Epidemiology, Diagnosis, and Management of Esophageal Adenocarcinoma

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Esophageal adenocarcinoma (EAC) is rapidly increasing in incidence in Western cultures. Barrett’s esophagus is the presumed precursor lesion for this cancer. Several other risk factors for this cancer have been described, including chronic heartburn, tobacco use, white race, and obesity. Despite these known associations, most patients with EAC present with symptoms of dysphagia from late-stage tumors; only a small number of patients are identified by screening and surveillance programs. Diagnostic analysis of EAC usually commences with upper endoscopy followed by cross-sectional imaging. Endoscopic ultrasonography is useful to assess the local extent of disease as well as the involvement of regional lymph nodes. T1a EAC may be treated endoscopically, and some patients with T1b disease may also benefit from endoscopic therapy. Locally advanced disease is generally managed with esophagectomy, often accompanied by neoadjuvant chemoradiotherapy or chemotherapy. The prognosis is based on tumor stage; patients with T1a tumors have an excellent prognosis, whereas few patients with advanced disease have long-term survival.

Keywords: Esophageal Neoplasms; Adenocarcinoma; Risk Factors; Endoscopic Therapy.

Esophageal adenocarcinoma (EAC) is among the most lethal conditions that gastroenterologists face. Only 16% of patients survive 5 years after diagnosis, and median survival is less than 1 year; in addition, relatively little progress has been made in stemming the toll of this condition.1 EAC is usually diagnosed at a late stage, with most patients presenting with T3 or T4 disease. This is in part responsible for its high mortality, because few therapies are available to cure patients with advanced-stage disease.

The incidence of EAC has increased greatly in the past 40 years (approximately 600% since the 1970s). The reasons for this increase are incompletely understood. Many investigators have suggested that the concurrent epidemic of obesity may explain at least part of this increase. Treatment of EAC has also evolved, especially for early-stage disease. In the past, gastroenterologists only performed endoscopy and biopsy to diagnose EAC; now, they are integral members of the care team and are involved in the care of many patients who are cured. For this reason, it is important for gastroenterologists to understand the risk factors and presentation of EAC, the treatment options, and the expected outcomes based on the treatment provided.

In this report, we review the epidemiology, risk factors, staging, and treatment of EAC, focusing on early-stage disease and endoscopic therapy, and the prognoses of patients who receive different therapies. We conclude with likely future developments in the care of these patients.

Epidemiology

Adenocarcinoma was once an exceedingly rare histological type of esophageal cancer. Beginning as early as the 1960s, the incidence of EAC began to increase in the United States.2 By the 1990s, adenocarcinoma was the predominant type of esophageal cancer in the United States, surpassing squamous cell carcinoma.3,4 In 2014, there were approximately 18,170 incident cases of esophageal cancer in the United States, 59.9% of which were adenocarcinomas.5,6 However, squamous cell cancer is still the predominant form of esophageal neoplasia worldwide. In fact, there were approximately 52,000 incident cases of EAC worldwide in 2012, compared with an estimated 398,000 cases of esophageal squamous cell carcinoma.7

EAC is most common in industrialized countries with populations of predominantly European ancestry; nearly 50% of all cases occur in northwest Europe and North America (Figure 1).7 The incidence of EAC is highest in the United Kingdom, Ireland, France, and The Netherlands, indicating a Northern European predilection.1 Cases of EAC are rare in Asia and Africa, but approximately 18% of all incident cases worldwide are found in China because of its large population.7 The incidence of EAC has continued to

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; CRT, chemoradiotherapy and external beam radiotherapy; CT, computed tomography; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; GERD, gastroesophageal reflux disease; IGF, insulin-like growth factor; OR, odds ratio; PET, positron emission tomography; RFA, radiofrequency ablation.
increase in the West but may be reaching a plateau (Figure 2)\(^8\)–\(^{10}\); the incidence of EAC in the United States was 2.5 per 100,000 people in 2011.\(^1\),\(^9\)

There are several risk factors for EAC (Figure 3). Perhaps the most familiar is gastroesophageal reflux disease (GERD). In 1995, Chow et al associated adenocarcinoma of either the esophagus or gastric cardia with prior documentation of GERD (adjusted odds ratio [OR], 2.1; 95% confidence interval [CI], 1.2–3.6).\(^{11}\) In 1999, Lagergren et al published a landmark population-based case-control study showing that the risk of EAC was approximately 8-fold greater in patients with recurrent GERD symptoms compared with those without GERD symptoms.\(^{12}\) In predisposed people, it is believed that GERD can lead to erosive esophagitis, followed by an aberrant healing process resulting in a metaplastic, specialized intestinal epithelium (Barrett’s esophagus).\(^{13}\) Barrett’s esophagus progresses to EAC in a small percentage of patients, at a rate of approximately 0.12% to 0.60% per year.\(^{14}\)–\(^{16}\) A meta-analysis of population-based studies estimated that weekly GERD symptoms increase the risk of EAC by approximately 5-fold.\(^{17}\) Patients with long-standing symptoms, nocturnal symptoms, or more frequent symptoms are at higher risk. However, the severity of symptoms is not associated with an increased risk of EAC.\(^{18}\)

Although GERD is undoubtedly an important risk factor for EAC, most patients with GERD never develop EAC.\(^{19}\) A systematic review of population-based studies found that a slight majority of patients with EAC deny any substantial prior symptoms of GERD.\(^{20}\) It is possible that chronic reflux of gastric contents could promote EAC without causing substantial symptoms before patients present with cancer.

Figure 1. Global differences in the incidence of histological subtypes of esophageal cancer. Age-standardized incidence rate (ASR) per 100,000 of (A) EAC and (B) SCC in men. AC, adenocarcinoma; SCC, squamous cell carcinoma. Reproduced with permission from Arnold et al.\(^7\)
Tobacco use is a strong risk factor for esophageal squamous cell carcinoma, but it is also a risk factor for EAC. Analyses of data from a consortium of researchers found that tobacco use increased the risk of EAC by 2.18-fold (95% CI, 1.84–2.58).²¹ Alcohol use is also a strong risk factor for esophageal squamous cell carcinoma but has not proven to be a consistent risk factor for EAC. In fact, there appears to be a moderate inverse association between alcohol use and risk of EAC.²² It is not clear whether alcohol use actually protects against EAC; it could be that patients who develop EAC avoid alcohol use because it worsens the symptoms of GERD.

Obesity is a clear risk factor for EAC. A body mass index (BMI) of 30 to 34.9 kg/m² is associated with a 2.39-fold increase in risk of EAC compared with a BMI of less than 25 kg/m², with stronger effects for those with even greater BMIs.²³ Abdominal obesity, in particular, is associated with Barrett’s esophagus and is also associated with EAC (summary OR, 2.51; 95% CI, 1.54–4.06).²⁴ How might abdominal obesity contribute to the development of EAC? Obesity has the mechanical effect of promoting formation of hiatal hernia, which is associated with an increased risk of GERD.²⁵,²⁶ However, abdominal obesity is associated with Barrett’s esophagus even after adjusting for GERD, and obesity is associated with EAC even in those without symptoms of GERD.²³ In addition to its mechanical effect, abdominal obesity is associated with alterations in circulating levels of peptides that are associated with

**Figure 2.** Trend of incidence of EAC in the United States. The graph shows the incidence of EAC and incidence-based mortality from 1975 to 2009 according to data from the Surveillance, Epidemiology, and End Results (SEER) Cancer Registry.⁹ From 1975 to 1997, the incidence of EAC increased at an annual percentage change (APC) of 8.4 (95% CI, 7.7–9.1), whereas the APC was 1.6 (95% CI, 0.0–3.3) from 1997 to 2009. For incidence-based mortality, the APC was 8.0 from 1975 to 1998 (95% CI, 7.2–8.8) and 1.1 from 1998 to 2009 (95% CI, 0.7–2.8). All rates were age adjusted to the 2000 standard population using 19 age groups. Reproduced with permission from Hur et al.⁹

**Figure 3.** Risk factors for EAC. The primary risk factors for EAC include male sex, advancing age, white race, GERD, obesity, and tobacco use. The effect of obesity is likely mediated both through a mechanical effect promoting GERD and a hormonal effect through alterations in circulating adipokines and other peptides and appears to be a major risk factor for both Barrett’s esophagus and EAC. A deranged gastroesophageal junction, noted with a large hiatal hernia, allows free reflux of gastric contents. H pylori infection protects against EAC, and Barrett’s esophagus is its only known precursor.
Barrett’s esophagus and may also promote EAC.\textsuperscript{27} Abdominal obesity is associated with insulin resistance and hyperinsulinemia, which have been associated with multiple epithelial cancers. Metabolic syndrome has been associated with Barrett’s esophagus and EAC.\textsuperscript{28,29} However, the evidence for an association between hyperinsulinemia or diabetes mellitus and Barrett’s esophagus or EAC has been inconsistent.\textsuperscript{27–30,35–37}

The insulin-like growth factor (IGF) pathway has been more strongly implicated in the development of EAC than insulin itself. Circulating levels of IGF binding protein 3 are inversely associated with the presence of Barrett’s esophagus.\textsuperscript{31} A polymorphism in the gene encoding IGF-I is associated with Barrett’s esophagus,\textsuperscript{36} and a polymorphism in the gene encoding the IGF-I receptor modifies the effect of obesity on the risk of Barrett’s esophagus and EAC.\textsuperscript{37} A polymorphism in the gene encoding IGF-II is also associated with EAC, perhaps more so among those who smoke.\textsuperscript{38} The IGF pathway may also be involved in the risk of progression from Barrett’s esophagus to EAC.\textsuperscript{39}

Studies have also found associations between blood levels of leptin and Barrett’s esophagus as well as progression of Barrett’s esophagus to EAC.\textsuperscript{37,39,40,43} Barrett’s esophagus and progression to EAC have been associated with decreased levels of adiponectin (particularly the low-molecular-weight form) in some, but not all, studies.\textsuperscript{27,34,40,42,43} These metabolic effects of obesity could have synergistic effects with GERD on the risk of Barrett’s esophagus and EAC.\textsuperscript{40,44} Although obesity has been the primary focus for studies examining the effect of body habitus on risk of EAC, a recent analysis of data from a consortium of researchers found that people with short stature are at greater risk for EAC than those who are taller.\textsuperscript{45} The reason for that association is unclear.

Given the association of obesity with EAC, it might be expected that physical activity and dietary habits would also be associated with EAC. Physical activity (either occupational or recreational) is weakly inversely associated with EAC (summary OR of greatest vs lowest category, 0.79; 95% CI, 0.66–0.94), with the strongest effects in people who exercise moderately or vigorously 5 days per week.\textsuperscript{46} The effect may persist, including after adjusting for obesity. Some forms of activity, such as working in a stooped position and weight lifting, have been positively associated with GERD, but their specific effects on the risk of EAC have not been adequately studied.\textsuperscript{47}

The association of dietary habits with the risk of EAC has been examined in many observational studies. Consumption of processed meats is associated with an approximate 23% to 37% increase in the risk of EAC when the highest levels of intake are compared with the lowest.\textsuperscript{48,49} Dietary fiber intake is inversely associated with EAC (summary OR for greatest vs lowest category of intake, 0.66; 95% CI, 0.44–0.98), but there is substantial heterogeneity in results from individual studies.\textsuperscript{50} Intake of the antioxidant vitamins A, C, and E is inversely associated with EAC.\textsuperscript{51} Caution is necessary before inferring that any of these dietary habits are causal in the development of EAC, because increased intake of one food type or micronutrient is inextricably linked with increased or decreased intake of other food types and micronutrients. Many observational studies have associated dietary habits with outcomes, but these findings were not supported by subsequent randomized trials of dietary supplementation.\textsuperscript{52–54}

Infection with Helicobacter pylori appears to protect against EAC. People with EAC are approximately half as likely to have H pylori infection as those without EAC (OR, 0.56; 95% CI, 0.46–0.68).\textsuperscript{55} In particular, the cytotoxin-associated gene A strain of H pylori appears to reduce the risk of EAC. Infection of predominantly the gastric body, or the body and the antrum, reduces gastric acid production, which reduces acidic GERD and the risk of EAC.\textsuperscript{56} However, infection predominantly in the antrum may be associated with increases in gastrin levels, with a subsequent increase in gastric acid production.\textsuperscript{57} In Western countries, most H pylori infections occur predominantly in the antrum,\textsuperscript{58} so it is not clear whether its inverse association with EAC is due to a reduced incidence of GERD. H pylori infection is inversely associated with GERD in Asian countries but does not appear to be so in Western countries.\textsuperscript{59}

Another potential mechanism by which H pylori infection reduces the risk of EAC could be that refluxed H pylori DNA reduces the inflammatory response to GERD.\textsuperscript{60,61} Additionally, people who are genetically predisposed to maintaining persistent infection with H pylori may also be predisposed to an inflammatory response to GERD.\textsuperscript{62–64} Lack of infection with H pylori may simply be a marker for other alterations in the microbiome of the esophagus and/or stomach that are directly related to the development of EAC.\textsuperscript{65} Further research is needed to understand the mechanisms of association between H pylori and EAC.

The strongest risk factors for EAC are advancing age and male sex. Men have approximately 6-fold the risk of EAC of women.\textsuperscript{21} Among men, circulating levels of free testosterone and free dihydrotestosterone are strongly associated with Barrett’s esophagus (adjusted ORs [95% CIs] for 4th vs 1st quartile, 5.36 [2.21–13.0] vs 4.25 [1.87–9.66], respectively).\textsuperscript{65} Among women who have had children, breastfeeding is inversely associated with the risk of EAC, suggesting hormone effects.\textsuperscript{66} However, no association among women has been found for the number of children, age of menarche or menopause, or use of hormone replacement therapy or oral contraceptives.\textsuperscript{66}

The risk of EAC may be greater in men because of differences between sexes in use of tobacco or types of obesity. The estimated relative effects of tobacco use on the risk of EAC (ever use or categorized by pack-years of use) are similar between men and women,\textsuperscript{21} but men more frequently use tobacco. Similarly, the effect of BMI on the risk of EAC is similar between men and women,\textsuperscript{23} as is the effect of waist circumference on Barrett’s esophagus.\textsuperscript{67} However, the prevalence of abdominal obesity is greater among men, which could account for some of the increased risk of EAC among men. It is likely that the etiology of the difference between sexes is multifactorial, with differential distribution of some risk factors increasing the risk of EAC in men.

The regional differences observed in the incidence of EAC indicate that race is a strong risk factor for EAC. In the
United Kingdom, the incidence of EAC is much lower among Asian and African people compared with white people. In the United States, Asian and black people have a greatly decreased risk of EAC compared with non-Hispanic white people, with white Hispanic people having an intermediate risk. The reasons for the differences across races are not clear. The effect of race might be mediated in part by differences in the prevalence of *H pylori* infection. In addition, although GERD symptoms are equally prevalent among the different races, white people are more likely to have erosive esophagitis, a lesion that is believed to be a necessary step in the development of EAC.

Three genome-wide association studies have associated loci with Barrett’s esophagus; these are near or within *CRTC1*, *BARX1*, *FOXF1*, *FOXP1*, GDF7, and *TBX5*. *CRTC1* encodes a transcription coactivator that regulates the invasiveness and migration of esophageal cancer cells; it is also associated with age at menarche and with obesity. *BARX1* encodes a homeobox transcription factor involved in esophageal differentiation. *TBX5*, *FOXF1*, and *FOXP1* encode transcription factors that regulate esophageal development. GDF7 encodes a protein in the bone morphometric protein pathway. Differences in these or other alleles among races might account for the increased risk of EAC among Northern European people and their descendants.

The use of certain medications has been associated with an increased or decreased risk of EAC. Observational studies of patients with Barrett’s esophagus have shown that the use of proton pump inhibitors reduces the risk of neoplastic progression by 71%, but results from later studies are heterogeneous. Conversely, medications that relax the lower esophageal sphincter and could thereby predispose people to GERD have been studied as potential risk factors for EAC. There appears to be no association between EAC and use of calcium channel blockers. Use of asthma medications such as theophylline or β-agonists has been associated with Barrett’s esophagus and EAC, but these findings could be confounded by the indication for the medications, because asthma is associated with GERD. Use of aspirin and nonsteroidal anti-inflammatory drugs is associated with a decreased risk of EAC, particularly when used daily and for a long duration. Finally, use of hydroxymethylglutaryl-CoA reductase inhibitors (statins) are associated with a decreased risk of EAC.

**Clinical Presentation and Diagnosis**

Typically, patients with EAC present with dysphagia that progresses rapidly over months. Symptoms begin with subtle difficulty with solids and progress to dysphagia for liquids as well. Oropharyngeal dysphagia is rare. The point of difficulty may be localized by the patient as far cephalad as the sternal notch, even when the mass is in the distal esophagus. Weight loss and fatigue are common. In rare instances, patients present with iron deficiency anemia. Although patients with GERD frequently undergo upper endoscopy and surveillance for Barrett’s esophagus, less than 15% of cases of EAC are detected during surveillance endoscopies. Most patients with EAC present with symptoms and advanced disease. Only approximately 25% of patients with EAC have localized disease at the time of presentation, severely limiting effective treatment options.

Cross-sectional imaging analysis, such as with computed tomography (CT), does not accurately identify localized EAC. Barium esophagrams can be used to identify irregular strictures or masses, but upper endoscopy with collection of biopsy specimens and histological analysis is the standard for diagnosis. During endoscopy, EAC can appear as a stricture, mass, raised nodule, ulceration, or subtle irregularity in the mucosa, including a depression. EAC has been detected in biopsy specimens from regions of Barrett’s esophagus that appear flat during endoscopy. During endoscopy, care should be taken to document the proximal and distal extents of the tumor and their relationship to the gastroesophageal junction, because these have implications for surgical management. For example, if the tumor involves the stomach more distally than the cardia, a gastric pull-up procedure may not be feasible, and colonic interposition might be required. For tumors that involve the entire circumference of the lumen, the normal anatomy of the gastroesophageal junction can be obliterated, making the documentation of its location inaccurate. Occasionally, smaller tumors are encountered that may be amenable to endoscopic therapy. As such, the size, location, and morphology of the tumor, as visualized by endoscopy, should be documented to aid in the planning of such therapy.

**Staging**

EAC is staged based on the American Joint Committee on Cancer staging system, which was last updated in 2010 (Table 1). This was the first time that staging of EAC was separated from that of squamous cell carcinoma. The esophageal wall has layers of mucosa, submucosa, muscularis propria, and adventitia (Figure 4). The mucosal layer includes the epithelium, lamina propria, and muscularis mucosae and is separated from the submucosa by a basement membrane. High-grade dysplasia is synonymous with carcinoma in situ (stage 0) and is confined to the epithelium. If cells with the same appearance have invaded the lamina propria, the lesion is classified as invasive cancer.

T1a cancers are confined within the mucosa and are often called intramucosal cancers; they can invade the lamina propria as deeply as the muscularis mucosae. The intraobserver agreement among pathologists for distinguishing high-grade dysplasia from T1a cancer is poor. Therefore, it should not be surprising that patients with high-grade dysplasia versus those with T1a cancers have similar times of survival (Supplementary Figure 1). In contrast, patients with tumors that invade even the submucosa (T1b) have a considerably worse prognosis, similar to that of patients with T2 tumors (Supplementary Figure 1). T2 tumors invade the muscularis propria, T3 tumors invade the adventitia, and T4 tumors invade adjacent structures (Figure 4). In the 2010 American Joint Committee on Cancer staging system, regional lymph node involvement includes periesophageal cervical nodes to the celiac nodes. In the earlier 2002 system, celiac nodes
were considered distant metastases. The 2010 system categorizes the number of lymph nodes involved as 0 (N0), 1 or 2 (N1), 3 to 6 (N2), and 7 or more (N3).

A number of modalities are available to stage esophageal cancer. For staging of the tumor depth, endoscopic resection distinguishes T1a from those that invade more deeply. Cross-sectional imaging techniques such as CT or positron emission tomography (PET) have no practical role in staging the depth of early-stage EACs. Although endoscopic ultrasonography (EUS) is more accurate than CT or PET for staging the tumor depth, none of these accurately stage shallow tumors. Furthermore, these techniques can over-stage superficial EAC, which is actually amenable to endoscopic therapy. Therefore, for cases in which EUS analysis indicates T1b disease, endoscopic mucosal resection (EMR) should still be considered. EUS may be particularly inaccurate if strictures prevent passage of the echoendoscope to the full extent of the tumor. A meta-

**Figure 4.** Tumor depth staging for EAC. There are 4 main layers of the esophageal wall: mucosa, submucosa, muscularis propria, and adventitia. The mucosa is further divided into the epithelium, lamina propria, and muscularis mucosae. Dysplasia is confined to the epithelium. Intramucosal tumors (T1a) invade the lamina propria or muscularis mucosae. Tumors that invade the submucosa are classified as T1b. T2 tumors invade the muscularis propria, T3 tumors invade the adventitia, and T4 tumors invade adjacent structures.
analysis of studies of regional lymph node staging found that EUS detects T1b disease with the highest level of sensitivity (80%) but slightly less specificity (70%) than PET (57% sensitivity and 85% specificity).90

EUS only rarely identifies distant metastases, such as those to the liver or peritoneum. CT with intravenous contrast is the main modality used to identify distant metastases. PET can identify incrementally more metastases than CT alone.90 Increasingly, PET is performed with a hybrid scanner that performs noncontrast CT in the same setting to aid in localizing any uptake identified by PET. In practice, once EAC is diagnosed, based on analysis of mucosal biopsy specimens, patients typically undergo PET/CT or CT with intravenous contrast to identify distant metastases. PET/CT is the most accurate form of imaging for this purpose, with greater accuracy than either PET or CT alone. If no distant metastases are found, then EUS can be used to stage regional lymph nodes and, to a lesser extent, tumor depth. In cases in which the tumor appears to be subtle or small by endoscopy (typically in patients undergoing surveillance for Barrett’s esophagus), endoscopic resection of the lesion is often considered before additional imaging to determine whether the tumor was invasive and exclude dysplasia confined to the epithelium.

For patients with T1a tumors, the likelihood of metastasis is lower than the false-positive rates of PET/CT or EUS, meaning that most positive results are false.91 Given the extremely low likelihood of lymph node involvement in patients with T1a cancer, the value of PET/CT or EUS is questionable.92-94 Additionally, in patients with more advanced disease, PET/CT is not a good modality for assessing for brain metastases due to the avid glucose uptake of normal brain.95 Magnetic resonance imaging should be considered for patients with neurological symptoms to detect metastases to the brain. Locally advanced lesions that extend to the middle third of the esophagus could also involve the posterior membranous trachea. Bronchoscopy should be considered to assess invasion and, in the event of fistula formation, stent the bronchus.96

Treatment

Initial treatment approaches for EAC depend on several factors, including the stage and grade of the tumor, the location of the tumor, the comorbidities and age of the patient, and institutional expertise in providing therapy. Given that systemic therapy for EAC is often not curative, it is imperative to correctly identify patients who may be eligible for curative endoscopic or surgical therapy. Multimodal therapies are used for patients with late-stage disease, although the value of this approach has not been completely elucidated.

Superficially Invasive Adenocarcinoma (T1a and T1b Disease)

Perhaps no aspect of the treatment of EAC has evolved more in the past 10 years than endoscopic therapy for superficially invasive adenocarcinoma. Although surgical and endoscopic therapies are available for superficial disease, endoscopic therapies have moved to the forefront due to their high level of efficacy and low morbidity. New endoscopic treatment modalities and more widespread and aggressive use of endoscopic therapy have changed outcomes in the small proportion of patients with early-stage EAC.

Endoscopic therapy. Most endoscopic therapy for EAC begins with endoscopic resection.97 This is performed as a staging and a therapeutic measure in that complete excision of a mucosal EAC improves a patient’s prognosis. The resection can be performed as an EMR using either band ligation methods or cap-and-snare methods98 or as an endoscopic submucosal dissection (ESD).99 The chief advantage of ESD is that it allows for complete en bloc resection and assessment of the lateral margins of the lesion.100,101 However, ESD is technically more challenging, and relatively few US centers are capable of performing this procedure. The most important piece of prognostic information obtained from endoscopic resection is the depth of invasion; EMR and ESD each provide this information and allow for the tumor to be staged. More than one endoscopic session may be necessary to achieve complete resection.

Several features define tumors that are amenable to endoscopic therapy.102-105 Moderate- or well-differentiated grade, lack of lymphovascular invasion, lesion size less than 3 cm, and confinement to the mucosa are all features of a good prognosis. Invasion into the submucosa is a marker of T1b disease and is graded as superficial, moderate, or deep invasion (sm1, sm2, and sm3, respectively). Even superficial (sm1) invasion into the submucosa has been associated with a substantial rate of lymph node involvement, making endoscopic therapy inadequate for patients with any submucosal extension of disease.106-108 However, more recent data indicate that sm1 tumors can be effectively treated with endoscopy.109,110 Given the inconsistencies in results, such patients require multidisciplinary treatment teams that consider not only tumor characteristics but also patient features.

Studies of endoscopic management of superficial EAC at tertiary care centers have reported rates of local control of neoplasia greater than 95%.107 The survival times of these patients may not differ from those of age- and sex-matched cohorts without neoplasia. These excellent results were achieved by careful selection of patients for treatment; those with tumor invasion of the submucosa did not receive this conservative therapy but were instead sent for consultation for surgical therapy.102,110

After complete endoscopic resection, endoscopic eradication therapy is recommended to remove any residual Barrett’s esophagus. As many as 30% of patients who undergo endoscopic resection of EAC without adjuvant eradication therapy develop recurrent EAC.107,111-113 A number of eradication therapies are available, although there is no level 1 evidence for the superiority of one over another after endoscopic resection of superficial EAC.

The most reported modality is radiofrequency ablation (RFA). Data from prospective cohort studies have shown that ≥80% of patients with T1a EAC can achieve complete eradication of all dysplasia with RFA.114-115 However, in an
analysis of a cohort that included patients without cancer at baseline, 33% had recurrence of intestinal metaplasia within 2 years after complete eradication of Barrett’s esophagus. Rates of recurrence in patients with T1a tumors may be higher than those in patients who undergo RFA for less advanced lesions, such as Barrett’s esophagus with no dysplasia (Supplementary Figure 2). Additionally, these neoplasias might be of a higher grade in subjects treated endoscopically for EAC than those treated with RFA for Barrett’s esophagus. For these reasons, aggressive endoscopic surveillance is recommended in patients after they have undergone EMR and RFA for superficial EAC.

Although evidence-based guidelines are not available, experts recommend surveillance every 3 months for the first year after endoscopic therapy, every 6 months during the second year, and annually thereafter. Endoscopic cryotherapy and photodynamic therapy have also been shown to be effective in patients with EAC, although there are fewer data on outcomes. Stepwise radical endoscopic resection of residual Barrett’s esophagus can be successfully undertaken after EMR of superficial EAC but appears to be associated with an unacceptably high rate of stricture formation compared with ablative therapy. Figure 5 shows a suggested algorithm to manage patients with early-stage EAC.

**Esophagectomy.** Although surgery is less commonly used to treat superficial neoplasia, there are situations in which it is appropriate to consider esophagectomy. For instance, in subjects with poor esophageal transit secondary to strictureing and aperistalsis, preservation of the esophagus with endoscopic therapy can still have a poor functional outcome. In these situations, esophagectomy can address the neoplasia and the poor esophageal function. In tertiary care centers, esophagectomy for high-grade dysplasia or T1a cancer is associated with less than 3% mortality. However, morbidity, primarily in the form of pulmonary and wound infection, and anastomotic leaks occur in more than 30% of patients undergoing esophagectomy.

**Locally Advanced Adenocarcinoma**

Although several high-quality studies have been performed, the optimal approach to management of locally advanced EAC is unclear. In the United States, the most common approach involves neoadjuvant chemotherapy and external beam radiotherapy (CRT). There have been a range of results reported on the benefits of neoadjuvant chemotherapy or CRT before surgery compared with surgery alone. Some studies reported increases in survival and the likelihood of pathological R0 resection after combined therapy, whereas others did not. Study findings are difficult to interpret because patients with EAC and those with squamous cell carcinoma, as well as patients with different stages of disease, have been included in many studies. Meta-analyses of the value of CRT before resection have found that CRT increases overall survival times and rates of

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**Figure 5.** Endoscopic management of early EAC. Depth of invasion, as assessed by EMR or ESD, is the key to appropriate subsequent therapy. BE, Barrett’s esophagus; LVI, lymphovascular invasion.
R0 resection compared with surgery alone, making CRT the most common approach in the United States.132–134 In most trials, patients were given cisplatin or carboplatin with 5-fluorouracil. Concurrent external beam radiation dosage varied from 35 to 45 Gy. There are data to support the efficacy of an alternative approach in which only chemotherapy is given before resection; this is commonly used in the United Kingdom.135,136 It is unclear how much neoadjuvant CRT improves outcomes of patients with early-invasive EAC (T1b); surgical resection without neoadjuvant therapy can be recommended in this subgroup of patients.

Most patients with locally advanced neoplasia have been treated with surgery, not only with curative intent but also to relieve dysphagia and improve quality of life for patients who could not be cured. The advent of stenting has decreased the use of surgery for palliation.

Esophagectomy. Esophagectomy is an important component of therapy used to treat patients with locally advanced EAC. Several approaches have been described, and each has its merits. Ivor–Lewis esophagectomy involves abdominal and right thoracic incisions. The stomach is mobilized through the abdominal incision, the esophagus is removed, and lymph nodes are collected through the chest incision; an intrathoracic esophagogastric anastomosis is then made. This approach has the advantage of providing an excellent yield of lymph nodes for histological assessment and good exposure to the lesion, especially for cancers in the distal third of the esophagus.

Transhiatal esophagectomy involves left neck and abdominal incisions.137 The esophagus is mobilized by blunt dissection through the hiatus from the abdominal incision. An anastomosis is made via the neck incision. This approach generally avoids a thoracotomy but provides less exposure to the tumor site and potentially fewer lymph nodes for examination. Tri-incisional esophagectomy uses a laparotomy, a thoracotomy, and a neck incision, allowing excellent lymphadenectomy of abdominal and thoracic lymph nodes. Neck anastomosis is generally performed on the left side to decrease the likelihood of recurrent laryngeal nerve injury.

Minimally invasive esophagectomy is the most recently described approach and relies on thorascoscopic access to the chest and laparoscopic access to the abdomen to achieve excision of the esophagus.138 It is associated with the quickest recuperation, and because of the expanded abilities of thorascoscopy, it can, in expert hands, provide adequate lymph node yield to assess for metastatic disease.139,140

Which of these approaches is best is a hotly contested issue in the surgical literature.141–143 Single-center studies from groups with expertise in each of the 3 approaches have provided excellent results.138,144,145 There is no level 1 evidence that any single approach increases survival times compared with the others. Randomized studies have associated transhiatal approaches with less morbidity than transthoracic approaches, but the percentages of patients with long-term survival did not differ significantly.146 In general, local expertise is probably a better predictor of outcome than approach.

One recurrent theme in the surgical literature is that center volume of esophagectomy is an important deciding factor of outcome.147–149 Thirty-day mortality is associated with the number of esophagectomies performed at the center. In addition to operator technique, aspects of care such as intensive care unit management and early detection of complications likely play a role in these differential outcomes. Despite the availability of neoadjuvant therapy for patients with locally advanced disease, mortality is high. The median survival times reported for patients who received CRT in these trials ranged from 16 to 49 months; 3-year rates of overall survival ranged from 32% to 59%.

These disappointing results led to the development of newer chemotherapeutic agents designed to target cancer cells. Molecular profiling of individual cancers may allow the use of agents tailored to the susceptibility of the tumor. For example, gastric and gastroesophageal junction tumors, which overexpress human epidermal growth factor receptor 2, appear to respond to trastuzumab when combined with cisplatin and a fluoropyrimidine.150 Tumor characterization may also allow clinicians to discern the mechanisms by which the tumor protects itself from the effects of CRT. For instance, because standard CRT induces formation of DNA adducts, therapeutics might be developed to alter production of proteins that repair the adducts.151 Studies are under way to investigate both of these approaches. Ramucirumab, an antibody against vascular endothelial growth factor receptor 2, showed some efficacy as a salvage therapy for gastroesophageal junction and gastric cancers in early-stage trials.152 However, its effect was modest, increasing median survival time by 1.4 months (hazard ratio, 0.77; 95% CI, 0.603–0.998).

Patients With Unresectable or Metastatic Disease and Patients Who Cannot Undergo Surgery

Chemoradiation or chemotherapy is a definitive therapy for patients with advanced disease that cannot be cured by surgery. They are generally treated by chemotherapy or CRT, and their 5-year rate of survival is less than 15%. For these patients, multimodal therapy with chemoradiation appears superior to radiation alone, increasing median survival by approximately 4 months.153,154

Endoscopic therapy also has an important role in palliating locally advanced and distant metastatic disease. Dilation using balloons or bougies may provide transient relief of dysphagia but is unlikely to have a long-lasting effect given the aggressive nature of the lesion. Palliative tumor debulking of more advanced lesions via resection, thermal therapies, cryotherapy, and/or photodynamic therapy have all been described and can improve quality of life and in some instances forestall stent placement.121,155–158 A program of intermittent palliative endoscopic treatments at 2- to 3-month intervals may attain local control of the disease, allowing adequate oral intake and decreased dysphagia.121

Placement of endoscopic stents has become increasingly less difficult with improved technology. Covered self-expandable metal stents are often used for this indication,
and their use is associated with marked improvement in symptoms of dysphagia.\textsuperscript{159,160} However, this therapy has not been shown to increase survival times, and patients and clinicians must be familiar with the potential adverse effects of stent placement. One common adverse effect is stent migration, which occurs in up to 15% of patients and can require surgery for removal.\textsuperscript{159} Chest pain is also common and can be difficult to distinguish from pain secondary to the EAC.\textsuperscript{161,162} The most catastrophic complication is erosion into a major blood vessel, which is often a terminal event.\textsuperscript{163,164} Because of excellent initial rates of response of tumors to CRT, stenting at the time of tumor discovery is generally not recommended given the additional risk it entails, the chance of migration after tumor debulking from CRT, and the impediment it presents for possible future endoscopic cytotherapy.

**Conclusion**

EAC is an increasingly common and highly lethal tumor that is associated with Barrett's esophagus, its precursor lesion. Barrett's esophagus and EAC are most common in elderly, overweight white men with symptoms of GERD. Other risk factors include use of tobacco, lack of \textit{H pylori} infection, and use of certain medications; there is an inverse association between EAC and use of nonsteroidal anti-inflammatory drugs. EAC most commonly presents with dysphagia, but patients may also present with weight loss, anemia, or manifestations of distant metastases. Only a small minority of these cancers in most series present as part of an endoscopic surveillance program for Barrett's esophagus.

Diagnostic analysis generally begins with upper endoscopy. The lesion is usually obvious during white light endoscopy, and analysis of biopsy specimens of the lesion confirm the presence of EAC. For tumors that are not bulky, EMR is required to differentiate between T1a and more deeply invasive EAC. PET/CT can identify distant metastases. In cases in which the disease is confined to the mediastinum, EUS, potentially with sampling of any pathological-appearing lymph nodes, can help define depth of invasion and nodal status. In some cases, bronchoscopy and/or magnetic resonance imaging of the brain is necessary to rule out tumor involvement of the trachea or brain.

Multiple disease- and patient-specific characteristics must be considered in selecting the optimal treatment for patients with EAC. The most important of these is the stage of the tumor at diagnosis. T1a tumors can be effectively treated with endoscopic therapy, most commonly by endoscopic resection followed by ablative therapy. Invasion into the submucosa, especially the deep submucosa, is associated with an increased rate of lymph node involvement, making endoscopic therapy a suboptimal approach in the good surgical candidate. For patients with stage T1b tumors, esophagectomy may be used as a sole therapeutic modality. For patients with locally advanced disease without distant metastases, the most common treatment in the United States is neoadjuvant CRT followed by esophagectomy in patients who are candidates for surgery. For those with distant metastatic disease, definitive CRT is often used. In patients with locally advanced disease, as well as those with distant metastases, endoscopic therapy can offer significant palliation of dysphagia. Because of the vital role of endoscopic therapy in the diagnosis and treatment of patients with EAC, endoscopists must be included in the cancer care team and should be engaged in multimodal planning conferences.

Despite remarkable advances in the care of patients with EAC, overall mortality remains high, with 5-year survival rates of less than 20%. This is because most patients present with late-stage disease and are not eligible for the highly effective, usually curative, endoscopic therapies that have evolved over the past 15 years. Although advances in radiotherapy and surgical technique have reduced the toxicity of these therapies, the likelihood of R0 resection, based on pathological analysis, and long-term survival after these nonendoscopic therapies is unacceptably low. This points to a need for improved screening for this condition to detect disease at earlier, more curable stages, as well as improved prevention with endoscopic, behavioral, and medical approaches. In addition, molecular characterization of these tumors may allow for less toxic and more tumor-specific therapies.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of \textit{Gastroenterology} at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.04.053.

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Conflicts of interest
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Supplementary Figure 1. Survival after esophagectomy according to T classification in pN0 M0 disease. (A) Current (2002) classification. The numbers of patients in each classification and traced at 5 years, respectively, were as follows: Tis, 44 and 21; T1, 98 and 26; T2, 31 and 8; T3, 57 and 12; and T4, 4 and 0. (B) Proposed subclassification of T1 into T1a (intramucosal, n = 66, 18 traced at 5 years) and T1b (submucosal, n = 32, 8 traced at 5 years). Shown for reference are Tis (high-grade dysplasia) and T2. Vertical bars represent 68% confidence limits. Reproduced with permission from Rice et al.86

Supplementary Figure 2. Durability of complete eradication for intramucosal adenocarcinoma compared with Barrett’s esophagus of varying degrees of dysplasia. (A) Overall recurrence rate of the cohort. (B) Recurrence rate broken out by baseline histology. IMC (T1a) has a higher recurrence rate than nondysplastic Barrett’s esophagus. LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma (T1a). Reproduced with permission from Pasricha et al.118