Multidisciplinary Evaluation and Management of Early Stage Esophageal Cancer

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KEYWORDS

- Esophageal cancer • Endoscopic submucosal dissection
- Endoscopic mucosal resection • Esophagectomy

KEY POINTS

- Endoscopic submucosal dissection allows for en-bloc resection of early esophageal cancer, despite the size or associated fibrosis of a lesion.
- Poor differentiation, lymphovascular invasion, and deep submucosal invasion are high-risk features, and even if margin-negative endoscopic resection is achieved, additional therapy should be considered.
- For patients with high-risk pathology after endoscopic submucosal dissection, we recommend esophagectomy for medically fit patients; for nonsurgical candidates, we recommend discussing the risks and benefits of radiation and/or chemotherapy.
- One the limitations of endoscopic resection is that the at-risk organ is left in place, and patients are at risk of developing local and metachronous recurrence.
- Modern surgical and perioperative care has significantly improved morbidity and mortality after esophagectomy; despite these improvements, the risk of perioperative mortality remains approximately 3.4%.

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer related mortality worldwide, with a 5-year survival rate of approximately 20%.[1,2] There are 2 main histologic subtypes, esophageal squamous cell cancer (SCC) and esophageal adenocarcinoma (EAC). SCC is the predominant subtype worldwide, representing 87% of all

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esophageal cancer cases.[3] The incidence of EAC in the West has increased rapidly over the last few decades and it has become the predominant form of esophageal cancer in Western countries.[4–6] The majority of esophageal cancer is diagnosed at a late stage with a dismal prognosis. In contrast, early stage esophageal cancer has a more favorable prognosis.[7–9] Early stage esophageal cancer is defined as a cancer involving the mucosal or submucosal layer of the esophagus, encompassing Tis, T1a, and T1b tumors.[10] The management of early esophageal cancer requires a multidisciplinary approach, and management should be tailored to the individual patient. Management involves accurate tumor staging, treatment, and surveillance. Treatment options include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), esophagectomy, radiation therapy, brachytherapy, and chemotherapy. Although endoscopic resection has become the preferred method for management of early stage esophageal cancer, it is not feasible or sufficient in all early stage esophageal cancers. Therefore, an upfront multidisciplinary evaluation can help to orchestrate appropriate local therapy based on patient and tumor characteristics and available institutional expertise.

CLINICAL PRESENTATION

Although advanced esophageal tumors commonly present with dysphagia or bleeding, the majority of early esophageal are asymptomatic and found incidentally on upper endoscopy while investigating upper gastrointestinal symptoms, or surveillance of Barrett's esophagus (BE). Owing to the distensible nature of the esophagus, obstructive symptoms do not develop until late in the disease, and any patient referred with a reported early esophageal cancer with dysphagia should be evaluated for potentially more advanced disease versus a concomitant nonmalignant cause, such as a stricture, that can complicate local therapy.

STAGING OF EARLY ESOPHAGEAL CANCER

Stage directed therapies are used in esophageal cancer and accurate staging is paramount. Endoscopic ultrasound (EUS) examination is best for assessing the depth of tumor invasion and locoregional lymph node involvement. PET scan identifies incrementally more metastases than a computed tomography (CT) scan alone, and hybrid scanners that perform both PET and CT scan are increasingly being used.[11] The 2 techniques are complementary and the National Comprehensive Cancer Network (NCCN) recommends clinical staging with combination of integrated PET/CT scan and EUS before initiating therapy for esophageal cancer.[10]

ENDOSCOPIC ULTRASOUND EXAMINATION

Since the introduction of EUS examination in the early 1980s, it has played a vital role in esophageal cancer staging. EUS examination is able to visualize the individual wall layers of the esophagus, and is superior to cross-sectional imaging in determining the T stage and locoregional lymph involvement.[12–14] Although the benefits of EUS in advanced esophageal cancer are established, the role of EUS examination in early stage esophageal cancer is more controversial. Multiple studies have now shown that EUS examination can be unreliable in differentiating T1a from T1b tumors, raising doubts about the usefulness of EUS examination in early stage esophageal cancer. The recently published American Society for Gastrointestinal Endoscopy guideline

on screening and surveillance of BE, has recommended against the routine use of EUS examination in BE patients with early EAC (Fig. 1).[15–18]

In our experience, we see usefulness in EUS assessment of early esophageal cancer. EUS assessment of depth of invasion becomes particularly important when selecting patients for ESD. To perform ESD, there needs to be some submucosal plane to expand and dissect through, when the submucosal layer cannot be clearly delineated on EUS examination, we find it is unlikely a plane for submucosal dissection will be present. In the ESD era, larger tumors are being referred for endoscopic resection and EUS examination allows us to rule out invasion of the muscularis propria and local lymph node involvement before endoscopic resection is undertaken.

PET/COMPUTED TOMOGRAPHY SCANS

Although the PET/CT scan is a staple in staging advanced esophageal cancer, its role in early esophageal cancer is less clear. Two studies have shown that PET/CT scan does not reliably detect early esophageal cancer and is unable to differentiate T1a from T1b tumors.[19,20] In addition, and of more concern, in 1 study on patients with early esophageal cancer undergoing PET/CT scan, all 18 fluorodeoxyglucose-avid nodes seen were false positives, with biopsies showing no metastatic disease.[19] In clinical practice, this could lead to overtreatment of early esophageal cancer. These limitations have to be weighed against the limitations of performing PET/CT scan after endoscopic resection, where the inflammation from the postendoscopic resection site limits PET/CT scan's diagnostic usefulness. This can lead to diagnostic uncertainty in patients after endoscopic resection with a high-risk pathology who require additional treatment. In our practice, when performing staging endoscopic resection for bulkier esophageal tumors that may undergo surgery if a high-risk pathology is found, we perform a PET scan before ESD, while being cognizant of its limitations.

ENDOSCOPIC TREATMENT OPTIONS

Risk of Lymph Node Metastasis in Early Esophageal Cancer

The main difference between the endoscopic and surgical resection of a tumor is the absence of lymph node dissection with endoscopic techniques. Thus, endoscopic resection should only be considered in tumors with a very low risk of lymph node

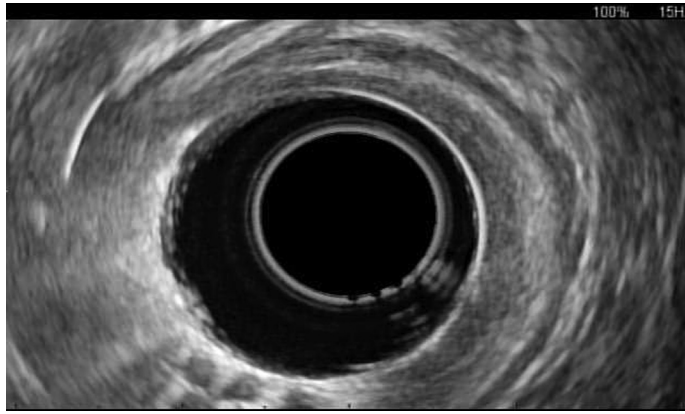

Fig. 1. Radial EUS imaging suggestive of T1b cancer, final resection pathology T1a, highlighting the limitations of EUS examination in early esophageal cancer.

metastasis, or an estimated risk that is lower than the acceptable morbidity and mortality of esophagectomy. The assessment of risk of lymph node metastases is based on the depth of tumor invasion, the presence of poorly differentiated pathology, and/or the presence of lymphovascular invasion (LVI). The esophageal wall is unique in the gastrointestinal tract, in that the lymphatics penetrate through the muscularis mucosa and are present in the lamina propria, giving even T1a esophageal cancer a theoretic risk of lymph node metastasis (**Fig. 2**).[21] In BE-related neoplasia, 1 systemic review showed mucosal-based tumors had a risk of lymph node metastasis of 1% to 2%.[22] As EAC invades deeper in the submucosa, the risk of lymph node metastasis increases. In a surgical series involving primarily EAC, the risk of lymph node metastasis in tumors involving SM1 (superficial submucosal invasion) was 7.5%, SM2 (middle third of SM layer) was 10%, and SM3 (deep submucosal invasion) was 45%.[21] In surgical series of esophageal SCC, M1 (intraepithelial) and M2 (invading the lamina propria) tumors were not associated with lymph node metastasis, M3 (reaching or infiltrating the muscularis mucosae) tumors had a risk of lymph node metastasis of 8% to 18%, tumors with submucosal invasion of less than 200 microns had a risk of lymph node metastasis risk of 11% to 53%, and tumors with SM invasion of more than 200 microns were associated with a lymph node metastasis risk of 30% to 54%.[23–26] Deciding between endoscopic and surgical resection of a tumor is done by weighing the risk of lymph node metastasis versus the mortality and morbidity associated with esophagectomy in a patient.

Endoscopic Mucosal Resection

The first endoscopic polypectomy was performed in Japan in 1974, and since then there have been several advances in endoscopic resection of gastrointestinal tract lesions. EMR is one of the most widely used and successful techniques. It involves raising a lesion with either injection of fluid or suction then removing it with a snare.[27] In the esophagus, the most commonly used EMR techniques are the band ligation

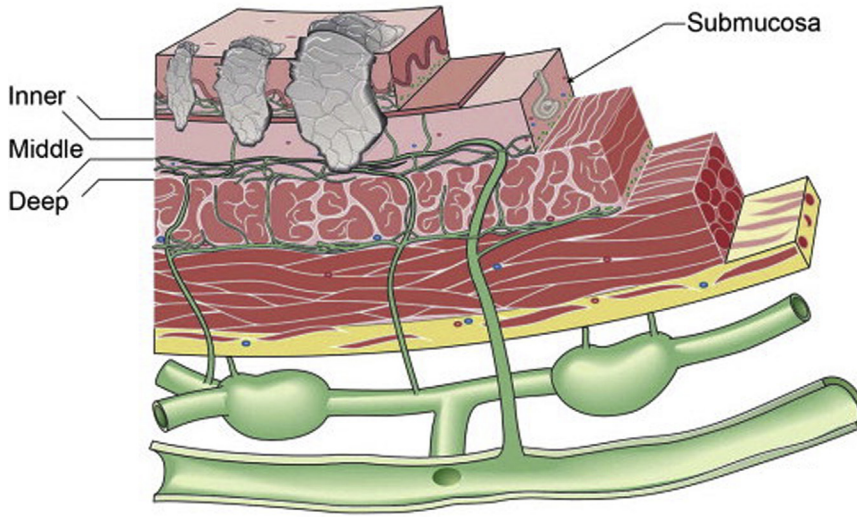

Fig. 2. Wall layers and lymphatics of the esophageal wall. (*From* Raja S, Rice TW, Goldblum JR, et al. Esophageal submucosa: the watershed for esophageal cancer. The Journal of thoracic and cardiovascular surgery. 2011;142(6):1403-1411 e1401.)

method and the cap snare method. A randomized trial between the techniques showed no significant differences in area of the resected specimens, efficacy or safety.[28] Band ligation EMR is more commonly used owing to its lower cost and shorter procedure time.[29]

Among the first investigators to describe EMR in EAC were Ell and colleagues,[30] who reported EMR results in 64 patients; 61 with EAC and 3 with high-grade dysplasia. In the low-risk tumor group, based on tumor size, macroscopic appearance, and tumor grade, 49 EMR procedures were performed and achieved complete resection in 34 of 35 patients, with recurrence noted in 6 of 35 patients (17%) during an average follow-up of 12 $\pm$ 7 months. In the high-risk tumor group, 71 EMR procedures were performed and achieved complete resection in 13 of 22 patients, with recurrence noted in 3 of 22 patients (14%) during an average follow-up of 10 $\pm$ 8 months. A hallmark study that secured the role of EMR in EAC, was performed by Pech and colleagues,[31] that evaluated EMR in 1000 patients with T1a EAC tumors. A total of 2687 EMR procedures were performed and achieved complete remission in 963 of 1000 patients (96.3%) with T1a EAC, with recurrence noted in 140 of 963 (14.5%) patients during a median follow-up of 26.5 months, with 115 of 140 recurrences (82%) successfully treated endoscopically. The long-term complete remission rate was 93.8% after a mean follow-up period of 56.6 $\pm$ 33.4 months.

Esophageal EMR has a low risk of adverse events, including bleeding (1.2%), stricture formation (1.0%), and perforation (with rates varying from 0.2% to 1.3%). The safety profile, technical ease, and success rate of EMR has led to its widespread use in the treatment of early esophageal cancer.

EMR is not without its flaws. It can only achieve en bloc resection of lesions less than 15 to 20 mm; larger lesions require piecemeal resection, which is associated with a higher risk of recurrence.[32,33] This finding was seen in the studies from Pech and colleagues[31] and Ell and colleagues,[30] as discussed elsewhere in this article, where numerous EMR procedures were sometimes required to achieve complete resection, and there was a high rate of recurrence noted on follow-up.

Endoscopic Submucosal Dissection

ESD was developed in Japan in the 1990s to overcome the limitations of EMR. ESD is an advanced endoscopic technique with precise control of both lateral and deep margin dissection allowing for en bloc resection of a lesion despite its size or associated fibrosis (**Fig. 3**).[34] Achieving en bloc resection results in higher curative resection rates, lower recurrence rates, and allows for precise histopathologic analysis. The basic steps to perform ESD are shown in **Fig. 4** and include:

- Marking the periphery of the lesion with cautery marks
- Expanding the submucosal layer with the injection of a viscous solution
- Performing a circumferential mucosal incision around the lesion with an electrocautery knife
- Dissecting the submucosal layer beneath the lesion with an electrocautery knife releasing the lesion in one en bloc piece

Although the steps of performing ESD are relatively straightforward, ESD is technically challenging to perform, has a flat (difficult) learning curve, and can be time consuming, especially while learning the procedure. A study in a porcine model from our group showed with expert video-based supervision 2 trainees reached technical competency in ESD within a porcine model after 25 procedures. Although initial human cases performed after this training were technically successful, they had long procedure times, highlighting the challenges of learning ESD.[35] Performing ESD in the

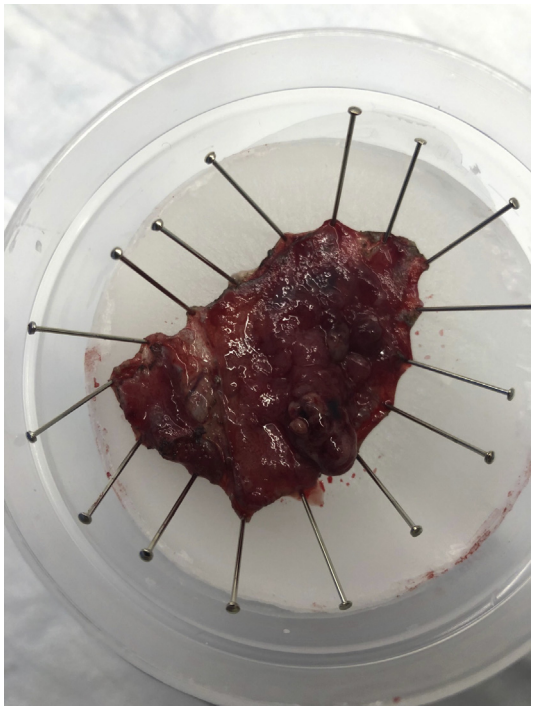

Fig. 3. En bloc ESD resection specimen pinned to wax.

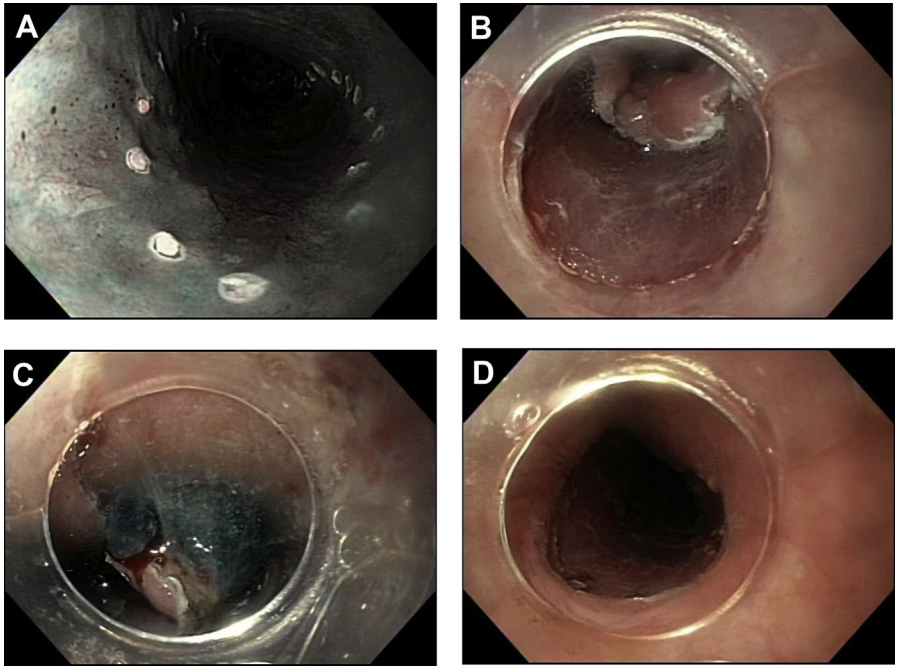

Fig. 4. Steps of ESD resection. (*A*) Marking, (*B*) mucosal incision, and (*C*) submucosal dissection. (*D*) Completed resection.

esophagus has its unique challenges. (1) The specimen retracts distally making orientation and traction difficult to maintain. (2) The thin muscularis propria of the esophageal wall increases the risk of perforation. (3) Finally, the narrow esophageal lumen limits scope maneuverability and gravity counter-traction.[36] Innovations in technique have helped to address the unique challenges of performing ESD in the esophagus. Yoshida and colleagues[37] showed in a randomized multicenter trial that clip line traction assisted ESD resulted in significantly shorter procedure time than conventional ESD (44.5 minutes vs 60.5 minutes, respectively; $P<.001$). Our group recently evaluated a new esophageal ESD technique—an insulated-tip knife tunneling technique with C-shaped incision—and achieved excellent technical results with an en bloc resection rate of 97.6%, R0 resection rate of 88.1%, and 0% perforations.[38]

The majority of the initial literature on ESD originated from Japan, where ESD was developed, but primarily focused on SCC, because EAC is rare in Japan. More recently, major studies have been published in the West evaluating ESD in BE-related neoplasia. A multicenter retrospective study from 5 academic tertiary referral centers in the United States that evaluated 46 patients with BE-related neoplasia (high-grade dysplasia and EAC) who underwent ESD, reported en bloc and curative resection rates of 96% and 70%, respectively, with 1 perforation that was managed endoscopically.[39] The European Barrett's Endoscopic Submucosal Dissection Trial performed a retrospective analysis of 143 ESDs for BE-related neoplasia in 3 tertiary referral centers; the en bloc resection rate was 90.8%, R0 resection rate of 79%, and 0 perforations.[40] It should be noted that these studies were performed during the introductory phase of ESD in the West and likely reflected the early learning period of the procedure. Despite this factor, the results are respectable and show the efficacy and safety of esophageal ESD in the West. This finding was further confirmed in a meta-analysis of 11 studies including 524 BE-related neoplasia lesions that underwent ESD, the en bloc resection rate was 92.9%, the R0 resection rate was 74.5%, the perforation rate was 1.5%, and the bleeding rate was 1.7%.[41] The reported benefits of ESD over EMR also include more precise histopathologic analysis, and this was evaluated in a recent study by Podboy and colleagues[42] (**Fig. 5**). They evaluated 31 EMR and 20 ESD BE-related neoplasia specimens and found more equivocal lateral

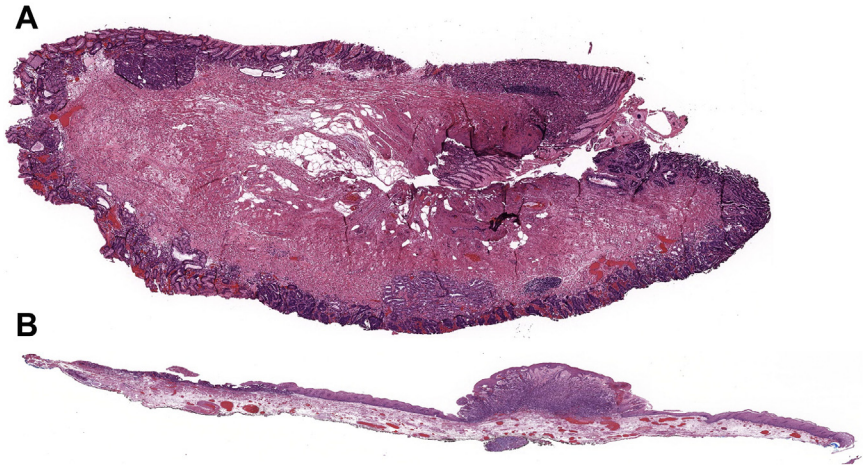

Fig. 5. Showing the quality difference of (*A*). EMR specimen and (*B*) ESD specimen.

margins (EMR 13/31 [41.9%] vs ESD 1/20 [5%]; $P<.05$) and vertical margins (EMR 13/31 [41.9%] vs ESD 0/20 [0%]; $P<.05$) in the EMR group. This process led to diagnostic uncertainty in 13 EMR patients, with 4 of the 13 undergoing esophagectomy owing to unclear diagnosis.

The results of the only Western randomized controlled trial on ESD versus EMR has questioned the role of ESD in BE-related neoplasia.[43] They evaluated 40 patient with BE-related neoplasia, 20 randomized to ESD, and 20 to EMR. Although the ESD arm had higher en bloc (ESD 20/20 [100%] vs EMR 3/20 [15%]) resection rates, and higher R0 resection rates (ESD 10/17 [58.8%] vs EMR 2/17 [11%]), it also had an alarmingly higher perforation rate (ESD 2/20 [10%] vs EMR 0/20 [0%]). In addition, there was no difference in complete remission from neoplasia at 3 months (ESD 15/16 vs EMR 16/17). The authors concluded ESD does not seem to offer clinical advantages over EMR, was more time consuming, and may cause more severe adverse events. The limitations of the study are that the outcomes in the ESD arm are significantly worse than what has been presented in numerous other studies on esophageal ESD, and the study was neither powered or had appropriate length of follow-up to properly assess for complete remission or recurrence rates. In contrast, the preliminary results of our retrospective multicenter study of ESD versus EMR for BE-related neoplasia showed not only that ESD had higher en bloc (ESD 96% vs EMR 33%; $P<.0001$) and R0 resection rates (ESD 76% vs EMR 54%; $P = .0009$), but that ESD had lower recurrence rates (ESD 3% vs EMR 39%; $P<.0001$) and required significantly fewer endoscopic resection procedures (ESD 0 [0,2] versus EMR 0.5 [0,8]; $P<.001$) to acquire complete remission than EMR.[44] These study results suggest ESD results in more definitive treatment of BE-related neoplasia than EMR.

INDICATIONS FOR ENDOSCOPIC SUBMUCOSAL DISSECTION

Barrett's-Related Neoplasia

As outlined in the European Society of Gastrointestinal Endoscopy ESD guideline and American Gastroenterological Association ESD practice update, ESD should be considered in superficial visible lesions with EAC or high-grade dysplasia in BE, when[45,46]

- Lesion size is greater 15 mm
- There are poorly lifting lesions
- Lesions are at risk of submucosal invasion

ESD should be considered in lesions greater than 15 mm, because EMR may not be able to achieve en bloc resection. Poorly lifting lesions with fibrosis may not be amenable to complete resection with EMR, but ESD is able to dissect through a fibrotic submucosal layer and remove these lesions en bloc, although this procedure can be technically challenging. In lesions at risk for submucosal invasion, ESD allows for precise histopathologic analysis and precise measurement of depth of submucosal invasion, differentiating superficial from deep submucosal invasion. Lesions less than 15 mm, without features suggestive of submucosal involvement or fibrosis, should be treated with EMR, because it performs well in this group of lesions.

Squamous Cell Cancer and Dysplasia

In SCC and dysplasia, ESD should be considered in[45] superficial lesions greater than 10 mm in size. The reason for the smaller lesion size recommendation in SCC than EAC is that, in a meta-analysis of 12 studies, ESD had higher en-bloc resection rates than EMR even in lesions 10 mm in size.[47]

POSTENDOSCOPIC RESECTION PATHOLOGIC RESULTS

The European Society of Gastrointestinal Endoscopy ESD guidelines define histologic outcomes as discussed in this section.[45]

Esophageal Adenocarcinoma

Curative criteria
- En bloc R0 resection of mucosal EAC well-differentiated or moderately differentiated tumors without LVI

Low-risk lesion
- En bloc R0 resection of sm1 lesions ($\leq$500 μm) with well-differentiated or moderately differentiated pathology and no LVI.

Noncurative lesion
- Lesions with LVI, poorly differentiated tumors, submucosal invasion greater than 500 μm, or positive vertical margins.

Squamous Cell Cancer

Curative criteria
- En bloc R0 resection of superficial well-differentiated SCC with histology no more advanced than m2 SCC, with no LVI

Low-risk lesion
- En bloc R0 resection of well differentiated m3/sm1 ($\leq$200 μm) without LVI

Noncurative lesions
- Lesions with greater than 200 μm submucosal invasion, poorly differentiated tumor, LVI, or positive vertical margin.

Patients with tumors within the curative criteria should undergo surveillance. Patient with low-risk tumors should undergo multidisciplinary discussion to weigh the risk of lymph node metastasis with surveillance versus the risks of morbidity and mortality with surgery. Surgery is recommended in patients with noncurative resections. If the patient is not a surgical candidate, other adjuvant treatment like chemotherapy and/or radiation should be considered.

SURGERY FOR EARLY ESOPHAGEAL CANCER

Until this decade, the treatment for all esophageal cancer was limited to some combination of esophagectomy, chemotherapy and radiation. Even the treatment of BE, a premalignant condition, involved surgical resection. Although the treatment of locally advanced esophageal cancer in the modern era is relegated to these aggressive modalities, earlier cancers are at times treated with less intensive therapies.

Lymph node metastasis, or the risk of spread, seems to be the watershed that separates aggressive disease requiring aggressive therapy and localized disease amenable to local therapy. With the unchanged goal of potential cure, lesser or local therapies are aimed only at esophageal cancers that are localized. Early attempts to define early cancers had been hindered by confusing early cancers with superficial cancers. Traditionally, tumors limited to the mucosa (T1a) and submucosa (T1b) were considered superficial cancers based on the limited depth of invasion. However, we have since identified, as previously noted, T1b cancers as having around a 25% risk of lymph node metastasis, making it an advanced stage.[21] In contrast, T1a cancers can have a less than 1% risk of local-regional spread making a perfect candidate of local therapies such as EMR or ESD.[7,48]

Within superficial cancers, recent works have been aimed at risk stratification within superficial cancers. Typically, poorly differentiated cancers with lymphatic invasion are considered high risk of local-regional metastasis.[21] As such, T1a cancers with high risk factors may be considered for radical surgery and T1b cancers without high risk features can be considered for local therapy.[22,49]

Local therapy for clinical mucosal (cT1a) cancers has quickly replaced esophagectomy as the treatment of choice. For cT1a cancers, esophagectomy is limited to medically fit patients with multifocal disease, patients with positive margins, and those patients with recurrent disease after local therapy.

Esophagectomy for patients with cT1a cancers is indeed a subject of debate. The dearth of information about the true risk of lymph node metastasis in this clinical entity is the underlying cause of this debate. At our institution, surgery is offered to patients whose T1a cancers show high-risk features on pathology after endoscopic resection after discussion in a multidisciplinary conference and a thorough evaluation for fitness to undergo surgery. The role of esophagectomy is accepted in clinical submucosal cancers (cT1b) cancers and is the treatment of choice for this stage of disease in medically fit patients.

Contemporary surgical and perioperative care has significantly improved morbidity and mortality after esophagectomy. Despite these improvement the risk of perioperative mortality remains at approximately 3.4%.[50] As such, when the risk of regional spread is between 3% and 4%, it can be difficult to justify a therapy that carries a 3% to 4% mortality rate. Furthermore, this is a procedure that can carry a 33% perioperative major morbidity. Long-term sequelae such as regurgitation, aspiration, and dumping syndrome are also not inconsequential. Therefore, when clinically appropriate, an organ-preserving strategy should be the preferred approach.

CHEMOTHERAPY AND RADIATION IN EARLY ESOPHAGEAL CANCER

Although the optimal management of early esophageal cancer is primarily endoscopic or surgical resection, there is a role for chemotherapy and radiation in patients who are not candidates for resection or those who choose nonresection therapy. The majority of the data come from nonrandomized studies conducted in Japan that included older patients with esophageal squamous cell carcinoma and multiple comorbidities. The data for chemoradiation for patients with early EAC are lacking.

Chemoradiation

One study enrolled 320 patients between 2001 and 2011 with T1bN0M0 esophageal squamous cell carcinoma who underwent either esophagectomy (102 patients) or definitive chemoradiation (dCRT) with 5-fluoracil and cisplatin combined with 60 Gy radiation in 30 fractions (218 patients). It showed superior 5-year overall survival with esophagectomy compared with dCRT (88.2% vs 80.2%; $P = .004$).[51] The Japan Clinical Oncology Group (JCOG)0502 trial also prospectively compared esophagectomy with dCRT in patients with stage T1bN0M0 esophageal squamous cell carcinoma, although in a nonrandomized fashion. The study included 368 evaluable patients, most of whom were older men. Of the 209 patients who underwent esophagectomy versus 159 patients who received dCRT (5-fluoracil and cisplatin combined with 60 Gy radiation in 30 fractions), overall survival was similar at 3 years (94.7% vs 93.1%) and 5 years (86.5% vs 85.5%) (adjusted hazard ratio, 1.05; 95% CI, 0.67–1.64). Two patients who underwent esophagectomy died; there were no deaths in the dCRT group.[52] Several other smaller studies, including the JCOG9708 trial, have shown that esophagectomy leads to improved local recurrence rates and better disease-free

survival, but overall survival is comparable between esophagectomy and dCRT.[53–57] Of note, a radiation dose of 50.4 Gy seems to be noninferior and less toxic for patients with noncervical esophagus cancer based on multiple studies and is the recommended dose by the NCCN.[10,58–60]

Chemoradiation can also be used after ESD for nonsurgical candidates, particularly for patients with high-risk features such as LVI, poorly differentiated histology, a positive margin, and tumors greater than 2 cm in size.[10] The JCOG0508 study examined the role of chemoradiation after ESD in 2 groups: patients with pT1b tumors with a negative resection margin or pT1a tumors with LVI (group B) or with a positive vertical resection margin (group C). Group A patients had pT1a tumors with a negative resection margin and no LVI and were observed. They found the 3-year overall survival rate was 90.7% for group B patients and 92.6% for all included patients. Toxicities overall were expected and manageable, with only 1 patient experiencing a grade 3 esophageal stricture and 1 patient experiencing late grade 4 cardiac ischemia. Of note, 7 patients underwent salvage surgery for local recurrence.[61] Multiple other series support these findings, although prospective, randomized studies are lacking.[62–64] However, the data consistently show that esophagectomy offers significantly improved disease-free survival and local control over chemoradiation and should remain the standard of care for surgical candidates.[52,62–65] Radiotherapy alone after ESD may also improve local control, particularly in those with resection defects involving more than 75% of the esophageal circumference.[66]

Radiation Therapy

Radiotherapy alone is also a reasonable approach for older patients who are not candidates for surgery or endoscopic resection and would not tolerate concurrent chemotherapy. One retrospective study that compared 29 patients who underwent esophagectomy with 38 patients who received definitive radiation (of note 14 received brachytherapy and 15 received concurrent chemotherapy) found that the 3-year overall survival was similar between the groups, but 3-year relapse-free survival was significantly better with esophagectomy. For patients with T1a tumors, the 3-year overall survival and relapse-free survival in the surgery group were 83% and 83%, respectively, versus 77.8% and 55.6%, respectively, in the radiation group. For patients with T1b tumors, the 3-year overall survival and relapse-free survival in the surgery group were 76.2% and 73%, respectively, versus 73.1% and 52.3%, respectively, in the radiation group ($P = .0219$).[64] Data from other small series support these findings; however, their retrospective designs and lack of standardization in radiation dose and use of concurrent chemotherapy and/or brachytherapy make it challenging to draw definitive conclusions.[18–20] Another propensity score matching study of 185 patients age 80 or older treated with either concurrent chemoradiation or radiation alone showed there was no difference in the 3-year overall survival, cause-specific survival, or progression-free survival between the groups, suggesting that chemotherapy can safely be omitted in this elderly population.[67]

Brachytherapy

The role for brachytherapy in early-stage esophageal cancer remains unclear. The data for brachytherapy alone are limited, with 1 series of 13 patients treated with high dose rate brachytherapy showing a high initial treatment failure rate of 39%.[68] One study of 59 patients with T1 esophageal cancers evaluated the benefit of brachytherapy in addition to external beam radiation therapy (EBRT) compared with EBRT alone. There was no improvement in the response rate and although the locoregional recurrence rate was numerically better in the EBRT + brachytherapy group compared

with EBRT alone (17% vs 35%), this difference did not reach statistical significance ($P = .2$). The 5-year cause-specific survival rate was improved in the EBRT + brachytherapy group compared with the EBRT alone group (86% vs 62%).[69] Late complications including esophageal fistula can be a major concern with brachytherapy.[69–71] For example, the Radiation Therapy Oncology Group (RTOG) 9207 study showed a 12% incidence of esophageal fistula, a complication that seems to be exacerbated when concurrent chemotherapy is used.[70] Overall, brachytherapy likely has a limited role in this setting that remains poorly defined.

We use dCRT for patients with T1b tumors that are not amenable to surgery or endoscopic resection. For patients with high-risk pathology after ESD (LVI, poorly differentiated histology, positive margin, and tumors >2 cm in size), we recommend esophagectomy for those who are surgical candidates. For nonsurgical candidates, chemoradiation is an appropriate alternative. Radiation alone is also a reasonable approach for older patients with multiple comorbidities to achieve local control and prevent local complications.

SURVEILLANCE

One of the limitations of organ preserving endoscopic resection for esophageal cancer is that the at-risk tissue remains in situ. This remnant might be in the form of the adjacent mucosa that may be subject to a field defect or in the form of regional lymph nodes that can harbor undetected spread. As such, there is a risk of developing local as well as regional recurrence and surveillance should address both. There is a lack of evidence to define the most effective follow-up after endoscopic resection of esophageal cancer, and Western gastroenterology guidelines have not provided specific recommendations. It is clear that, after ESD resection of EAC, patients should undergo radiofrequency ablation of any residual BE to decrease the risk of developing metachronous cancer. We wait 3 months for the ESD scar to heal, before starting radiofrequency ablation of BE. Regarding surveillance intervals, for T1a cancers, the NCCN guidelines recommend upper endoscopy surveillance be performed every 3 months for the first year, then every 6 months for the second year, and then annually indefinitely; imaging studies are not recommended.[10] For T1b cancers, the NCCN recommends upper endoscopy every 3 months for the first year, every 4 to 6 months for the second year, then annually indefinitely. They also state that EUS examination may be considered in conjunction with EGD, and CT chest/abdomen scans with contrast may be consider every 12 months for 3 years.[10] It should be stated, however, that the NCCN does not give any references to support these recommendation. The recently published Japan Gastroenterological Endoscopy Society ESD/EMR guidelines for esophageal cancer have strongly recommended patients undergo endoscopic examination at least once a year after endoscopic resection of SCC. For patients who underwent endoscopic resection of SCC with muscularis mucosa or submucosal involvement, they weakly recommend a CT scan at least once a year.[72] They make no specific recommendations in regard to EAC, given its rarity in Japan.

In our practice, we follow the NCCN recommended guidelines on upper endoscopy surveillance for low-risk small esophageal cancer lesions that undergo EMR resection. Because ESD resection of larger and more aggressive EAC tumors is a newer phenomenon, and there are no established data yet to help guide surveillance, we proceed cautiously with close observation. We perform an upper endoscopy with EUS examination every 6 months for the first 2 years, then yearly indefinitely. For higher risk tumors that do not undergo surgical resection, we perform even closer

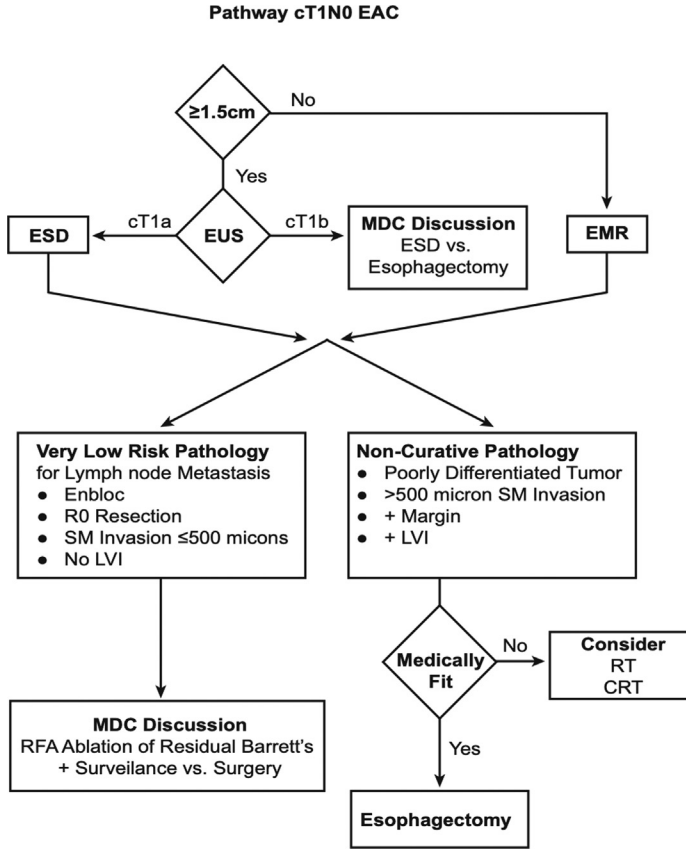

Fig. 6. Proposed pathway for management of clinically staged T1 N0 EAC. CRT, chemoradiation therapy; MDC, multidisciplinary committee; RT, radiation therapy; SM, submucosal.

surveillance, every 3 months for the first year. We also perform CT scans annually for 4 to 5 years based on our own data showing recurrences after esophagectomy for pT1aN0M0 cancers for can happen in the first 4 years.[7]

SUMMARY

The management paradigms for early esophageal cancer continue to evolve in favor of organ-preserving local therapies. However, early stage esophageal cancers can be a heterogeneous group that is best managed through a multidisciplinary approach to diagnosis, management and therapy (**Fig. 6**). As such, achieving optimal outcomes for patients with these cancers requires aligning the cancer characteristics with patient characteristics and institutional expertise.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

2. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019;69(5):363–85.
3. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64(3):381–7.
4. Abrams JA, Sharaiha RZ, Gonsalves L, et al. Dating the rise of esophageal adenocarcinoma: analysis of Connecticut Tumor Registry data, 1940-2007. Cancer Epidemiol Biomarkers Prev 2011. https://doi.org/10.1158/1055-9965.EPI-10-0802.
5. Trivers KF, Sabatino SA, Stewart SL. Trends in esophageal cancer incidence by histology, United States, 1998–2003. Int J Cancer 2008;123(6):1422–8.
6. Devesa SS, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83(10):2049–53.
7. Li Z, Rice TW, Liu X, et al. Intramucosal esophageal adenocarcinoma: primum non nocere. J Thorac Cardiovasc Surg 2013;145(6):1519–24, 1524.e1-3.
8. Zhang Y, Ding H, Chen T, et al. Outcomes of endoscopic submucosal dissection vs esophagectomy for T1 esophageal squamous cell carcinoma in a real-world cohort. Clin Gastroenterol Hepatol 2019;17(1):73–81.e3.
9. Wani S, Drahos J, Cook MB, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. Available at: http://www.seer.cancer.gov. Accessed March 30, 2020.
10. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers, Version 2.2019. JNCCN J Natl Compr Cancer Netw 2019;17(7):855–83.
11. Van Vliet EPM, Heijenbrok-Kal MH, Hunink MGM, et al. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer 2008;98(3):547–57.
12. Kimmey MB, Martin RW, Haggitt RC, et al. Histologic correlates of gastrointestinal ultrasound images. Gastroenterology 1989;96(2 Pt 1):433–41.
13. Takizawa K, Matsuda T, Kozu T, et al. Lymph node staging in esophageal squamous cell carcinoma: a comparative study of endoscopic ultrasonography versus computed tomography. J Gastroenterol Hepatol 2009;24(10):1687–91.
14. Akdamar MK, Cerfolio RJ, Ojha B, et al. A prospective comparison of computerized tomography(CT), 18 fluoro-deoxyglucose positron emission tomography(FDG-PED) and endoscopic ultrasonography (EUS) in the preoperative evaluation of potentially operable esophageal cancer patients. Am J Gastroenterol 2003;98:S5–6.
15. May A, Günter E, Roth F, et al. Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 2004;53(5):634–40.
16. Thomas T, Gilbert D, Kaye PV, et al. High-resolution endoscopy and endoscopic ultrasound for evaluation of early neoplasia in Barrett's esophagus. Surg Endosc 2010;24(5):1110–6.
17. Rampado S, Bocus P, Battaglia G, et al. Endoscopic ultrasound: accuracy in staging superficial carcinomas of the esophagus. Ann Thorac Surg 2008;85(1):251–6.
18. ASGE Standards of Practice Committee, Qumseya B, Sultan S, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc 2019;90(3):335–59.e2.
19. Betancourt Cuellar SL, Carter BW, Macapinlac HA, et al. Clinical staging of patients with early esophageal adenocarcinoma: does FDG-PET/CT have a role? J Thorac Oncol 2014;9(8):1202–6.

20. Little SG, Rice TW, Bybel B, et al. Is FDG-PET indicated for superficial esophageal cancer? Eur J Cardiothorac Surg 2007;31(5):792–7.
21. Raja S, Rice TW, Goldblum JR, et al. Esophageal submucosa: the watershed for esophageal cancer. J Thorac Cardiovasc Surg 2011;142(6):1403–11.e1.
22. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol 2012;107(6):850–62 [quiz: 863].
23. Tajima Y, Nakanishi Y, Tachimori Y, et al. Significance of involvement by squamous cell carcinoma of the ducts of esophageal submucosal glands. Analysis of 201 surgically resected superficial squamous cell carcinomas. Cancer 2000; 89(2):248–54.
24. Yachida T, Oda I, Abe S, et al. Risk of lymph node metastasis in patients with the superficial spreading type of esophageal squamous cell carcinoma. Digestion 2019. https://doi.org/10.1159/000499017.
25. Natsugoe S, Baba M, Yoshinaka H, et al. Mucosal squamous cell carcinoma of the esophagus: a clinicopathologic study of 30 cases. Oncology 1998;55(3): 235–41.
26. Bollschweiler E, Baldus SE, Schröder W, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 2006;38(2):149–56.
27. Mejía-Pérez LK, Abe S, Stevens T, et al. A minimally invasive treatment for early GI cancers. Cleve Clin J Med 2017;84(9):707–17.
28. May A, Gossner L, Behrens A, et al. A prospective randomized trial of two different endoscopic resection techniques for early stage cancer of the esophagus. Gastrointest Endosc 2003;58(2):167–75.
29. Pouw RE, van Vilsteren FGI, Peters FP, et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. Gastrointest Endosc 2011;74(1):35–43.
30. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000;118:670–7.
31. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146(3):652–60.e1.
32. Katada C, Muto M, Manabe T, et al. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005;61(2):219–25.
33. Tanabe S, Koizumi W, Higuchi K, et al. Clinical outcomes of endoscopic oblique aspiration mucosectomy for superficial esophageal cancer. Gastrointest Endosc 2008;67(6):814–20.
34. Bhatt A, Abe S, Kumaravel A, et al. Indications and Techniques for Endoscopic Submucosal Dissection. Am J Gastroenterol 2015;110(6):784–91.
35. Bhatt A, Abe S, Kumaravel A, et al. Video-based supervision for training of endoscopic submucosal dissection. Endoscopy 2016;48(8). https://doi.org/10.1055/s-0042-106722.
36. Abe S, Oda I, Suzuki H, et al. Insulated tip knife tunneling technique with clip line traction for safe endoscopic submucosal dissection of large circumferential esophageal cancer. VideoGIE 2017;2(12):342–5.
37. Yoshida M, Takizawa K, Nonaka S, et al. Conventional versus traction-assisted endoscopic submucosal dissection for large esophageal cancers: a multicenter, randomized controlled trial (with video). Gastrointest Endosc 2020;91(1): 55–65.e2.

38. Mehta N, Abushahin A, Sarvepalli S, et al. Tu1189 insulated-tip knife tunneling technique for esophageal endoscopic submucosal dissection: an initial western experience. Gastrointest Endosc 2018;87(6):AB561.
39. Yang D, Coman RM, Kahaleh M, et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Gastrointest Endosc 2017;86(4):600–7.
40. Subramaniam S, Chedgy F, Longcroft-Wheaton G, et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc 2017;86(4):608–18.
41. Yang D, Zou F, Xiong S, et al. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc 2018;87(6):1383–93.
42. Podboy A, Kolahi KS, Friedland S, et al. Endoscopic submucosal dissection is associated with less pathologic uncertainty than endoscopic mucosal resection in diagnosing and staging Barrett's-related neoplasia. Dig Endosc 2020;32(3):346–54.
43. Terheggen G, Horn EM, Vieth M, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut 2017;66(5):783–93.
44. Mejia Perez LK, Alaber OA, Jawaid S, et al. Endoscopic submucosal dissection vs. endoscopic mucosal resection for treatment of Barrett's related superficial esophageal neoplasia. Am J Gastroenterol 2019;114(Supplement):S209.
45. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47:829–54.
46. Draganov PV, Wang AY, Othman MO, et al. AGA institute clinical practice update: endoscopic submucosal dissection in the United States. Clin Gastroenterol Hepatol 2019;17(1):16–25.e1.
47. Cao Y, Liao C, Tan A, et al. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 2009;41(9):751–7.
48. Ancona E, Rampado S, Cassaro M, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol 2008;15(11):3278–88.
49. Manner H, May A, Pech O, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008;103(10):2589–97.
50. Raymond DP, Seder CW, Wright CD, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a society of thoracic surgeons general thoracic surgery database risk adjustment model. Ann Thorac Surg 2016;102(1):207–14.
51. Zhao H, Koyanagi K, Kato K, et al. Comparison of long-term outcomes between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal squamous cell carcinoma. J Thorac Dis 2019;11(11):4654–62.
52. Kato K, Igaki H, Ito Y, et al. Parallel-group controlled trial of esophagectomy versus chemoradiotherapy in patients with clinical stage I esophageal carcinoma (JCOG0502). J Clin Oncol 2019;37(4_suppl):7.
53. Jethwa KR, Deng W, Gonuguntla K, et al. Multi-Institutional Evaluation of Curative Intent Chemoradiotherapy for Patients with Clinical T1N0 Esophageal Adenocarcinoma. Int J Radiat Oncol 2019;105(1):E186–7.

54. Kato H, Sato A, Fukuda H, et al. A Phase II Trial of Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 2009;39(10):638–43.
55. Motoori M, Yano M, Ishihara R, et al. Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. Ann Surg Oncol 2012;19(7):2135–41.
56. Koide Y, Kodaira T, Tachibana H, et al. Clinical outcome of definitive radiation therapy for superficial esophageal cancer. Jpn J Clin Oncol 2017;47(5):393–400.
57. Yamamoto S, Ishihara R, Motoori M, et al. Comparison between definitive chemoradiotherapy and esophagectomy in patients with clinical stage I esophageal squamous cell carcinoma. Am J Gastroenterol 2011;106(6):1048–54.
58. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20(5):1167–74.
59. Nemoto K, Kawashiro S, Toh Y, et al. Comparison of the effects of radiotherapy doses of 50.4 Gy and 60 Gy on outcomes of chemoradiotherapy for thoracic esophageal cancer: subgroup analysis based on the Comprehensive Registry of Esophageal Cancer in Japan from 2009 to 2011 by the Japan Esophageal Society. Esophagus 2020;17(2):122–6.
60. Wang S, Liao Z, Chen Y, et al. Esophageal cancer located at the neck and upper thorax treated with concurrent chemoradiation: a single-institution experience. J Thorac Oncol 2006;1(3):252–9.
61. Minashi K, Nihei K, Mizusawa J, et al. Efficacy of endoscopic resection and selective chemoradiotherapy for stage I esophageal squamous cell carcinoma. Gastroenterology 2019;157(2):382–90.e3.
62. Hamada K, Ishihara R, Yamasaki Y, et al. Efficacy and safety of endoscopic resection followed by chemoradiotherapy for superficial esophageal squamous cell carcinoma: a retrospective study. Clin Transl Gastroenterol 2017;8(8):e110.
63. Kawaguchi G, Sasamoto R, Abe E, et al. The effectiveness of endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer. Radiat Oncol 2015;10(1). https://doi.org/10.1186/s13014-015-0337-4.
64. Matsumoto S, Takayama T, Tamamoto T, et al. A comparison of surgery and radiation therapy for cT1 esophageal squamous cell carcinoma. Dis Esophagus 2011;24(6):411–7.
65. Suzuki G, Yamazaki H, Aibe N, et al. Endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer: choice of new approach. Radiat Oncol 2018;13(1):246.
66. Hisano O, Nonoshita T, Hirata H, et al. Additional radiotherapy following endoscopic submucosal dissection for T1a-MM/T1b-SM esophageal squamous cell carcinoma improves locoregional control. Radiat Oncol 2018;13(1):14.
67. Jingu K, Takahashi N, Murakami Y, et al. Is concurrent chemotherapy with radiotherapy for esophageal cancer beneficial in patients aged 80 years or older? Anticancer Res 2019;39(8):4279–83.
68. Maingon P, D'Hombres A, Truc G, et al. High dose rate brachytherapy for superficial cancer of the esophagus. Int J Radiat Oncol Biol Phys 2000;46(1):71–6.
69. Ishikawa H, Nonaka T, Sakurai H, et al. Usefulness of intraluminal brachytherapy combined with external beam radiation therapy for submucosal esophageal cancer: long-term follow-up results. Int J Radiat Oncol Biol Phys 2010;76(2):452–9.
70. Gaspar LE, Winter K, Kocha WI, et al. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized

carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. Cancer 2000;88(5):988–95.
71. Pasquier D, Mirabel X, Adenis A, et al. External beam radiation therapy followed by high-dose-rate brachytherapy for inoperable superficial esophageal carcinoma. Int J Radiat Oncol Biol Phys 2006;65(5):1456–61.
72. Ishihara R, Arima M, Iizuka T, et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc 2020. https://doi.org/10.1111/den.13654.