CME MOC

Esophageal adenocarcinoma: A dire need for early detection and treatment

Abel Joseph, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Siva Raja, MD, PhD
Department of Thoracic and Cardiovascular Surgery, Heart, Vascular, and Thoracic Institute, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Suneel Kamath, MD
Department of Hematology and Medical Oncology, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Sunguk Jang, MD
Department of Gastroenterology and Hepatology, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Daniela Allende, MD
Department of Pathology, Cleveland Clinic; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Mike McNamara, MD
Department of Hematology and Medical Oncology, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Gregory Videtic, MD
Department of Radiation Oncology, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Sudish Murthy, MD
Department of Thoracic and Cardiovascular Surgery, Heart, Vascular, and Thoracic Institute, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Amit Bhatt, MD
Department of Gastroenterology and Hepatology, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

ABSTRACT

Esophageal cancer is the sixth most common cause of cancer-related death worldwide. Esophageal adenocarcinoma is the most common subtype of esophageal cancer in the United States, and its incidence has risen dramatically in the last few decades. Modern endoscopic and surgical techniques have significantly improved morbidity and mortality rates of patients undergoing treatment for esophageal cancer. However, most cases are diagnosed at a late stage when the prognosis is poor, emphasizing the need for an effective screening strategy. This clinical overview focuses on screening, multidisciplinary evaluation, and treatment of early esophageal adenocarcinoma.

KEY POINTS

The 2 major subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma, and they have different clinical presentations and natural history. The incidence of adenocarcinoma of the esophagus has increased dramatically over the past few decades in the Western world.

There are currently no standard or routine screening tests for esophageal cancer. However, many tests are under investigation for screening patients at high risk.

Management of early esophageal adenocarcinoma is based on patient and tumor characteristics and available institutional expertise.

E SOPHAGEAL CANCER IS THE SIXTH most common cause of cancer-associated death worldwide, accounting for an estimated 1 in every 20 cancer deaths.[1] More than 500,000 new cases are reported every year.[1]

Worldwide, squamous cell carcinoma is the most common type of esophageal cancer, followed by adenocarcinoma, while small-cell carcinoma, melanoma, sarcoma, and lymphoma are rare. However, in Western countries, esophageal adenocarcinoma is much more common than esophageal squamous cell carcinoma (**Table 1**),[2] and its incidence is rapidly growing in developed countries owing in part to the rising prevalence of obesity and gastroesophageal reflux disease.

Esophageal adenocarcinoma has a favorable prognosis if diagnosed early, when it is isolated to the mucosal and submucosal layers of the esophagus. Unfortunately, most cases are diagnosed at a late stage, when the prognosis is dismal. The 5-year overall survival rate of patients with esophageal adenocarcinoma is less than 20%, comparable

TABLE 1

Esophageal adenocarcinoma vs squamous cell carcinoma

	Adenocarcinoma	Squamous cell carcinoma
Proportion of esophageal cancers [a]	64%	29%
Risk factors	Barrett esophagus Gastroesophageal reflux disease Central obesity Age > 50 Male sex	Heavy alcohol consumption Smoking Hot tea consumption Nitrite consumption Head and neck cancer Tylosis (autosomal dominant syndrome, mutation in *RHBDF2* gene)

[a] Based on 2018 data from National Cancer Institute Surveillance, Epidemiology, and End Results Program, reference 2.

to that of patients who have liver, lung, or pancreas cancer.[3] Thus, there is a dire need for effective screening strategies to diagnose it earlier.

Treatment has primarily focused on resection, either surgical or, more recently, endoscopic. Radiation therapy and chemotherapy have historically been considered in patients in whom resection is less feasible because the cancer has already spread. For esophageal cancer in general, a multidisciplinary approach may help identify the best therapeutic strategy based on patient and tumor characteristics and local expertise.

This review provides strategies relevant to the subset of esophageal adenocarcinoma that is detected early, and highlights the need for a multidisciplinary approach.

◼ RISK FACTORS

Obesity
A meta-analysis of over 16,000 cases confirmed a strong association between body mass index, obesity, and esophageal adenocarcinoma.[4]

Multiple risk factors
In another study, the prevalence of Barrett esophagus (the precursor lesion of esophageal adenocarcinoma) was found to have a positive linear relationship with the number of risk factors, which included gastroesophageal reflux disease, male sex, age over 50, family history of Barrett esophagus or esophageal adenocarcinoma, and obesity (defined as body mass index > 35 kg/m^2).[5]

Other, unreliable factors
Symptoms. Most patients with early-stage esophageal adenocarcinoma are over age 65 and have no symptoms. The esophagus, being a distensible tube, can accommodate smaller tumors that remain asymptomatic until the lesion grows to a significant size.

Since gastroesophageal reflux disease involves mostly the distal esophagus and gastroesophageal junction, 94% of cancers associated with Barrett esophagus are found below the tracheal bifurcation. Significant dysphagia in early lesions should raise suspicion of more advanced disease or, rarely, a concurrent nonmalignant cause such as peptic stricture, inflammation, or concurrent submucosal tumor.

Eosinophilic esophagitis causes chronic inflammation of the esophagus, raising concerns that it may increase malignant transformation. However, a recent large database study could find no relationship between eosinophilic esophagitis and esophageal cancer.[6]

Alcohol consumption does not appear to increase the risk of esophageal adenocarcinoma, and some studies suggest wine may actually be protective.[7]

◼ WHO SHOULD BE SCREENED?

Barrett esophagus, the major precursor of esophageal adenocarcinoma, is believed to progress through pathologic stages, from metaplasia to low-grade dysplasia, high-grade dysplasia, and esophageal adenocarcinoma. The rise in esophageal adenocarcinoma and its poor prognosis in its advanced stages have

Esophageal adenocarcinoma has a favorable prognosis if diagnosed early, but it usually isn't
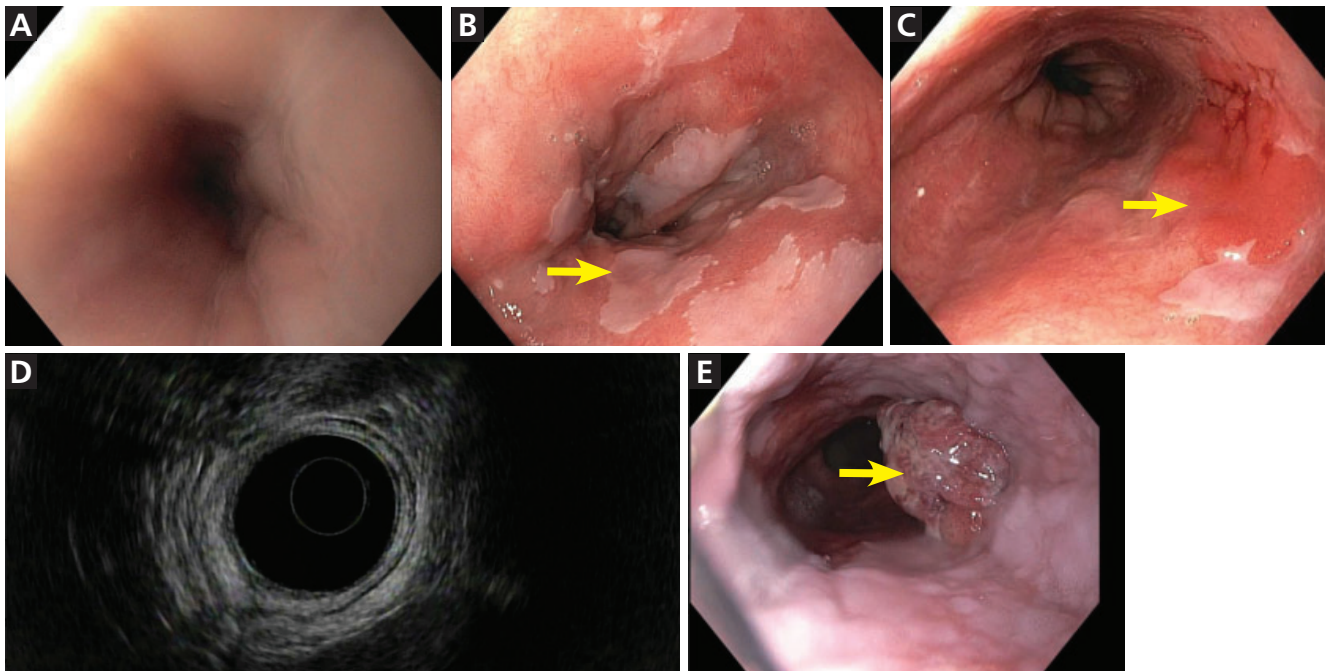
Figure 1. Endoscopic views of the esophagus. (A) Normal esophagus. (B) Barrett esophagus with islands of normal squamous mucosa (arrow). (C) Barrett esophagus with a discrete erythematous mass 4 × 2 cm (arrow) in the involved segment. (D) Barrett esophagus, endoscopic ultrasonographic view. (E) Esophageal adenocarcinoma (arrow).

raised interest in screening for Barrett esophagus and following it closely when discovered.[8]

In a prospective study, when patients with Barrett esophagus underwent endoscopic surveillance, the cases of esophageal cancer that arose were diagnosed at an earlier stage than in the general population.[9] However, studies have failed to identify an accurate, cost-effective, widely applicable tool that can lower the mortality rate.

Current guidelines, which are based on low-quality evidence and expert opinion, restrict screening to a very specific patient population: ie, those with long-standing gastroesophageal reflux disease (> 5 years) and those with frequent reflux symptoms (weekly or more) with 2 or more risk factors for Barrett esophagus or esophageal adenocarcinoma.[10] These risk factors include male sex, age over 50, central obesity (a waist circumference > 102 cm or a waist-hip ratio > 0.9), current or past history of smoking, White race, first-degree family history of Barrett esophagus or esophageal adenocarcinoma, or hiatal hernia. Patients diagnosed with Barrett esophagus without dysplasia should undergo endoscopy every 3 to 5 years.

In a large nationwide study, the annual risk of esophageal adenocarcinoma after a diagnosis of Barrett esophagus was 0.12%, much lower than the assumed risk of 0.5%, which is the basis for current guidelines.[11] However, nearly 90% of cases of esophageal adenocarcinoma are diagnosed in patients not known to have Barrett esophagus.[12] This shows that the current screening guidelines continue to miss a large number of patients at risk.

Upper endoscopy (**Figure 1**) is the gold standard for screening, but it necessitates sedation and is relatively expensive and inconvenient for a screening procedure. An ideal screening tool needs to be relatively inexpensive, well-tolerated, and applicable to general practice.

Detection rates of Barrett esophagus have been improved with advances in endoscopy such as high-definition imaging, chromoendoscopy (which uses special staining to enhance mucosal visualization), and narrowband imaging (which enhances the mucosal resolution by selecting specific wavelengths of light).

Endoscopy is the gold standard for screening, but is expensive, inconvenient, and requires sedation
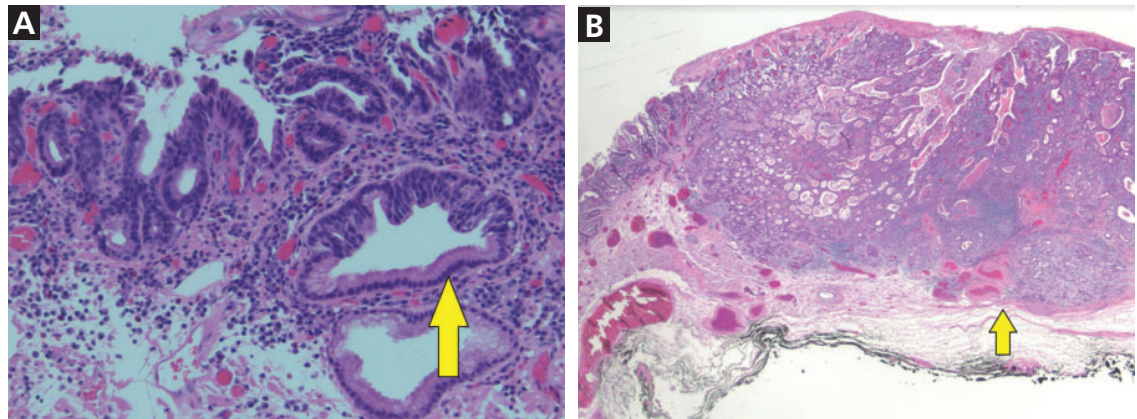
Figure 2. (A) High-grade dysplasia (arrow) from the periphery of a Barrett esophagus lesion (hematoxylin and eosin, magnification × 4). (B) Complex atypical glandular proliferation diagnostic of adenocarcinoma and involving the submucosa (arrow highlights submucosa) (hematoxylin and eosin, magnification × 20).

Swallow studies such as barium swallow do not allow for histologic assessment for metaplasia or dysplasia. Therefore, they must not be used for screening or surveillance of Barrett esophagus.

Newer screening methods for Barrett esophagus

Screening methods for Barrett esophagus that do not require endoscopy with sedation are under investigation.

Cytosponge (Medtronic) is an ingestible capsule containing a sponge attached to a string. The capsule dissolves on reaching the stomach and releases the sponge, which can be withdrawn from the esophagus out of the mouth by pulling the string. The sponge collects epithelial cells on its way out of the esophagus and is then tested for biomarkers of Barrett esophagus such as trefoil factor 3. Cytosponge is inexpensive and safe, and a prospective study found it to have a sensitivity of 73% and a specificity of 94% for detecting lesions measuring at least 1 cm.[13] A systematic review had similar findings.[14]

A swallowable balloon device can similarly sample the distal esophagus and detect DNA methylation markers. Its reported sensitivity in detecting Barrett esophagus metaplasia was 90.3% and its specificity 91.7%.[15]

Transnasal endoscopy, another office-based technique, uses a reusable endoscope with a disposable outer sterile sheath. It seems to be better tolerated than standard endoscopy while showing similar findings.[16]

Breath testing using an "electronic nose" to detect volatile organic compounds in exhaled air has shown promising results, with a sensitivity of 91% and specificity of 74%.[17]

These novel screening tools may prove to be efficient and cost-effective in primary care. However, more research is needed before they can be widely adopted. Clinical trials are under way to assess patient acceptance and preference for these different tools.

Possible preventive measures

Although epidemiologic studies suggested aspirin and nonsteroidal anti-inflammatory drugs might prevent Barrett esophagus and esophageal adenocarcinoma, clinical trials of these drugs to prevent esophageal adenocarcinoma have been unsuccessful.[18]

Retrospective data from multiple centers show that diets rich in antioxidants, fruits, vegetables, omega-3 fatty acids, polyunsaturated fat, and fiber are associated with lower risk of Barrett esophagus.[19,20]

■ BIOPSY IS THE GOLD STANDARD FOR DIAGNOSIS

On endoscopy, early lesions of esophageal adenocarcinoma can be flat, polypoid, or slightly depressed. Advanced tumors present as masses that may obstruct the esophageal lumen. The gold standard for diagnosing esophageal adenocarcinoma is tissue sampling by endo-

Breath testing using an 'electronic nose' to screen for Barrett esophagus has shown promising results
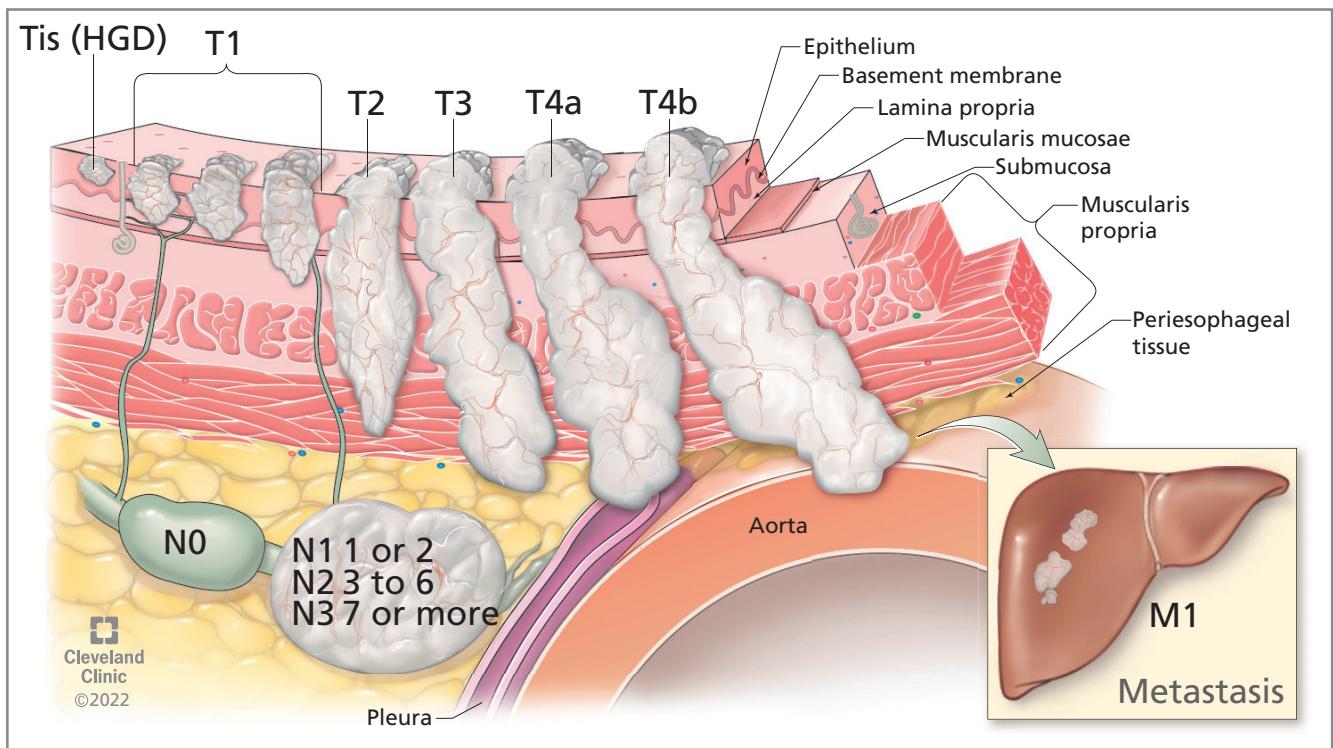
Figure 3. The tumor, node, metastasis (TNM) staging system for esophageal cancer helps determine prognosis and treatment based on tumor depth, number of affected lymph nodes, and metastasis to distant organs.

HGD = high-grade dysplasia

scopic biopsy (**Figure 2**). A prospective trial revealed a diagnostic accuracy of 93% with a single biopsy, and additional biopsy specimens increased the yield to over 98%.[21]

■ CANCER STAGING IS PARAMOUNT

Once esophageal adenocarcinoma is diagnosed, its stage needs to be assessed to determine prognosis and treatment. This involves the TNM system (**Figure 3**), as follows:
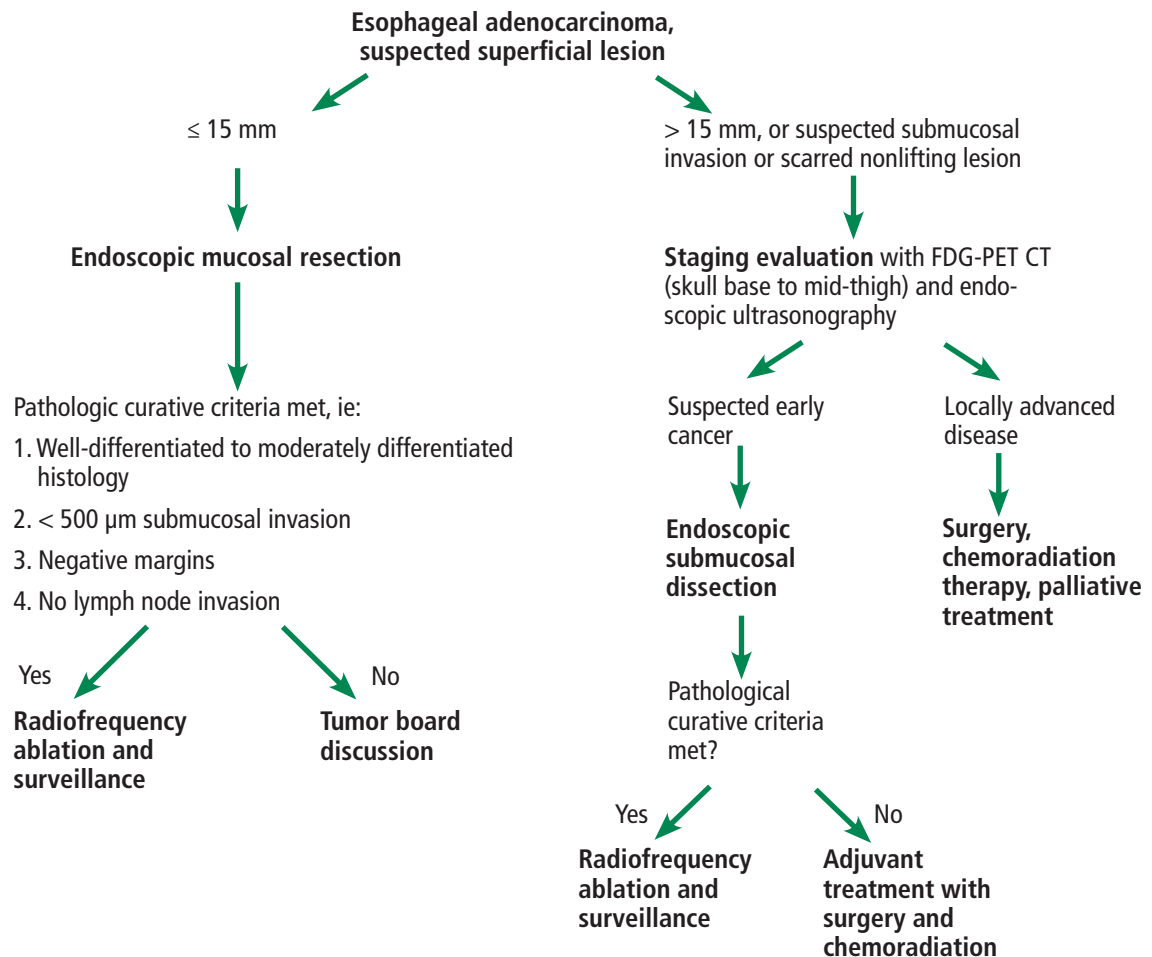
- **T**umor depth (categorized on a scale of Tis through T4b)
- **N**odes, ie, number of lymph nodes affected (categorized on a scale of N0 through N3)
- **M**etastasis in distant organs (M0 for no distant metastasis, or M1 for distant metastasis).

Positron emission tomography with computed tomography. The role of 18-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) and endoscopic ultrasonography in early esophageal adenocarcinoma staging is controversial. However, the National Comprehensive Cancer Network guidelines[22] recommend staging by PET/CT and endoscopic ultrasonography in cases of advanced cancer (≥ T1b) to evaluate for nodal spread.

PET/CT is less beneficial in early esophageal adenocarcinoma than in advanced disease. Some studies found that it could not reliably detect early esophageal adenocarcinoma stages such as T1a and T1b tumors.[23,24] A study of 79 patients with clinically staged T1a and T1b esophageal adenocarcinoma who underwent preoperative PET/CT showed all FDG-avid nodes seen were false positives[23]; another study had similar findings.[24] This suggests that PET/CT could lead to more unnecessary biopsies. However, if a tumor is found to be more advanced on pathologic study after endoscopic submucosal dissection, performing PET/CT after resection has limited utility, as inflammation of the resection bed is often FDG-avid on PET.

For this reason, we consider PET/CT before resecting bulky or borderline tumors

**Esophageal adenocarcinoma,
suspected superficial lesion**

≤ 15 mm → **Endoscopic mucosal resection**

> 15 mm, or suspected submucosal invasion or scarred nonlifting lesion → **Staging evaluation** with FDG-PET CT (skull base to mid-thigh) and endoscopic ultrasonography

Pathologic curative criteria met, ie:

1. Well-differentiated to moderately differentiated histology
2. < 500 μm submucosal invasion
3. Negative margins
4. No lymph node invasion

Yes → **Radiofrequency ablation and surveillance**

No → **Tumor board discussion**

Suspected early cancer → **Endoscopic submucosal dissection** → Pathological curative criteria met?

Locally advanced disease → **Surgery, chemoradiation therapy, palliative treatment**

Yes → **Radiofrequency ablation and surveillance**

No → **Adjuvant treatment with surgery and chemoradiation**

Figure 4. Our care path for early esophageal adenocarcinoma.

FDG-PET CT = 18-fluorodeoxyglucose positron-emission tomography with computed tomography

larger than 15 mm or lesions with suspected superficial submucosal invasion (SM1) greater than 500 μm.

Endoscopic ultrasonography can assess for the depth of tumor invasion and locoregional lymph node spread. However, it has a high false-positive rate of up to 10%.[25] Consequently, the American Society for Gastrointestinal Endoscopy guidelines strongly recommend against its routine use in early esophageal adenocarcinoma to stage mucosal (T1a) and submucosal (T1b) disease.[10]

These days, more advanced tumors are being referred for endoscopic resection. Thus, accurate staging and ruling out advanced disease before proceeding with endoscopic treatment is paramount. Further research is re-

quired to understand the role of PET/CT and endoscopic ultrasonography in large T1a (> 15 mm) and early T1b disease that is increasingly being elected for endoscopic resection.

■ **TREATMENT OPTIONS**

Our suggested care path for early esophageal adenocarcinoma is shown in **Figure 4**.

Surgery

For decades, the first-line treatment for early esophageal adenocarcinoma, including Barrett esophagus, has been open surgical resection. Technical advances in surgery such as robot-assisted minimally invasive esophagectomy, minimally invasive esophagectomy, and 3-dimensional imaging have improved re-

covery times and lymph node yield and have significantly decreased postoperative pain, intraoperative bleeding, and hospital length of stay.[26]

Minimally invasive approaches have become preferred, with long-term results that are not inferior to those of open esophagectomy. A study of more than 5,500 patients undergoing surgical resection showed a 90-day mortality rate of approximately 7%, which did not differ by surgical approach.[27] However, mortality rates were lower for patients with T1a tumors (3.1%) and T1b tumors (6.0%).[27]

The role of surgical esophagectomy remains controversial in early T1a tumors with high-risk features such as poor differentiation and large size, due to high rates of perioperative mortality (3%–6%) and morbidity, with a similar risk of locoregional spread (4.2%).[27] However, T1b tumors in otherwise healthy patients are considered for immediate esophagectomy due to the higher risk of lymph node metastasis (22%–28%).[28] In a 2020 study, esophagectomy for T1b tumors was found to be associated with higher rates of overall survival and histologic remission compared with endoscopic resection.[28] However, the patients treated endoscopically were older and had multiple comorbidities.

Postoperative surgical complications affect long-term mortality rates. Procedure-specific complications include conduit abnormalities, and recurrent laryngeal nerve injury; systemic complications include atrial fibrillation, myocardial infarction, and pneumonia. Long-term sequelae of esophagectomy include functional disorders such as dysphagia, delayed gastric emptying, reflux, and dumping syndrome. However, esophagectomy is usually well tolerated long-term with lifestyle changes such as eating frequent small-portion meals slowly and avoiding foods and beverages high in sugar.

Endoscopic surgery

Modern endoscopic techniques and devices have led to a shift to endoscopic treatment of early esophageal cancer rather than surgery, although not all early esophageal adenocarcinomas are amenable to curative endoscopic resection.

The esophageal architecture is unique in that the lymphatics penetrate through the muscularis mucosa and reach the lamina propria, leading to a theoretical risk of lymph node metastasis in early (T1a) tumors.[29] Barrett esophagus-related cancer involving the mucosa is believed to have a small risk (1%–2%) of lymph node metastasis, which increases with deeper invasion of the submucosa[30]:

- 7.5% with superficial submucosal invasion
- 10% with invasion in the middle third of the submucosa
- 45% with deep submucosal invasion.

Endoscopic resection can be considered in tumors at low risk for lymph node metastasis or in higher-risk tumors in patients who are medically unfit for surgery. The risks of perioperative death and of regional spread are between 3% and 4%.[29,31] Therefore, it is important to weigh the risk of lymph node metastasis and the risk of morbidity and mortality of surgery in a patient before deciding the best therapeutic approach for early esophageal adenocarcinoma.

There are 2 main endoscopic resection techniques: endoscopic mucosal resection and endoscopic submucosal dissection.

Endoscopic mucosal resection can be performed by 2 main methods: cap-assisted endoscopic mucosal resection (**Figure 5**), in which a cap is attached to the tip of the endoscope to depress mucosal folds and allow better visualization, and banding.[32] Esophageal endoscopic mucosal resection poses a 1.2% risk of bleeding, a 1% risk of stricture formation, and a low risk of perforation (0.2% to 1.3%).[33] The safety, success rates, and procedural ease of endoscopic mucosal resection have established it as a mainstay in the treatment of early esophageal adenocarcinoma. However, for larger lesions, endoscopic mucosal resection requires removing the tumor in multiple pieces, which is associated with higher recurrence rates.

Endoscopic submucosal dissection can allow removal of even larger tumors in a single piece (en bloc) and is associated with higher rates of cure and a lower risk of recurrence, and it allows for precise histopathologic analysis.[34–36]

A prospective trial comparing endoscopic mucosal resection and endoscopic submucosal dissection for Barrett esophagus and esophageal adenocarcinoma found the en bloc resection rate to be 100% with endoscopic submucosal dissection, but only 15% with endoscopic

Accurate staging is paramount before proceeding with endoscopic treatment
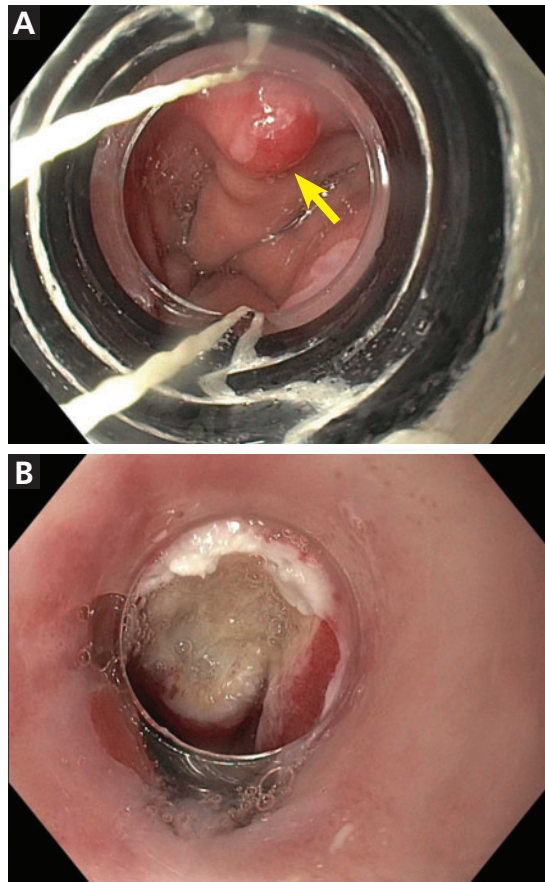
Figure 5. Band endoscopic mucosal resection of Barrett esophagus nodule. (A) Barrett esophagus nodule (arrow). (B) Resection bed after successful band endoscopic mucosal resection.

Radiotherapy alone can be an option for elderly patients who cannot undergo surgery or endoscopic therapy and concurrent chemotherapy

mucosal resection.[37] Likewise, a meta-analysis showed higher rates of R0 resection (margins free of neoplasia) (92.3% vs 52.7%) and lower rates of local recurrence (0.3% vs 11.5%) with endoscopic submucosal dissection than with endoscopic mucosal resection.[38]

Further information on these endoscopic techniques can be found in our earlier article in this Journal.[39]

Chemoradiation

Early esophageal adenocarcinoma (T1a, T1b) is primarily managed with endoscopic resection or surgery. However, recent evidence suggests that there may be a role for neoadjuvant (before resection) or adjuvant (after resection) chemoradiation therapy in early disease, particularly in patients with high-risk tumors (incomplete resection, positive deep margins,

lymphovascular invasion, poorly differentiated tumors, tumors larger than 2 cm) who are medically unfit for surgery with lymph node dissection.[28]

The ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study[40] included patients with T1 to T3 and N0 to N1 resectable esophageal adenocarcinoma and showed higher survival rates when patients underwent neoadjuvant chemoradiation therapy before surgery. Of note, data on this topic are limited by studies that included only patients with esophageal squamous cell carcinoma.

Paclitaxel and carboplatin are commonly used with concurrent radiotherapy. Another combination that is increasingly being used is 5-fluorouracil and oxaliplatin concurrent with radiotherapy. An ongoing randomized trial is comparing these 2 adjuvant regimens for resectable esophageal adenocarcinoma.[41]

Radiotherapy alone (external-beam or brachytherapy) can be an option for patients over age 65 with esophageal adenocarcinoma who cannot undergo surgery or endoscopic therapy and concurrent chemotherapy. The data on radiation treatment alone are primarily from retrospective series in patients with esophageal squamous cell carcinoma. Poor surgical candidates who are definitively treated with chemoradiation therapy can have residual, recurrent, or metachronous disease. These patients can be managed with salvage endoscopic submucosal dissection or ablation therapy.

Further study is needed to explore the utility of neoadjuvant or adjuvant chemoradiation therapy in early esophageal adenocarcinoma.[22]

Adjuvant treatment after noncurative endoscopic resection

Patients with early esophageal adenocarcinoma are increasingly being treated with endoscopic resection. However, some resections are noncurative, with poor differentiation, lymphovascular invasion, deep submucosal invasion, or positive margins. These patients are at higher risk of lymph node metastasis and progressive disease.

Ideally, esophagectomy with or without adjuvant chemoradiation therapy is the treatment of choice for these patients. However, patients who have high-risk features after endoscopic resection and who are poor surgical

candidates for definite esophagectomy with lymph node dissection can be referred for chemoradiation therapy.

A prospective trial in patients with T1a esophageal squamous cell carcinoma who underwent endoscopic submucosal dissection found a 3-year recurrence-free survival rate of 100% in those who received adjuvant radiotherapy and 85.3% in those who did not.[42] Interestingly, no severe radiation adverse events were noted.

Surveillance following curative endoscopic resection

In esophageal adenocarcinoma, endoscopic resection is considered curative if the resection histology is well-differentiated to moderately differentiated with no lymph node invasion, with less than 500 μm submucosal invasion combined with negative lateral and deep margins.[43] In comparison, squamous cell carcinoma endoscopic curative resection criteria include en bloc R0 resection of superficial lesions invading the lamina propria (T1a m2) with well-to-moderately differentiated histology with no lymphovascular invasion. En bloc R0 resection of a well-differentiated m3 or sm1 tumor (< 200 μm) without lymphovascular invasion has a low risk of lymph node metastasis, and these features are a relative indication for endoscopic submucosal dissection.[43]

Patients who undergo complete endoscopic resection of Barrett esophagus or esophageal adenocarcinoma are enrolled in a posttreatment surveillance program. Posttreatment surveillance is stratified based on postresection pathologic staging[44]:

For Barrett esophagus with high-grade dysplasia, upper endoscopy every 6 months for 2 years and then yearly is recommended.[45]

For T1a esophageal adenocarcinoma, endoscopic ultrasonography and CT can be considered, as these lesions have a 1% to 2% risk of lymph node metastasis. Surveillance consists of endoscopic ultrasonography every 6 months for 2 years, then endoscopic ultrasonography yearly and CT of the chest and abdomen yearly for 5 years.[45]

For higher-risk resections, surveillance includes endoscopic ultrasonography every 3 months for the first year followed by every 6 months for 1 year and then yearly. CT of the chest and abdomen is recommended at shorter intervals: every 6 months for the first year and yearly for the next 5 years.

■ THE BOTTOM LINE

Early esophageal adenocarcinoma is commonly diagnosed serendipitously in patients without symptoms undergoing upper endoscopy for other reasons. Due to the unique anatomy of the esophagus, even early esophageal adenocarcinoma has a risk of lymph node metastasis, and appropriate management is necessary.

For small esophageal adenocarcinoma lesions (ie, < 1.5 cm), multiple studies have shown endoscopic mucosal resection to be an effective strategy with good long-term results. For larger lesions or suspected deeper invasion or squamous cell carcinoma, a multidisciplinary approach is warranted. Endoscopic submucosal dissection can be effectively used to remove superficial tumors, despite their size or associated fibrosis. However, for lesions involving more than two-thirds of the circumference of the esophagus, there is a risk of esophageal stricture formation.

Patients with early esophageal adenocarcinoma and risk of lymph node metastasis are best treated with surgical resection, which allows for lymph node dissection, but many patients over age 65 or those with significant comorbidities may not be candidates for surgery. In these patients, endoscopic resection with adjuvant chemotherapy or radiotherapy can be considered. Some patients with early esophageal adenocarcinoma may not be candidates for either endoscopic or surgical resection owing to deep submucosal invasion, scarred disease, prior radiotherapy to the field, or severe comorbidities preventing anesthesia for procedure. In these patients, neoadjuvant radiotherapy, brachytherapy, chemotherapy, or a combination of these can be performed. ■

Neoadjuvant or adjuvant chemoradiation may have a role in early disease

■ DISCLOSURES

■ REFERENCES

1. **Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A**. 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. doi:10.3322/caac.21492

2. **National Cancer Institute**. Surveillance, Epidemiology, and End Results Program. SEER*Explorer: an interactive website for SEER cancer statistics. https://seer.cancer.gov. Accessed April 22, 2022.

3. **Siegel RL, Miller KD, Jemal A**. Cancer statistics, 2020. CA Cancer J Clin 2020; 70(1):7–30. doi:10.3322/caac.21590

4. **Tian J, Zuo C, Liu G, et al**. Cumulative evidence for the relationship between body mass index and the risk of esophageal cancer: an updated meta-analysis with evidence from 25 observational studies. J Gastroenterol Hepatol 2020; 35(5):730–743. doi:10.1111/jgh.14917

5. **Qumseya BJ, Bukannan A, Gendy S, et al**. Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. Gastrointest Endosc 2019; 90(5):707–717.e1. doi:10.1016/j.gie.2019.05.030

6. **Syed A, Maradey-Romero C, Fass R**. The relationship between eosinophilic esophagitis and esophageal cancer. Dis Esophagus 2017; 30(7):1–5. doi:10.1093/dote/dox050

7. **Anderson LA, Cantwell MM, Watson RG, et al**. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Gastroenterology 2009; 136(3): 799–805 doi:10.1053/j.gastro.2008.12.005

8. **Codipilly DC, Chandar AK, Singh S, et al**. The effect of endoscopic surveillance in patients with Barrett's esophagus: a systematic review and meta-analysis. Gastroenterology 2018; 154(8):2068-2086.e5. doi:10.1053/j.gastro.2018.02.022

9. **Kastelein F, van Olphen SH, Steyerberg EW, Spaander MC, Bruno MJ; ProBar-Study Group**. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. Gut 2016; 65(4):548–554. doi:10.1136/gutjnl-2014-308802

10. **ASGE Standards of Practice Committee, Qumseya B, Sultan S, Bain P, et al**. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc 2019; 90(3):335–359.e2. doi:10.1016/j.gie.2019.05.012

11. **Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P**. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011; 365(15):1375–1383. doi:10.1056/NEJMoa1103042

12. **Tan MC, Mansour N, White DL, Sisson A, El-Serag HB, Thrift AP**. Systematic review with meta-analysis: prevalence of prior and concurrent Barrett's oesophagus in oesophageal adenocarcinoma patients. Aliment Pharmacol Ther 2020; 52(1):20–36. doi:10.1111/apt.15760

13. **Kadri SR, Lao-Sirieix P, O'Donovan M, et al**. Acceptability and accuracy of a non-endoscopic screening test for Barrett's esophagus in primary care: cohort study. BMJ 2010; 341:c4372. doi:10.1136/bmj.c4372

14. **Iqbal U, Siddique O, Ovalle A, Anwar H, Moss SF**. Safety and efficacy of a minimally invasive cell sampling device ('Cytosponge') in the diagnosis of esophageal pathology: a systematic review. Eur J Gastroenterol Hepatol 2018; 30(11):1261–1269. doi:10.1097/MEG.0000000000001210

15. **Moinova HR, LaFramboise T, Lutterbaugh JD, et al**. Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. Sci Transl Med 2018; 10(424):eaao5848. doi:10.1126/scitranslmed.aao5848

16. **Shariff MK, Varghese S, O'Donovan M, et al**. Pilot randomized crossover study comparing the efficacy of transnasal disposable endosheath with standard endoscopy to detect Barrett's esophagus. Endoscopy 2016; 48(2):110–116. doi:10.1055/s-0034-1393310

17. **Peters Y, Schrauwen RWM, Tan AC, Bogers SK, de Jon B, Siersema PD**. Detection of Barrett's oesophagus through exhaled breath using an electronic nose device. Gut 2020; 69(7):1169–1172. doi:10.1136/gutjnl-2019-320273

18. **Heath EI, Canto MI, Piantadosi S, et al**. Secondary chemoprevention of Barrett's esophagus with celecoxib: results of a randomized trial.

19. **Kubo A, Levin TR, Block G, et al**. Dietary antioxidants, fruits, and vegetables and the risk of Barrett's esophagus. Am J Gastroenterol 2008; 103(7):1614–1624. doi:10.1111/j.1572-0241.2008.01838.x

20. **Kubo A, Block G, Quesenberry CP Jr, Buffler P, Corley DA**. Effects of dietary fiber, fats, and meat intakes on the risk of Barrett's esophagus. Nutr Cancer 2009; 61(5):607–616. doi:10.1080/01635580902846585

21. **Graham DY, Schwartz JT, Cain GD, Gyorkey F**. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982; 82(2):228–231. pmid:7054024

22. **Ajani JA, D'Amico TA, Bentrem DJ, et al**. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019; 17(7):855–883. doi:10.6004/jnccn.2019.0033

23. **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):1202–1206. doi:10.1097/JTO.0000000000000222

24. **Little SG, Rice TW, Bybel B, et al**. Is FDG-PET indicated for superficial esophageal cancer? Eur J Cardiothorac Surg 2007; 31(5):791–796. doi:10.1016/j.ejcts.2007.01.037

25. **Choi J, Chung H, Lee A, Kim JL, Cho SJ, Kim SG**. Role of endoscopic ultrasound in selecting superficial esophageal cancers for endoscopic resection. Ann Thorac Surg 2021; 111(5):1689–1695. doi:10.1016/j.athoracsur.2020.07.029

26. **Espinoza-Mercado F, Imai TA, Borgella JD, et al**. Does the approach matter? Comparing survival in robotic, minimally invasive, and open esophagectomies. Ann Thorac Surg 2019; 107(2):378–385. doi:10.1016/j.athoracsur.2018.08.039

27. **Newton AD, Predina JD, Xia L, et al**. Surgical management of early-stage esophageal adenocarcinoma based on lymph node metastasis risk. Ann Surg Oncol 2018; 25(1):318–325. doi:10.1245/s10434-017-6238-z

28. **Otaki F, Ma GK, Krigel A, et al**. Outcomes of patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Gastrointest Endosc 2020; 92(1):31–39.e1. doi:10.1016/j.gie.2020.01.013

29. **Yang J, Lu Z, Li L, et al**. Relationship of lymphovascular invasion with lymph node metastasis and prognosis in superficial esophageal carcinoma: systematic review and meta-analysis. BMC Cancer 2020; 20(1):176. doi:10.1186/s12885-020-6656-3

30. **Raja S, Rice TW, Goldblum JR, et al**. Esophageal submucosa: the watershed for esophageal cancer. J Thorac Cardiovasc Surg 2011; 142(6):1403–1411.e1. doi:10.1016/j.jtcvs.2011.09.027

31. **Seder CW, Wright CD, Chang AC, Han JM, McDonald D, Kozower BD**. The Society of Thoracic Surgeons General Thoracic Surgery Database Update on Outcomes and Quality. Ann Thorac Surg 2016; 101(5):1646–1654. doi:10.1016/j.athoracsur.2016.02.099

32. **Zhang YM, Boerwinkel DF, Qin X, et al**. A randomized trial comparing multiband mucosectomy and cap-assisted endoscopic resection for endoscopic piecemeal resection of early squamous neoplasia of the esophagus. Endoscopy 2016; 48(4):330–338. doi:10.1055/s-0034-1393358

33. **Mejia Perez LK, Yang D, Draganov PV, et al**. Endoscopic submucosal dissection vs endoscopic mucosal resection for early Barrett's neoplasia in the West: a retrospective study. Endoscopy 2021; 10.1055/a–1541–7659. doi:10.1055/a-1541-7659

34. **Peng W, Tan S, Ren Y, et al**. Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal neoplastic lesions: a systematic review and meta-analysis. J Cardiothorac Surg 2020; 15(1):33. doi:10.1186/s13019-020-1074-9

35. **Mejia Perez LK, Alaber O, Jawaid S, et al**. Mo1204 Endoscopic submucosal dissection vs endoscopic mucosal resection for treatment of Barrett's related superficial esophageal neoplasia: retrospective multicenter study. Gastrointest Endosc 2019; 89(6):AB462–AB3.

36. **Joseph A, Draganov P, Maluf-Filho F, et al**. Outcomes for ESD of pathologically staged T1b esophageal cancer: a multi-center study.

J Natl Cancer Inst 2007; 99(7):545–557. doi:10.1093/jnci/djk112

Gastrointest Endosc 2022; S0016-5107(22)00123-7. doi:10.1016/j.gie.2022.02.018

37. **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):783–793. doi:10.1136/gutjnl-2015-310126

38. **Guo HM, Zhang XQ, Chen M, Huang SL, Zou XP**. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. World J Gastroenterol 2014; 20(18):5540–5547. doi:10.3748/wjg.v20.i18.5540

39. **Mejía-Pérez LK, Abe S, Stevens T, et al**. A minimally invasive treatment for early GI cancers. Cleve Clin J Med 2017; 84(9):707–717. doi:10.3949/ccjm.84a.16063

40. **Shapiro J, van Lanschot JJB, Hulshof MCCM, et al**. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16(9):1090–1098. doi:10.1016/S1470-2045(15)00040-6

41. **Messager M, Mirabel X, Tresch E, et al**. Preoperative chemoradiation with paclitaxel-carboplatin or with fluorouracil-oxaliplatin-folinic acid (FOLFOX) for resectable esophageal and junctional cancer: the PROTECT-1402, randomized phase 2 trial. BMC Cancer 2016; 16:318. doi:10.1186/s12885-016-2335-9

42. **Zhang Y, Liu L, Wang Q, et al**. Endoscopic submucosal dissection with additional radiotherapy in the treatment of T1a esophageal squamous cell cancer: randomized controlled trial. Endoscopy 2020; 52(12):1066–1074. doi:10.1055/a-1198-5232

43. **Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al**. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015; 47(9):829–854. doi:10.1055/s-0034-1392882

44. **Standards of Practice Committee, Wani S, Qumseya B, et al**. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. Gastrointest Endosc 2018; 87(4):907–931.e9. doi:10.1016/j.gie.2017.10.011

45. **Bhatt A, Kamath S, Murthy SC, Raja S**. Multidisciplinary evaluation and management of early stage esophageal cancer. Surg Oncol Clin N Am 2020; 29(4):613–630. doi:10.1016/j.soc.2020.06.011

Address: *Abel Joseph, MD, Department of Internal Medicine, NA1, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; abeljosephmd@gmail.com*