



# Endoscopic Management of Early Esophageal Cancer

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## Abstract

Although esophagectomy is an effective treatment of early esophageal cancer, due to high rates of morbidity and potential mortality, and also, importantly, the potentially reduced quality of life, endoscopic therapy represents a favorable approach where appropriate. Endoscopic resection therapies have been successfully applied to selected patients with early tumors of the esophagus with equivalent oncological outcomes. This chapter will address the selection of tumors appropriate for endoscopic resection and review the technical approaches and outcomes of the two main technical approaches, including Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD).

## Keywords

Esophageal cancer · Early esophageal cancer · EMR · ESD

## Introduction

Esophageal cancer has exponentially increased annually in the contemporary era, with a shift in anatomical and histological subtype from esophageal squamous cell carcinoma to adenocarcinoma in North America and Western Europe [1]. Although the overall 5-year relative survival rate is only approximately 20%, patients with early-stage disease have a better chance of survival, and cure rates of successfully treated early esophageal cancer approach 90%.

The conventional treatment of localized disease consists of esophagectomy, open initially and currently minimally invasively. Although traditional surgical resection is an effective treatment of early esophageal cancer, due to high rates of morbidity 50–60%, and potential mortality of 1–3%, and also, importantly, the potentially reduced quality of life, endoscopic therapy represents a favorable approach where appropriate [2]. Indeed, endoscopic resection therapies have been successfully applied to selected patients with early tumors of the esophagus with equivalent oncological outcomes. This chapter will address the selection of tumors appropriate

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for endoscopic resection and review the technical approaches and outcomes of the two main technical approaches, including Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD).

## Selecting the Appropriate Tumors for Endoscopic Resection

To justify an organ-sparing endoscopic resection approach for cure, two main criteria must be met: (1) negligible rate of occult lymph node metastasis and (2) ability to resect the lesion completely en bloc with negative margins, particularly the deep margin. Staging investigations are often required to eliminate clinically apparent regional/distant disease, including cross-sectional imaging, endoscopic ultrasound, and PET scans.

There is an exponentially increased incidence of nodal disease with advancing T stage. Consequently, it is essential to appropriately stage the patient ab initio to delineate patients suitable for endotherapy versus those necessitating a formal resection. The esophageal wall comprises four layers, with the mucosa being the most superficial layer. The mucosa encompasses the epithelium, lamina propria, and muscularis mucosa. Immediately beyond is the submucosa, which is made of connective tissue, including blood vessels, lymphatics, and

Meissner's plexus. The submucosa connects the mucosa to the muscularis propria, made of inner circular and outer longitudinal muscle layers along with the Auerbach plexus. The deepest level comprised of connective tissue is called the adventitia.

The incidence of nodal metastases directly correlates to the subclassification of T1a and T1b disease, with invasion confined to the epithelium (m1), lamina propria (m2), or muscularis propria (m3) for T1a disease, and lesions infiltrating the submucosa (T1b) can be further categorized into sm1 (inner third), sm2 (middle third) and sm3 (outer third) (Table 1 and Fig. 1).

For decades, oncological surgical resection was the conventional curative therapy for malignancies of the esophagus. Endoscopic therapy of early carcinomas is now increasingly established as the gold standard, with the main challenge still to diagnose and carry out endoscopic therapy in good time before metastasis. It is also important to note that tumors over 2 cm with adverse features of tumor biology, such as poor differentiation, have higher incidences of metastases, with late diagnosis still common due to the indolent nature of the disease. Some scoring algorithms have been devised as simple metrics to predict those at risk of lymph node metastasis (LNM) to aid decision-making in patients with T1 esophageal adenocarcinoma undergoing endoscopic resection [3].

**Table 1** Incidence of lymph node metastases by depth of invasion into mucosa and submucosal layers (from Araki et al., Endo et al., Westerterp et al., Leers et al., Bollschweiler et al., and Leers et al.)

Tumors	Depth of invasion (AJCC staging)	Rate of lymph node metastasis adenocarcinoma %	Rate of lymph node metastasis squamous cell cancer %
Mucosal M1	Limited to the epithelial layer (Tis)	0	0
M2	Invades the lamina propria (T1a)	0	0
M3	Invades into, but not through, the muscularis mucosae (T1a)	0–6	0–8
Submucosal SM1	Penetrates the shallowest one-third of the submucosa (T1b)	0–22	8–33
SM2	Penetrates into the intermediate one-third of the submucosa (T1b)	0–35	17–30
SM3	Penetrates the deepest one-third of the submucosa (T1b)	26–78	36–69



**Fig. 1** Risk of nodal metastases increases exponentially with submucosal invasion

## Diagnostic and Staging Work-Up

To facilitate patient stratification, pre-treatment evaluation of esophageal cancer consists of locoregional staging and evaluation for distant metastases. Locoregional staging assesses both the degree of extension of the tumor into the esophageal wall and the nodal status. As already alluded to, as tumor depth progresses, so does the risk of LNM. From older surgical series, the rate of LNM in treatment-naïve resected esophageal adenocarcinoma ranges between 0 and 7%. Most series have a clinically negligible rate of regional disease on pathology for pathology T1a tumors [4]. In comparison, this risk increases to up to 27% for T1b adenocarcinoma.

The Society of Thoracic Surgeons has published guidelines on staging patients with esophageal cancer [5]. Fluorodeoxyglucose (FDG) positron-emission tomography (PET) scans can improve overall staging by detecting metastatic disease in up to 15–20% of patients and should complement conventional CT imaging to identify metastatic disease [6]. In addition, FDG-PET has also been shown to have prognostic value that can be applied to patient management and aid in developing emerging therapies.

EUS aids locoregional staging and can guide treatment planning of esophageal cancer in the

absence of distant metastases. In early esophageal cancer, T staging may help select appropriate cases for minimally invasive treatment using EMR and ESD techniques. Puli and colleagues reported the sensitivity and specificity of EUS for staging esophageal cancer to be 81.6 and 99.4% in T1 tumors [7]. The specificity and the sensitivity for identifying lymph node disease are better when EUS is combined with fine-needle aspiration (FNA) or fine needle biopsy (FNB) compared to EUS alone [8].

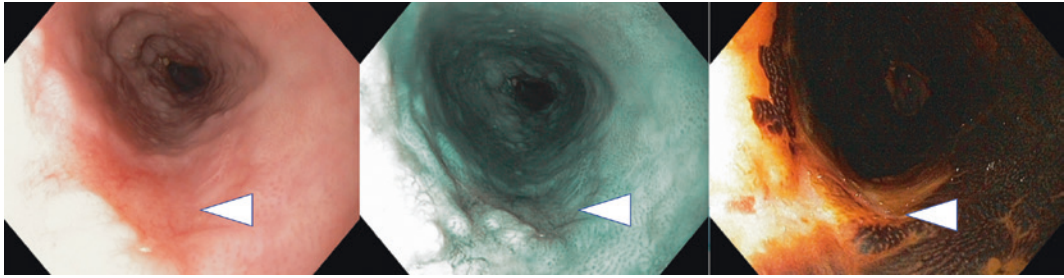
There are occasions where additional studies may be worthwhile before therapies are initiated, such as bronchoscopy considered for tumors in the upper and middle esophagus to rule out airway invasion. Although staging laparoscopy has been suggested for locally advanced esophagogastric junction adenocarcinoma, in early esophageal disease, the risk of peritoneal involvement is nominal, and thus this diagnostic test can be avoided.

Chromoendoscopy and advanced endoscopic imaging techniques have the potential to improve the workup of patients with early esophageal neoplastic lesions. It involves using dye stains such as Lugol's iodine for squamous cell cancer, acetic acid for Barrett's esophagus, and Narrow Band Imaging (NBI), enabling detailed lesion assessment and extent (Figs. 2 and 3).

Lugol's solution highlights glycogen-rich nonkeratinized squamous epithelium. An abnormal staining pattern is present in conditions that deplete glycogen in squamous cells, including dysplastic and early neoplastic lesions. Lugol's iodine has a sensitivity of 91–100% and a specificity of 40–95% for detecting squamous neoplasia in the esophagus.

Acetic acid improves the diagnostic yield for identifying Barrett's esophagus specialized columnar epithelium in comparison to random biopsies (57% vs. 26%,  $P=0.12$ ) [9, 10].

NBI has been combined with magnification endoscopy to predict the invasion depth of superficial squamous cell cancer [11]. Lugol's chromoendoscopy is a simple technique in which the liquid is sprayed into the mucosa



**Fig. 2** Mid esophageal squamous cell carcinoma under white light, NBI, and Lugol's Iodine



**Fig. 3** Esophageal adenocarcinoma in field of Barrett's esophagus under white light and NBI

through an injection spray catheter via the endoscope's working channel. The iodine-potassium iodide forms a dark brown complex with the physiological squamous epithelium, which allows the delineation of dysplastic carcinoma cells that do not stain, and this helps with the sometimes-difficult differentiation from healthy tissue, which is essential for R0 resection. NBI can also enhance the mucosa and the underlying vascular pattern, providing greater convenience for evaluation.

### Endoscopic Mucosal Resection (EMR)

Endoscopic mucosal resection (EMR) is a technique that was originally pioneered and introduced in 1978 in Japan for early gastric cancer [12]. In the contemporary era,

endoscopic techniques have replaced the traditional process of esophagectomy as the preferred treatment modality for high-grade dysplastic Barrett's, intramucosal cancer [13], and in cases of early invasive cancer, with the decision influenced by the risk of LNM.

"Early carcinoma of the esophagus" is not uniformly defined and refers in the following to in situ and T1 tumors in non-metastatic disease. Notwithstanding higher cure rates are achieved with esophagectomy, the decision on treatment strategy must be borne in mind with the significant treatment-related morbidity and mortality, even in very experienced high volume tertiary referral centers, between 2 and 7% and up to 20% in others [14, 15]. In addition to this, high-risk cardiovascular patients may not be able to tolerate the anesthesia or esophagectomy itself, leaving very few options available for these patients.

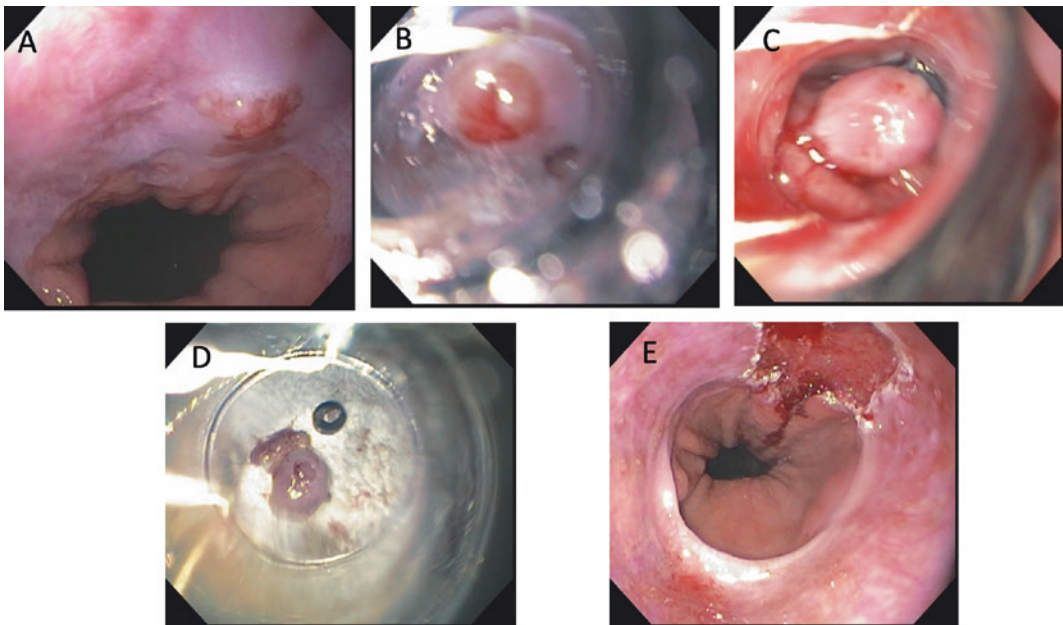


Curative endoscopic resection for mucosal carcinomas is possible in adenocarcinoma, analogous to early squamous cell carcinoma. Consequently, endoscopic resection has evolved to become the first-line therapy for managing superficial early esophageal neoplasia. The term *superficial*, however, is in some ways confusing, because it is not directly related to histology or invasiveness of a GI cancer but simply describes the endoscopic appearance of a lesion, which looks to be restricted to *superficial* layers of the GI tract. EMR is an established simpler and faster technique compared to endoscopic submucosal dissection (ESD) but is limited by its inability to resect large lesions en bloc. In essence, piecemeal EMR of large lesions includes a high rate of recurrence and arduous tissue specimen histologic evaluation for accurate staging and margin assessment for R0 resections.

There is a significant risk of leaving disease behind with up to 30% local recurrence with EMR of lesions > 1 cm [16]. Alternatively, ESD, on the other hand, is technically more complex, and traditionally has been associated with a higher rate of adverse events but facilitates en bloc resection regardless of lesion size, reducing

risk for recurrence and facilitating precise histologic staging. Ultimately, the optimal endoscopic technique should be selected based on organ location, type of neoplastic lesion, and local expertise. The role of ESD has expanded in Eastern regions beyond squamous cell lesions in the esophagus and gastric cancer to include superficial Barrett's esophagus (BE). However, there is controversy in Western regions over the use of ESD for BE. Thus, focusing on practical considerations for formulating the most appropriate endoscopic resection approach for each patient must be applied.

Although there are several approaches for EMR, we prefer the band ligation technique (Fig. 4). After a lesion is sucked into the overtube, a rubber band is released to form a pseudopolyp. Once the ligation device is detached, the pseudopolyp is removed at the base with a diathermy snare under or above the rubber band. The standard multi-bander ligation devices necessitate the removal of the endoscope to disassemble the ligation device and reintroduce the endoscope to remove the pseudopolyp with a standard polypectomy snare. Although some endoscopists recommend a prior submucosal



**Fig. 4** Steps of endoscopic mucosal resection (EMR) of an early esophageal adenocarcinoma

injection to facilitate elevation of the mucosa [17], we have found that this is not necessary in the vast majority of cases and do not perform this technical step routinely. The specimen is then fixed for the pathologist. For larger lesions, several sequential EMRs are required, complicating accurate pathological assessment of mucosal margin status.

The recommendation for endoscopic resection for m1 to m3 adenocarcinoma remains steadfast and is made based on patient factors and the risk of metastatic disease with high-risk disease or poor prognostic factors such as adverse biology [17, 18]. In the case of sm1 carcinomas, a deep infiltration of  $<500\ \mu\text{m}$  is required for endoscopic resection, otherwise, there is a borderline case between surgical and endoscopic therapy [19]. The Japan Esophageal Society provides primary endoscopic resection for m1/m2 carcinomas. In the case of m3 carcinomas, the general condition essentially determines whether surgical, endoscopic, or radio/chemotherapy is indicated. The recommendations apply regardless of the histopathological typing/grading [20].

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## Endoscopic Submucosal Dissection (ESD)

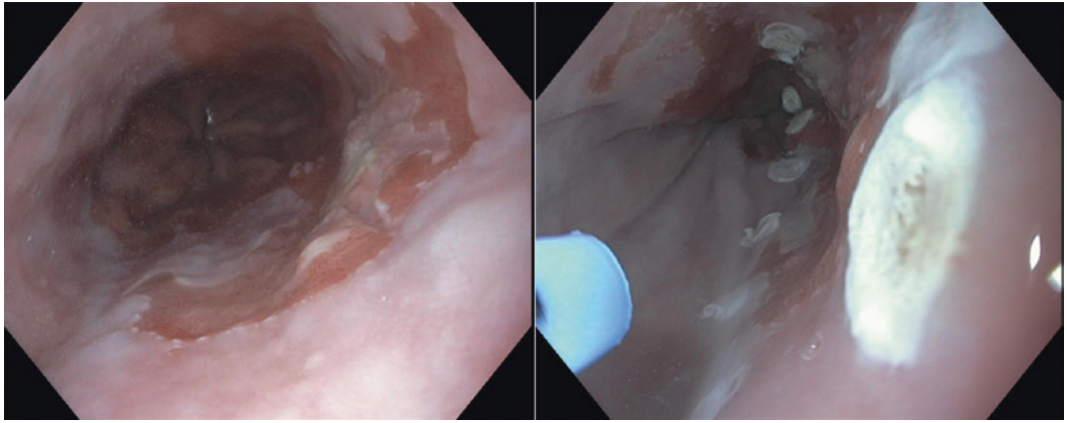
Endoscopic submucosal dissection (ESD) was developed in Japan as an alternative to the limitations of the well-established modality of EMR for the curative treatment for early GI cancer facilitating en bloc resection and, therefore, histopathologic assessment [21].

The European Society of Gastrointestinal Endoscopy (ESGE) guidelines which have been updated as of June 2022 advocate ESD as the first option for superficial esophageal squamous cell carcinoma (SCC) with a series of 15 studies on ESD for superficial SCC finding en bloc resection rates of 83–100%, complete resection rates of 78–100%, and low rates of local recurrence of 0–2.6% [22]. Consequently, ESD is the preferred treatment modality for M1 (intraepithelial) and M2 (invasion into the lamina propria) disease.

To ensure the correct patient cohort is selected, tumor morphology should be employed to predict tumor depth. Paris classification lesions 0-IIa, 0-IIb, and 0-IIc are typically intramucosal and the Japan Esophageal Society guidelines have advocated Paris 0-II lesions with m1–m2 invasion and  $<2/3$  circumferential extent as absolute indications for endoscopic resection. The rationale for this recommendation is based on the negligible risk of LNM for M1 and M2 disease as well as the morbidity and mortality of esophagectomy.

The role of ESD in Barrett's esophagus-related adenocarcinoma is limited due to the high efficacy of EMR. Endoscopic ablation of Barrett's esophagus is a gold standard treatment for patients with high-grade dysplasia in the absence of visible lesions. Endoscopic resection is the treatment of choice for patients with visible or flat neoplasia. EMR is a technically limited resection as it is piecemeal resection which hinders determination of negative margins. A systematic review compared outcomes of ESD and EMR and there were no significant differences in local recurrence rates, positive margins, lymph node positivity, complications, or patients requiring surgery [23, 24].

ESD is performed with a standard, single accessory-channel endoscope. Carbon dioxide is used for insufflation. Special equipment necessary for ESD is a transparent cap, submucosal injection needle and solutions, ESD knives, coagulation devices, and endoclips. Typical ESD is accomplished in a stepwise manner, including marking the lesion, incision and submucosal dissection with simultaneous hemostasis. Pre-resection definition of the border of esophageal neoplasms is essential to avoid compromising the margins. Chromoendoscopy or NBI, as illustrated above, can be useful for pre-procedural assessment. An argon plasma coagulation (APC) or ESD knife using a soft coagulation current can be applied to mark the resection borders with dots around the lesion (Fig. 5). This should be at least 1 mm away from the margin of the invasive component of the tumor. If resecting early cancer within a field of Barrett's esophagus, it is not necessary to resect all of the flat columnar



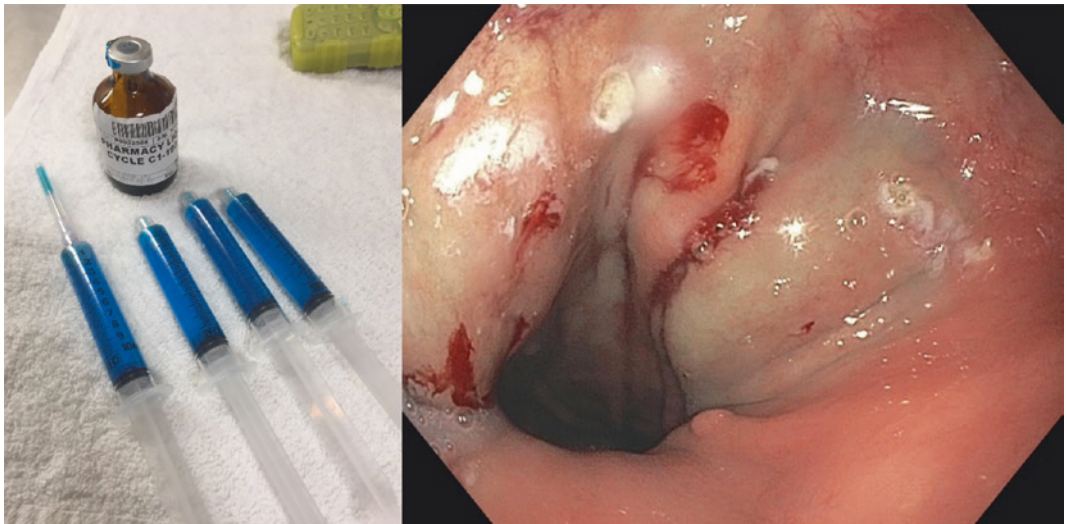
**Fig. 5** Marking margins of resection with argon plasma coagulation (APC)/dual knife in a patient with C4M5 Barrett's in a cT1b lesion

mucosa, which can be addressed by subsequent ablative therapies at a separate setting.

After the resection borders are marked, an injectable liquid can be injected beneath the mucosa and submucosa off of the muscularis propria by an injection needle through the endoscopic channel to create a cushion. Although several elevating liquids have been proposed, such as hyaluronic acid, we have generally used cheaper options, such as glycerol 10% or a

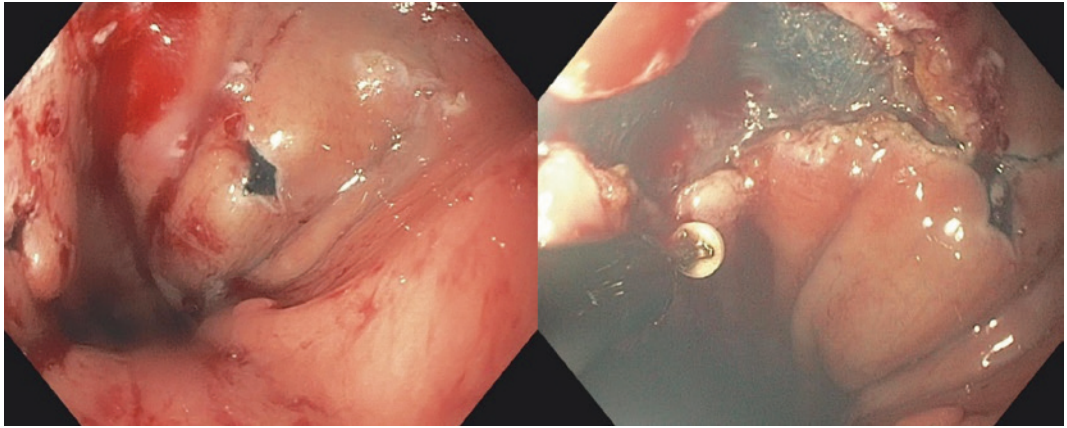
readily available intravenous starched-based volume expander (Fig. 6).

A circumferential incision is made along the marginal markings. For esophageal ESDs we usually mark the distal extent of the lesion first to define the end point (Fig. 7), followed by the proximal incision (Fig. 8). Then, the mucosal incision is imitated with an uncovered needle knife or a short blunt-tip knife prior to generating a submucosal tunnel.

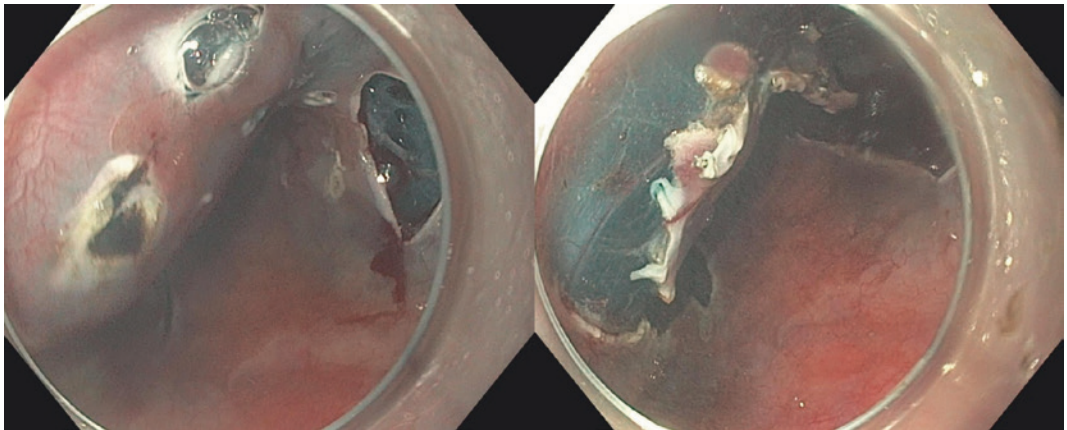


**Fig. 6** Submucosa injected with Glycerol 10% (displayed) or commercially available intravenous starch volume expander





**Fig. 7** Initiating the distal margin mucosal incision



**Fig. 8** Identifying and defining the proximal margin

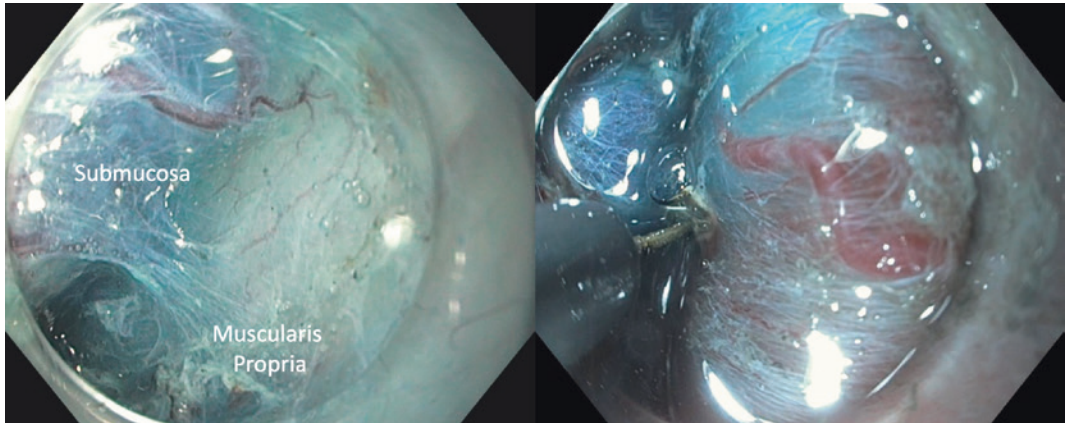
Starting at the proximal cut, we begin a submucosal tunnel to cut the distal mucosal margin (Fig. 9). The entire lesion is stripped or peeled from the muscularis propria by ESD knives in

the submucosal space. During this step, the submucosal injection needle and ESD knives are used interchangeably to lift the lesion and dissect the submucosal tissue (Fig. 10).



**Fig. 9** Sequential imaging of the submucosal tunnel during dissection from proximal to end of the tunnel





**Fig. 10** Submucosal dissection lifting mucosa/submucosal (blue) off of the muscularis propria with the distal cap and dissection submucosa-MP junction with IT2 or Dual knife

## EMR/ESD Complications

### Bleeding

A potential complication of ESD is bleeding, which can occur during the procedure or as a delayed phenomenon. Therefore, meticulous and prophylactic coagulation and prompt identification and treatment are essential for successful patient outcomes, with various tools available to do so. All ESD knives have at least a limited capacity for hemostasis on small bleeding points. The ball tip knives typically have improved hemostatic efficiency compared with standard needle knives [25]. Hybrid knives have been demonstrated to reduce the need for hemostatic devices and regular hemostasis compared with conventional knives [26]. It is important to balance the use of these coagulation devices with potential thermal injury.

For larger vessels and associated bleeds, specific hemostatic devices may be necessary. The Coagrasper (Olympus, Tokyo, Japan) is a monopolar forceps which is commonly used during ESD. Clips are not widely used for bleeding intraprocedural as they can interfere with continued dissection. They are thus reserved for uncontrolled bleeding or at the end of dissection.

### Perforation

There is also an increased risk of perforation with ESD compared to EMR. Risk estimates range from 0 to 6.9% in esophageal ESD, and 2.4 to 9.6% in gastric ESD [27, 28]. Perforation may be visualized as a definite defect during the procedure or delayed after the procedure is diagnosed clinically or on radiograph or CT demonstrating pneumoperitoneum.

The use of conservative decompression with nasogastric or nasoduodenal tubes to divert gastrointestinal fluid and nutritional support during healing post-repair is also advocated for the successful management of these complications. A chest drain may also be warranted for pneumothoraxes or defects in the pleura resulting in effusions. Small defects of approximately 1 cm can generally be treated by through the scope clips, while over-the-scope clips may be considered for holes less than 2 cm [29], and fully covered self-expanding metallic stents are always a salvage option.

### Strictures

Strictures are common after any esophageal resection, with the phenomenon more frequently encountered post esophageal ESD than other

GI tract areas. Esophageal strictures occur in patients who undergo more than a 75% circumference ESD resection of the esophagus. The multimodal treatment of strictures includes one or more sessions of endoscopic balloon dilatation which may be combined with local injection of steroids (triamcinolone, betamethasone) or implantation of a temporal esophageal stent.

### Specimen Processing and Histological Evaluation

After specimen retrieval, it is placed on the cork board and orientated. After fixation and sectioning, it is essential to critically assess pathology for (a) mucosal and deep margins, and (b) histological features predicting occult lymph node metastasis to provide a consistent and accurate diagnosis (Fig. 11).

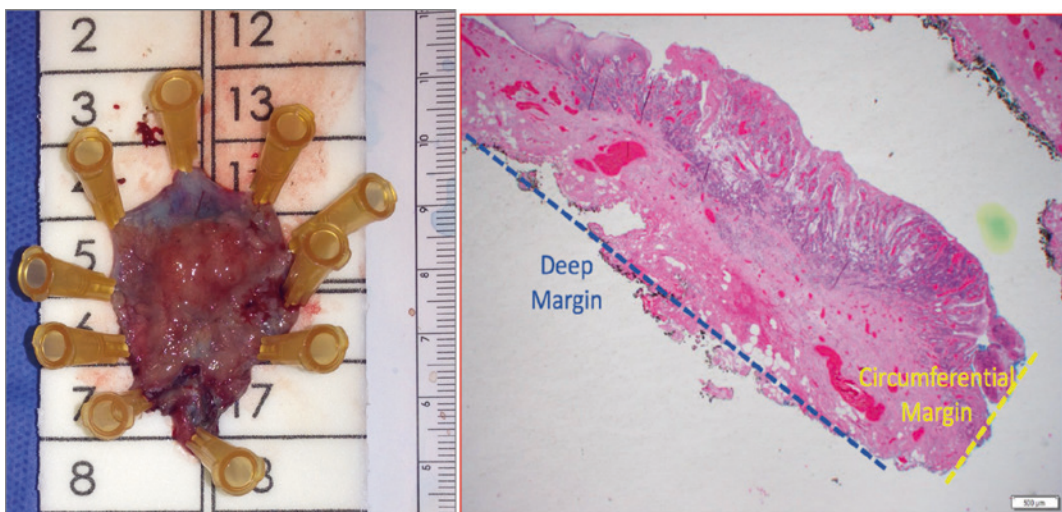
Several factors, such as maintenance of proper orientation, meticulous macroscopic examination, accurate mapping of the lesion, and appropriate morphologic diagnosis are the main concerns. It is important to mention that the maintenance of orientation is crucial in slicing, histological analysis, and reporting. The factors relevant to prognosis and further

treatment decisions, include histologic type, the size of the lesion, depth of invasion, association conditions (ulcer/scar), lymphovascular/venous invasion, and cut margin status (horizontal and vertical), which should always be carefully evaluated and reported.

After careful analysis by an appropriately experienced pathologist and discussion at the tumor board, any cases with positive margins should be considered for an esophagectomy [30]. There is no robust data available on surveillance endoscopy for such cases [31, 32]. However, mitigating circumstances such as those who are heavily co-morbid may be more appropriately managed with a watch and wait approach.

### Conclusions

Endoscopic resection of early esophageal cancer is a feasible and safe treatment strategy in appropriately selected early esophageal lesions. EMR and ESD are acceptable endoscopic treatment modalities for these early esophageal cancer lesions. ESD requires technical expertise but is associated with higher rates of en bloc, R0, and curative resections and lower recurrence



**Fig. 11** Orientating the specimen of an early esophago-gastric junctional tumor with histological analysis for assessment of deep and circumferential (mucosal) margins

rates compared to EMR. It is paramount to ensure sufficient training and institutional support for obtaining safe and high-quality resections. Ultimately, the choice of resection technique is made individually and not least depending on the circumstances of the treating center. Hybrid techniques are being evaluated to provide an optimal approach to combine the advantages of ESD and EMR.

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