumferential resection and limited modalities are available to reduce the risk for significant stenosis.

INTRODUCTION

Early detection of neoplastic change in the esophagus is paramount in preventing esophageal cancer-related mortality. Once early cancer is detected, endoscopic resection (ER) offers detailed pathologic diagnosis and minimally invasive treatment to eradicate neoplastic change with lower morbidity compared with surgical therapy. Endoscopic submucosal dissection (ESD) is a new technique to remove mucosal lesions with a dedicated knife (or knives) by free-hand technique, which has become popular worldwide in the past decade. It offers the unique ability to control size, shape, and depth of ER removal in one piece (*en bloc*). With refinement of ESD techniques

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Abbreviations	
ER	Endoscopic resection
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic Submucosal Dissection
AC	Adenocarcinoma
SCC	Squamous cell carcinoma
HGD	High Grade Dysplasia
MM	Muscularis Mucosae
SM	Submucosa
LVI	Lymphovascular invasion
LNM	Lymph Node Metastasis
GEJ	Gastroesophageal Junction
APC	Argon Plasma Coagulator
EUS	Endoscopic Ultrasound

and reported excellent outcomes, wider application of ESD is now accepted in treating early neoplastic lesions in the esophagus. In this article, indications, techniques, and outcomes of esophageal ESD will be discussed.

INDICATIONS

The dominant histologic type of esophageal cancer shifted from squamous cell carcinoma (SCC) to adenocarcinoma (AC) in the United States. AC is predominantly found in Caucasians, whereas SCC is the dominant type in Blacks and Asians.[1] AC is commonly associated with a presence of Barrett's esophagus and eradication therapy for dysplastic Barrett's esophagus has reduced the incidence of esophageal AC.[2,3] For eradication therapy, nodular lesions or visible lesions in the Barrett's esophagus is recommended to be removed endoscopically by ER. Squamous cell cancer metastasizes to lymph nodes even in the early luminal invasive stage (invasion to muscularis mucosae [MM]; m3 stage), and removal of earlier disease (m1–m2; high-grade dysplasia or invasive only to lamina propria) by ER is considered to be curative if margins are negative.[4–6]

Endoscopic mucosal resection aided by band or cap are useful techniques to perform ER, however, it is limited by the precision on the area and the size of resection. Margin-negative resection is often possible for lesions less than 1 cm (10 MM) but becomes less successful if lesions are larger.[7] For SCC, 15 MM cutoff has been suggested at expert centers with excellent technique.[8] ESD offers the ability to resect a wider area even in the setting of irregular shape. It also offers better pathologic evaluation that translates to better stratification of the patient for further treatment and surveillance.

SQUAMOUS CELL CARCINOMA

There is no effective screening program in the United States, and the finding of squamous dysplasia is mostly an incidental finding during upper endoscopy. An increase in vascular pattern, which is reflective of abnormal intrapapillary capillary loops, would be detected on white light endoscopy. Detailed inspection is important because features of large granularity, nodule, depression, or ulceration indicate MM–SM invasion or deeper pathologic condition.[9,10] Advanced imaging and virtual chromoendoscopy to enhance the vascular pattern are increasingly used to demarcate the lesion and are helpful to determine the T stage.[11,12] Lugol chromoendoscopy is of a great help to delineate the margins of the lesion vividly; however, the major role is now being replaced by digital chromoendoscopy.[11,13,14]

ER is effective for flat lesions with smaller sizes. Both band-EMR and cap-EMR are effective. Cap-EMR using oblique caps (hard and soft) increases the size of the resection but the use of cap-EMR requires submucosal (SM) lifting and training on the proper technique to reduce the risk for perforation. Ensuring the negative margin reduces the need for close endoscopic follow-up. ESD is beneficial and suitable for larger lesions or nodular lesions that are not well captured by EMR offering higher likelihood to obtain negative margins.[6–8,15]

Curative resection is defined by negative resection margins with minimum risk for lymphatic or vascular spread. Those lesions include squamous low-grade and high-grade dysplasia and early cancers that only invades to lamina propria (m1–m2) without lymphovascular invasion (LVI). Once SCC invades MM, it has similar metastatic risk as one with shallow SM invasion (m3–SM1). SM invasion is considered shallow (SM1) if the invasion depth is less than 200 μm.[16] Due to the endoscopic and endosonographic limitation to separate m1–m2 from m3–SM1, ER is a beneficial tool to provide a precise pathologic stage that may offer curative resection.[4–6] Any nodularity within squamous cell dysplasia is suggestive of m3 disease or deeper and the indication for ER should be carefully sought.

ADENOCARCINOMA

Dysplastic change within Barrett's esophagus is an indicator of a risk for a presence or a development of AC. Nodular or visible dysplasia should be removed by ER to obtain a pathologic diagnosis recommended by multiple societies.[2,3,17] EMR is effective for smaller lesions as described in squamous cell neoplasia, and ESD has gained popularity and is accepted to be more effective than ER if lesions are more complex (larger, nodular, and multifocal).[6,15,17]

Intramucosal AC has very low risk for lymph node metastasis (LNM) and ER is considered curative if there is no poorly differentiated component and without LVI. There are lymphatic channels within the lamina propria and there is duplication of the MM at distal esophagus, which makes the pathologic diagnosis challenging. Invasion into the connective tissue between MM layers are considered to be the same as MM invasion,[18] and it is important to recognize the presence of duplication because we have seen incorrect pathologic staging of T2 when the second layer of MM had invasion on the slide.

SM invasion is considered shallow (SM1) if the invasion depth is less than 500 μm. Shallow invasion (SM1) with no risky features such as poor differentiation, single-cell invasion, or LVI is considered as a low-risk lesion for LNM and careful surveillance can be an option rather than to offer esophagectomy with lymph node dissection.[19]

In summary, m1–m2 squamous cell dysplasia/carcinoma and m1–SM1 HGD/AC with no risky features are considered as a good indication for ER and often curative if margin-negative resection is achieved. An m3–SM1 SCC is considered as relative indication because its LNM risk increases. However, upfront ER with subsequent therapy per pathologic findings was shown to have similar outcomes as upfront surgery for SCC without signs of deep invasion (SM2-3 or T2)[20] and therefore, ER can be considered as a first-line therapy for lesions amenable for complete ER. If ER is applied as cancer resection, margin-negative resection is important to offer adequate local therapy and cure. Thus, pretreatment (resection) assessment and determination of method of ER is paramount. ESD offers precise margin determination and more effective negative margin resection for lesions more than 1 cm and should be considered as preferred method for all complex lesions.[6,15,17]

OTHER LESIONS (GRANULAR CELL TUMOR, LEIOMYOMA ARISING FROM MM, AND OTHERS)

ESD is reported to be useful in removing some subepithelial tumors. If the tumor is separated from muscularis propria (MP) layer by SM tissue, ESD is possible. ESD offers similar benefit of offering en bloc and R0 resection of tumors. Endoscopic ultrasound (EUS) is beneficial in identifying the clear SM layer that separates tumor from the MP layer before proceeding with ESD.

ANATOMY

The esophagus is a tubular organ that is easily approachable with an upper endoscope. SM dissection can be rather effortless because it is aided by the natural angle of approach that is nearly parallel to the esophageal wall. Two unique features are to be clearly understood. The esophageal muscle layer is thin, as in the colonic wall, and it lacks serosa, which is usually a protective layer for perforation or leak.

If the gastric cardia is included in the treatment area, approaching the cardia is always easier in retroflexion rather than a straight view approach. The cardia harbors penetrating vessels supplied from the left gastric artery and additional care is needed not to prematurely cut this vessel without adequate coagulation to avoid significant bleeding.

PREOPERATIVE/PREPROCEDURE PLANNING

Regular preprocedural preparation for EGD is sufficient. Water irrigation with the endoscope is ideal for an efficient ESD procedure and a use of an appropriate attachment cap is required. If the lesion involves gastroesophageal junction (GEJ) or cardia, the approach to the distal part of lesion may require a retroflexed view and selecting an endoscope with full retroflexion capability should be selected. It is important to consider patients with squamous neoplasms and ones with Barrett's-related neoplasms separately, as the latter often have thick mucosa and SM fibrosis. Preplanning on ESD methods (eg, conventional or tunneling) and a preparation of tools for traction are advisable (eg, string or snare and clips).

PREPARATION AND PATIENT POSITIONING

For esophageal ESD, general endotracheal anesthesia is ideal to prevent aspiration, to control respiratory rate and volume, and to control heart rate. Patient may be in the left lateral decubitus position similar to a diagnostic procedure or in the supine position. Routine use of a warm blanket and a sequential compression device for a possibly long ESD procedure is recommended by this author.

PROCEDURAL APPROACH

ESD in the esophagus deserves special attention. Esophagus is a tubular organ, and SM dissection is rather straightforward. However, the esophagus lacks a serosal layer outside that usually prevents leaks and also facilitates closure when perforation occurs. Therefore, deep SM dissection should be avoided unless clinically necessary due to fibrosis or suspected cancer invasion into SM layer. Moreover, GEJ is often included in the resection area, which demands different approaches and techniques.

ESD methods include (1) a traditional method where a circumferential mucosal incision is performed and SM dissection is completed afterward and (2) a tunneling method where the distal and proximal mucosal incision are made and dissected

down to SM layer, and then the SM dissection is completed from the proximal to distal end creating a tunnel.[21] Lateral mucosal incisions and subsequent SM dissection are performed. The tunneling method does not necessarily require traction method because traction is maintained by the residual tissue at the lateral sides of the lesion while the endoscope with cap is pushed forward. Traction method is very useful for the traditional method to facilitate SM dissection reducing adverse events. Simple clip and line technique or clips with snare technique would create traction to expose the SM layer facilitating dissection.[22]

Due to the proximity to greater vessels, heart, and diaphragm, extraesophageal movement can be complicating factors and those are best managed by anesthesia care with endotracheal intubation.

Tools:

a. Attachment cap or hood: Straight or cone/tapered shaped. Straight cap usually suffices.
b. Endoscope: One with water jet function is ideal.
c. Knife and scissors: Tip-knife with/without water jet capability, insulated-tip knife, and/or scissors-type device.
d. Injection fluid: Long-lasting fluid with dye (normal saline is not recommended for initial injection. However, saline solution is often used for additional injections via the knife during SM dissection).
e. Traction method: Clip and string or clip with snare.

Step 1: Mark 5 MM outside the lesion with the tip of a knife. Some use argon plasma coagulator (APC) probe; however, this adds additional cost.

Step 2: Determine the technique to be used: Conventional versus tunneling method.

Step 3: Mucosal incision at distal margin.

a. ESD within the esophagus

Incision at distal margin is done in a straight view position.

Injection of the fluid is to be done distal to the markings, and then mucosal incision is performed at or slightly proximal to the peak of the injected mound. It is important to incise down into the middle of SM layer but not down to expose the MP. The depth ensures recognition of the end point during SM dissection.

b. ESD for a lesion that includes the GEJ or the cardia

An incision in the cardia is best performed in a retroflexed position. A gradual incision from mucosal to SM is performed here because there is an abundant vascular network in SM layer at cardia. Coagulation of bleeding points or vessels needs to be done frequently to avoid ongoing blood loss and contamination of the dissection field with blood. Insulated tip knife works well in the cardia in retroflexion because the MP layer approaches more perpendicular to the knife when SM dissection progresses toward the Z line. An IT 2 knife needs to be used with caution so as not to make it parallel to the MP layer in order to avoid thermal damage or incision into the MP with the triangle electrode that is attached to the insulated tip.

Step 4: Mucosal incision at proximal margin.

Injection of the fluid is performed 5 MM *proximal* to the markings, and same process described in Step 3 (a) is repeated. The incision starts at the top or proximal to the peak of the injection mound.

Step 5: SM dissection and lateral mucosal incision.

a. Conventional method

Lateral mucosal incision is performed after additional fluid injection at the incision line outside the line created by marking. The dependent side (to gravity) should be incised first. With using a tip-knife, a proximal to distal direction is safer because the knife moves toward the lumen away from MP. With an insulated-tip knife, a distal to proximal movement works best. The full lateral mucosal incision beyond the MM should be completed to free up the lesion on both sides.

SM dissection begins at the proximal incision gradually moving distally. Once an adequate mucosal flap is created, a traction method may be used. The proximal edge is captured with a clip attached to the string or snare to provide traction. Two or more clips are recommended to secure the attachment to the snare.[23] Completion of SM dissection to free up the lesion is done by conducting SM dissection with either a tip-knife, insulated-tip knife, or scissor-type knives.

b. Tunneling method

SM dissection is performed from the proximal end to distal end until a tunnel is created. The width of dissection should be adequate to allow scope tip maneuvers but it is best to avoid expanding the tunnel width to the full width of the lesion.

Once a tunnel is created, the lateral mucosal incisions are done as in Step 5 (a). Then, the remaining SM layer at the sides are dissected from inside toward outside widening the tunnel or taking off the SM layer alternating one side to other side starting at proximal end moving distally. With an insulated-tip knife, SM dissection may be performed from the distal end moving proximally or follow the process described above.

c. Coagulation of vessels

Preemptive coagulation of vessels should be done whenever possible. Coagulation forceps with low voltage coagulation (SoftCoag) can be used to seal the vessel before dissection, or the knife can be used with low-energy coagulation mode (forced coagulation effect 1, 10 W, or very low wattage spray coagulation). Isolation of vessels by dissecting surrounding SM fibers (trimming) is an effective way to enhance the sealing effect of the vessels.

Step 6: Preemptive coagulation on vessels after resection.

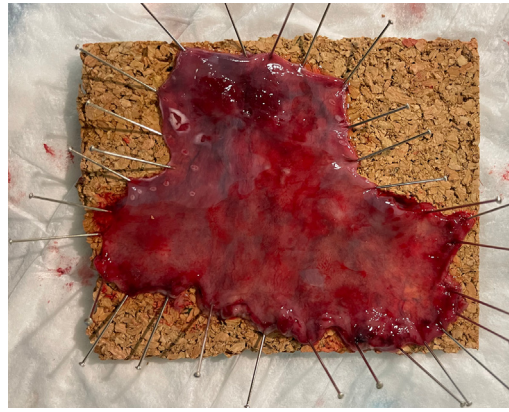

Fig. 1. C1M5 Barrett's esophagus with adenocarcinoma (IIa + IIc lesion) immediately after resection. Tissue was placed cut surface down and pinned on the cork board. Use of short thin clothing pin is recommended. Tissue should be stretched to the original shape while placing the pin.

Fig. 2. After formalin fixation. Photo documented before coloring the margin and sectioning for future reference.

Exposed vessels at the resection bed should be coagulated by coagulation forceps to reduce post ESD bleeding. Thermal damage must be reduced by pulling the grasped tissue off the MP when applying coagulation energy. Air bubbles signify adequate temperature increase and signals the end of treatment.

Step 7: Preparation of tissue specimen.

Resected tissue is best retrieved with a net to prevent damage to the tissue. The lesion should be pinned on the cork around the resection edge for a proper orientation of the section and a precise evaluation of the margins and the depth of invasion (**Figs. 1** and **2**). Discussion with a pathologist and pathology technician in the processing room is extremely helpful to set up proper processing of ESD specimens.

RECOVERY AND REHABILITATION

Post ESD care consists of dietary modification, observation status (outpatient vs admission), and the use of antibiotics. Diet will be restricted to clear liquids or nil per os (NPO) depending on the risk for bleeding and perforation. We often allow patients to have clear liquids on the day of the procedure to continue for 1 or 2 days depending on the size and location of the resection. Risk of bleeding is highest within 48 hours, and if there no bleeding during that time, the diet can be safely advanced. High doses of proton pump inhibitors should be prescribed for the initial 6 to 8 weeks to reduce chemical irritation and can be reduced to once daily afterward for patients with Barrett's-related neoplasm. Administration of antibiotics is not routine and is only advisable with evidence of intraprocedural MP injury or perforation. This author has been managing patients undergoing ESD as same day surgery patients unless patients have severe medical conditions (ie, cardiopulmonary, severe renal disease, or on anticoagulation or antithrombotic agent, which requires to be resumed soonest after ESD). Outpatient management is combined with a follow-up phone call on the next day to monitor patient's status.

OUTCOMES

The goals of the ER for esophageal lesions are to obtain tissue diagnosis and pathologic T stage, thus predicting the risk for recurrence and/or metastatic disease, and also to provide cure from the disease. Adverse events should be considered for any invasive treatments to weigh benefits against risks compared with other therapeutic modalities such as esophagectomy.

Successful technical outcomes of ER are defined by a resection of the lesion in one piece (*en bloc* resection) and ER of lesion with negative lateral and deep margins (R0 resection). Moreover, successful clinical outcomes are defined by the risk of local recurrence, and risk of metastatic recurrence (curative resection), and rates and degree of the adverse events.

a. Tissue resection and cancer risk assessment

Precise pre-ER staging of the tumor is often difficult and the separation of the T1a from T1b is challenging given the thinness of each layer in the esophagus. EUS allows more reliable separation of the T stage than computed tomographic scan, and EUS is recommended if there is no evidence of metastatic disease but separating T1a from T1b can be suboptimal.[24–28] Therefore, ER is a more definitive tool to provide pathologic T stage for early-stage cancer when endoscopic examination does not suggest deeper invasion. EUS confirmation may be beneficial to exclude tumor invasive to the MP or deeper (T2 or deeper). ER should be done not only to obtain pathologic diagnosis in this case but to aim for curative resection because the first resection is the best chance to obtain clear margins without prohibitive scarring.

Successful resections were achieved in most cases at the completion of ESD. Meta-analysis of published data on Barrett's ESD described ESD rates as follows: en bloc resection rate 96%, R0 resection 74.5%, and curative resection 64.9%.[29] Other systematic review and meta-analysis comparing EMR and ESD for esophageal cancer including both SCC and AC, from both East and West showed significantly high en bloc, R0, and curative resection rate for ESD with OR of 36.32, 4.77, and 9.74, respectively.[7] In this study, there was no difference was seen in outcomes between EMR and ESD for lesions less than 10 MM size.

Curative resection is defined by en bloc, margin-negative (R0) resection with very low risk for nodal and metastatic recurrence (ie, mucosal cancer or shallow SM invasion with no poor differentiation and no LVIs – *see indication section*). The risks for nodal and metastases differs between SCC and AC. SCC is known to spread to lymph nodes in the early tumor stage. Epithelial and cancer invasion into lamina propria (m1 and m2) are acceptable as low-risk invasion depth. Invasion to muscularis mucosae (MM) and shallow SM invasion up to 200 μm (m3 and SM1) are considered to have higher LNM up to 16% to 26.1%,[12,16,30] and thus, it is considered as a relative indication for ER because there would be higher risk for recurrence but ER may be of benefit if patients are at high risk for undergoing other therapy such as surgery or chemoradiation therapy.

There was a concern about ER being used as a therapeutic modality for SCC that may be invasive to MM or superficial SM because when pathologic evaluation later proved it to be noncurative, ER may adversely affect efficacy of subsequent treatment outcomes. Several studies tried to answer this question. In retrospective studies and a separate meta-analysis, survival outcomes did not differ between the patients who underwent primary ER compared with patients who underwent esophagectomy for T1b SCC.[20,31,32] In a propensity score–matched cohort study by Min and colleagues, the authors demonstrated that primary ER for T1 lesions with/without subsequent adjuvant surgery or chemoradiation achieved similar survival outcomes as primary surgery.[20] This study reinforced the appropriateness of ER as the primary therapeutic attempt providing pathologic diagnosis to stratify patients for further treatments.

Multiple societies recommend ER for any visible dysplastic nodule within Barrett's esophagus.[2,3,33] ER with pathologic evaluation offers definitive pathologic diagnosis and the risk stratification. Further eradication of remaining Barrett's epithelium is universally recommended to reduce metachronous HGD or cancer within the residual Barrett's. The risk of metastatic spread of shallow SM invasion without high-risk signs

was reported to be similar to T1a cancer[19] but the criteria is not accepted universally as curative resection criteria in the West, and further clarification on the risk of the patient group is needed. Multidisciplinary discussion is recommended to create the local institutional clinical pathway. A patient-centered approach that involves the patient for decision-making is ideal.

b. Adverse events

Most significant adverse events are bleeding, perforation, and resultant esophageal stricture. AE rates were reported as 1.8% for bleeding and 1.5% for perforation in meta-analysis[29] and compared with those for EMR, the bleeding rate was similar but perforation risk was higher (OR 2.47), especially for SCC.[7] Intraprocedural bleeding is almost always controllable during the procedure. Delayed bleeding can occur manifesting as fainting, hematemesis, and melena. Most commonly, patients develops nausea with subsequent hematemesis. Urgent endoscopy is necessary to achieve hemostasis and interventional radiology intervention is rarely required. Delayed perforation may require surgical intervention; however, a temporary fully covered esophageal stent can be placed to attempt to seal the leak. Endoscopic suture application may be of help if the perforation site is near or below GEJ. Exposed MP layer in the tubular esophagus would not hold clips or suture because the esophagus lacks serosa and attempts to apply such devices into the exposed MP layer should be avoided. Preemptive fully covered esophageal stent placement may be considered to reduce post ESD bleeding and leak.

Steroid injection or oral high-dose steroid administration were reported to reduce the risk of stenosis.[34–38] Steroid injection is effective in preventing stricture after ESD for squamous-related neoplasms but does not seem so effective after ESD for Barrett's related neoplasms likely due to coexisting acid and nonacid reflux. Strictures start to manifest around 3 weeks after ESD, and preemptive dilations are effective to maintain the esophageal diameter and to prevent dysphagia.[39]

SUMMARY

Esophageal ESD is highly effective in the removal of large areas in one piece (en bloc), offering the benefit of complete removal of neoplasms with negative margin. ESD steps are relatively established and standardized. Proper procedural planning and effective use of tools are paramount to achieve high clinical success and to reduce complications.

CLINICS CARE POINTS

- General endotracheal anesthesia is ideal for esophageal endoscopic submucosal dissection (ESD) for the best control of airway, respiratory effort, and cardiac movement to facilitate the procedure.
- Detailed inspection on the target lesion with the use of advanced imaging is the most critical first procedural step to plan and aim for successful resection with the proper techniques.
- The tubular esophagus lacks a protective serosal layer and submucosal dissection should be performed well above muscularis propriae to prevent muscle exposure or injury.
- Submucosal tissue is a protective layer to prevent leaks and to receive steroid injection for the prevention of stenosis. This author recommends dissection at SM2 layer (middle layer of submucosal [SM] layer) unless SM invasion of cancer is suspected.
- Pathologic evaluation is the key factor for the clinical success of ESD. Proper processing of the tissue needs to be established in the gastrointestinal (GI) laboratory and in the pathology

laboratory before the start of ESD practice.

DISCLOSURE

Author has relationship as consultant to the companies below: Creo Medical, Boston Scientific.

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