REVIEW ARTICLE

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Esophageal Carcinoma

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Esophageal adenocarcinoma has become the predominant type of esophageal cancer in North America and Europe, and gastroesophageal reflux disease (GERD) and obesity are the main risk factors. Barrett's esophagus, the recognized precursor lesion, can be detected by means of endoscopic screening, which is followed by treatment of precancerous lesions and monitoring for the development of neoplastic progression. Esophageal squamous-cell carcinoma remains the predominant esophageal cancer in Asia, Africa, and South America and among African Americans in North America. Alcohol and tobacco use are the main risk factors, and esophageal squamous dysplasia is the precursor lesion. The 5-year survival rate for patients with esophageal cancer, although generally poor, has improved during the past decade, and long-term survival is increasingly possible for patients with early or locally advanced disease. This review discusses the epidemiologic aspects and pathogenesis of these two esophageal cancers, as well as prevention and therapy, focusing on recent advances.

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Epidemiologic Aspects of Adenocarcinoma and Squamous-Cell Carcinoma

Esophageal cancer has two main subtypes — esophageal squamous-cell carcinoma and esophageal adenocarcinoma. Although squamous-cell carcinoma accounts for about 90% of cases of esophageal cancer worldwide, the incidence of and mortality rates associated with esophageal adenocarcinoma are rising and have surpassed those of esophageal squamous-cell carcinoma in several regions in North America and Europe. Esophageal carcinoma is rare in young people and increases in incidence with age, peaking in the seventh and eighth decades of life. Adenocarcinoma is three to four times as common in men as it is in women, whereas the sex distribution is more equal for squamous-cell carcinoma.

In the United States, more than 18,000 new cases of esophageal cancer and more than 15,000 deaths from esophageal cancer were expected in 2014. Over the past three decades, the rates of esophageal squamous-cell carcinoma have declined, while those of esophageal adenocarcinoma have been progressively increasing (Fig. 1).[1]

Environmental Risk Factors

Population-based case–control and cohort studies indicate that GERD, cigarette smoking, and obesity are the main risk factors for esophageal cancer. The odds that esophageal adenocarcinoma will develop increase by a factor of five for persons with weekly GERD symptoms and by a factor of seven for persons with daily GERD symptoms, as compared with those with less frequent episodes.[2] The absolute risk of esophageal adenocarcinoma developing in a person 50 years of age or older is

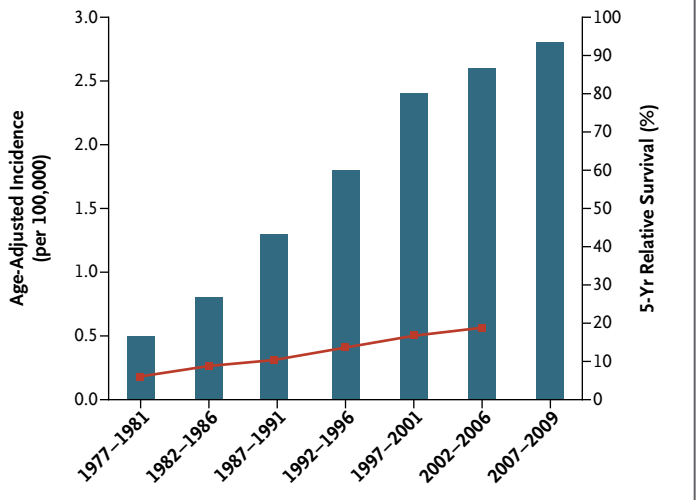

Figure 1. Temporal Trends in Incidence Rates and Survival Rates for Esophageal Adenocarcinoma.

Blue bars denote age-adjusted incidence rates and the red line 5-year survival rates for persons with esophageal adenocarcinoma diagnosed in the United States. Data are from population-based Surveillance, Epidemiology, and End Results cancer registries.

approximately 0.04% per year.[3] However, up to 40% of all patients with esophageal cancer do not report GERD symptoms.

The risk of esophageal adenocarcinoma is approximately twice as high among current smokers as it is among people who have never smoked, but smoking is a considerably stronger risk factor for esophageal squamous-cell carcinoma than for esophageal adenocarcinoma.[4,5] In contrast, population-based studies have not shown an association between alcohol consumption and esophageal adenocarcinoma.[6] Unlike adenocarcinoma, esophageal squamous-cell carcinoma is three to five times as likely among people who consume alcohol (three or more drinks daily), and the risk increases synergistically with tobacco smoking. High intake of red meats, fats, and processed foods is associated with an increased risk of both types of esophageal cancer, whereas high intake of fiber, fresh fruit, and vegetables is associated with a lower risk.[7,8]

The rising incidence of esophageal adenocarcinoma has been hypothesized to be related to the increasing prevalence of GERD alone and obesity plus GERD, combined with the declining prevalence of *Helicobacter pylori* infection. Obesity is associated with a risk of esophageal adenocarcinoma that is increased by a factor of 2.4 to 2.8.[9,10] Abdominal obesity in particular is associated with an increased risk of Barrett's esophagus and cancer,[11] possibly because increasing intragastric pressure relaxes the lower esophageal sphincter and leads to hiatal hernia, and these factors together may promote and exacerbate GERD.[12] Abdominal adiposity is more common in men, which has led to speculation that such adiposity explains some sex-related differences in cancer risk.

Populations in which *H. pylori* infection is prevalent have a reduced risk of esophageal adenocarcinoma. A meta-analysis of 15 observational studies showed that the risk of adenocarcinoma decreased by 41% among persons with *H. pylori* infection.[13] *H. pylori* infection, which leads to gastritis, may ultimately reduce acid production through gastric atrophy, thus decreasing the exposure of the esophageal epithelium to acidic contents and reducing the risk of Barrett's esophagus[14,15] and adenocarcinoma. However, treatment and eradication of *H. pylori* in infected patients neither causes nor exacerbates GERD in most cases.[16] Overall, no consistent association between *H. pylori* and esophageal squamous-cell carcinoma has been proved.[17]

Esophageal adenocarcinoma has been reported in association with alendronate use.[18] However, subsequent population-based studies and meta-analyses examining the association between bisphosphonate use and esophageal adenocarcinoma yielded conflicting results.[19-21] Oncogenic human papillomaviruses may increase the risk of esophageal squamous-cell carcinoma, but the evidence is inconclusive.[22] In addition, esophageal squamous-cell carcinoma is up to 10 times as likely to develop in patients with achalasia, an esophageal motility disorder, as it is in persons without achalasia.[23]

GENETIC RISK FACTORS

Familial clustering in Barrett's esophagus and adenocarcinoma has been observed. In one genomewide, combined linkage-association analysis, germline mutations were identified in one of three candidate genes — *MSR1*, *ASCC1*, and *CTHRC1* — in 11% of patients with Barrett's esophagus or adenocarcinoma.[24] Mutant MSR1 is associated with cyclin D1 overexpression, which results in more rapid cell-cycle progression.[25] In another

genomewide association study, susceptibility loci for Barrett's esophagus and adenocarcinoma were identified — in *CRTC1* (which encodes CREB-regulated transcription factor), *BARX1* (which encodes a protein involved in esophageal specification), and *FOXP1* (which encodes a protein involved in esophageal development).[26]

A rare familial form of esophageal squamous-cell carcinoma — tylosis palmaris et plantaris (also called palmoplantar keratoderma), an autosomal dominant disorder characterized by hyperkeratosis of the palms and soles — has been linked to a locus on chromosome 17q21-22[27]; missense mutations in *RHBDF2*, a gene that encodes an inactive rhomboid protease, have been identified.[28] Genomewide association studies have identified a number of other susceptibility loci in Chinese patients with esophageal squamous-cell carcinoma,[29-33] which suggests that there are complex gene–environment interactions involved.

A recent study analyzed the mutational spectra from whole-exome sequencing of paired samples of tumor and normal tissue obtained from patients with esophageal adenocarcinoma and found mutations in 28 genes, 5 of which (*TP53*, *CDKN2A*, *SMAD4*, *ARID1A*, and *PIK3CA*) are relevant to the pathogenesis of adenocarcinoma.[34] Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, lists genes and molecular pathways that have been found to have alterations reported as prevalent among patients with esophageal adenocarcinoma. Lineage-specific factors, especially transcription factors, appear to be important in the development of esophageal cancers.[34] Likewise, whole-genome and whole-exome sequencing in Chinese patients with esophageal squamous-cell carcinoma revealed eight mutated genes — six known tumor-associated genes (*TP53*, *RB1*, *CDKN2A*, *PIK3CA*, *NOTCH1*, and *NFE2L2*) and two novel genes (*ADAM29* and *FAM135B*).[35]

ANIMAL MODELS OF ESOPHAGEAL CANCERS

Several animal models of esophageal carcinoma are available. Surgical models in rodents, in which gastrectomy with esophagojejunal anastomosis or esophagoduodenal anastomosis is used to induce major biliary reflux, have permitted the recapitulation of Barrett's esophagus and subsequent progression to neoplasia. A mouse model in which p120-catenin, which normally stabilizes E-cadherin at the cell membrane, is ablated solely in the esophagus results in invasive esophageal squamous-cell carcinoma.[36]

Genetic models of esophageal adenocarcinoma also exist. For example, the esophageal-specific Epstein–Barr virus–L2 promoter, when fused to the gene encoding interleukin-1β, induces a proinflammatory microenvironment and can induce Barrett's esophagus in mice.[37] Bile acid in the drinking water or crossbreeding with other mice that harbor a null allele of the $p16^{INK4a}$ tumor-suppressor gene accelerates the development of esophageal adenocarcinoma. In a separate approach, the global knockout of *p63*, which is known to be critical in the proliferation of squamous epithelial stem or progenitor cells,[38] results in the postnatal migration of a Barrett-like cell population to the squamous–columnar junction.[39]

In an approach that is complementary to the use of animal models, three-dimensional cell-culture "organotypic" models have been developed to elucidate pathways in the development and maintenance of Barrett's esophagus.[40-42] Barrett's esophagus may involve a switch in the fate of resident stem or progenitor cells, resulting in either reprogramming or transdifferentiation of squamous esophageal basal cells or in the migration of gastric cardia cells. After Barrett's esophagus cells emerge, dysplasia and neoplastic progression occur within the lesions, influenced by local or systemic factors (see Fig. S2 in the Supplementary Appendix). Three-dimensional organotypic culture models have also been used to study esophageal squamous-cell carcinoma.[43]

ENDOSCOPIC SCREENING AND SURVEILLANCE

In Barrett's esophagus, which is considered the precursor of esophageal adenocarcinoma, specialized intestinal columnar epithelium replaces the normal squamous epithelium.[44] The results of large cohort studies suggest that the annual cancer risk for patients with nondysplastic Barrett's esophagus is 0.12 to 0.40%.[45,46] Dysplasia within Barrett's esophagus lesions signals a marked increase in cancer risk — the annual risk is approximately 1% for patients with low-grade dysplasia and more than 5% for patients with high-grade dysplasia. However, 80 to 90% of cases of esophageal ad-

enocarcinoma are diagnosed in patients without known Barrett's esophagus.[47] Endoscopic screening results in detection of Barrett's esophagus in 6 to 12% of patients with prolonged GERD symptoms, most frequently white men older than 50 years of age.[48,49] Endoscopic surveillance every 3 years is recommended for patients with known nondysplastic Barrett's esophagus.[48] Despite the absence of direct evidence from randomized trials,[50] most[51,52] but not all[53] observational studies have shown that patients in whom adenocarcinoma is detected during endoscopic surveillance for Barrett's esophagus are more likely to have early-stage cancer, receive curative therapy, and survive longer than symptomatic patients in whom adenocarcinoma is detected.

In addition to leading to early detection of cancer, radiofrequency ablation of Barrett's esophagus lesions with low-grade or high-grade dysplasia results in resolution of esophageal metaplasia in up to 77% of cases and resolution of dysplasia in 86% of cases, as well as in a lower risk of progression and fewer cancers.[54] Long-term follow-up has demonstrated the durability of such effects, but continued surveillance after radiofrequency ablation is essential because of recurrences, which are mostly nondysplastic and endoscopically manageable.[55] Current guidelines do not support the use of endoscopic ablation for nondysplastic Barrett's esophagus; however, in our opinion, high-risk patients with long-segment Barrett's esophagus, severe GERD, or a family history of Barrett's esophagus or adenocarcinoma should be considered for ablative procedures. Decisions for individual patients with precancerous conditions are usually personal and unconnected to societal cost-effectiveness calculations.[56,57] Although other tissue and blood biomarkers of Barrett's esophagus progression have been studied,[58] none have been shown to clearly outperform endoscopically detected dysplasia in predictive accuracy.

The precursor lesion for squamous-cell carcinoma is esophageal squamous dysplasia; patients with mild, moderate, or severe dysplasia have a risk of squamous-cell carcinoma that is increased by a factor of 3, 10, or 30, respectively.[59] Endoscopic screening or nonendoscopic use of balloon brush cytologic testing has been performed in some regions in China and may have merit; these techniques are also recommended for patients with achalasia or those with a history of lye ingestion resulting in stricture, although there are no evidence-based guidelines for the treatment of these patients.

PREVENTION

PROTON-PUMP INHIBITORS

Several observational, clinic-based cohort studies have shown a significant association between treatment with proton-pump inhibitors and a decreased risk of high-grade dysplasia and adenocarcinoma in patients with Barrett's esophagus,[60-62] although limitations of these studies included possible selection bias and limited adjustment for possible confounders.[63] Several retrospective cohort studies have shown no reduction in the risk of esophageal adenocarcinoma among patients with GERD or Barrett's esophagus after antireflux surgery,[64,65] which is not recommended for the sole purpose of cancer prevention.

ASPIRIN AND NSAIDS

Observational studies show a 40 to 50% reduction in the risk of esophageal adenocarcinoma and squamous-cell carcinoma with aspirin or nonsteroidal antiinflammatory drug (NSAID) treatment.[66] Given the additional cancer-reducing benefits of aspirin and NSAIDs, these medications have been recommended for general cancer chemoprevention in high-risk groups.[67] However, one randomized trial of daily celecoxib treatment did not show a reduction in cancer risk among patients with Barrett's esophagus and low-grade or high-grade dysplasia.[68] Another randomized trial showed that celecoxib did not affect the progression of esophageal squamous dysplasia.[69] Large trials examining the effects of proton-pump inhibitors and aspirin on clinical outcomes in Barrett's esophagus are ongoing.[70]

STATINS

A meta-analysis of 13 studies involving humans showed a 28% reduction in the risk of esophageal adenocarcinoma among overall statin users, as compared with nonusers, and a 41% reduction in the risk of esophageal adenocarcinoma among patients with Barrett's esophagus.[71] However, there was considerable inconsistency in these studies and no clear associations with dose, duration, or statin type.

The translation of other findings from epidemiologic studies into prevention recommendations — such as tobacco cessation, weight loss,[72]

Table 1. Management of Esophageal Adenocarcinoma.

Management	Approach
Staging	Endoscopy with or without mucosal resection, computed tomography of the chest and abdomen, endoscopic ultrasonography, and positron-emission tomography
Treatment	
Mucosal tumors (stage 0 or I)*	
All tumors except T1b	Endoscopic mucosal resection (first choice) or esophagectomy with lymphadenectomy
T1b tumors	Esophagectomy with lymphadenectomy
Localized tumors (stage IIA or IIB)†	Esophagectomy preceded by neoadjuvant chemoradiotherapy (or neoadjuvant chemotherapy)
Advanced tumors (stage III or IV)	Endoscopic palliation with the use of self-expanding metal stents, with or without brachytherapy
Advanced or recurrent tumors	Two-drug or three-drug combination chemotherapy, commonly FOLFOX (infusional fluorouracil plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin), or chemoradiotherapy

* Patients who are not healthy enough or are unwilling to undergo these procedures should be treated with definitive chemoradiotherapy.
† Patients who are not healthy enough or are unwilling to undergo these procedures should be treated with definitive chemoradiotherapy, especially if they have squamous-cell carcinoma.

and modification of diet to one of high fiber and low meat intake — although logical, has no clear basis. Prevention trials in China showed no benefit of nutritional supplements including vitamins and minerals in reducing the prevalence of premalignant lesions[73] or in reducing the incidence of or mortality associated with esophageal cancer, either in the general population[74] or among persons with esophageal squamous dysplasia.[75]

CLINICAL PRESENTATION OF ESOPHAGEAL CANCER

The clinical presentation is similar between esophageal adenocarcinoma and squamous-cell carcinoma, despite differences in demographic and risk factors. The endoscopic appearance is also similar, although approximately three quarters of all adenocarcinoma lesions are found in the distal esophagus, whereas squamous-cell carcinoma is more frequent in the proximal to middle esophagus. Common clinical presentations include progressive dysphagia, weight loss, and heartburn unresponsive to medical treatment, as well as signs of blood loss; however, an increasing number of essentially asymptomatic cases are being discovered as part of screening and surveillance endoscopy. Less common symptoms include hoarseness, cough, and pneumonia related to laryngeal nerve paralysis or invasion of the tracheobronchial tree. There is also an increased risk of synchronous and metachronous esophageal squamous-cell carcinoma in patients with head and neck squamous-cell carcinoma.

MANAGEMENT

An outline of the management of esophageal carcinoma is shown in Table 1. The management is generally similar for the two histologic types of esophageal carcinoma, except for several differences in the choice of chemotherapy or surgery. Adenocarcinoma involving the gastroesophageal junction is generally considered part of the continuum of esophageal adenocarcinoma.

STAGING

The prognosis and treatment for patients with esophageal carcinoma depend on accurate and reliable assessment of the depth of invasion and status with respect to lymph-node involvement (Fig. 2, and Table S2 in the Supplementary Appendix).[76] In the past decade, the use of endoscopic ultrasonography and positron-emission tomography (PET) has improved staging. Endoscopic ultrasonography has increased the accuracy of assessments of tumor and lymph-node status and is reported to have 70 to 80% accuracy; adding

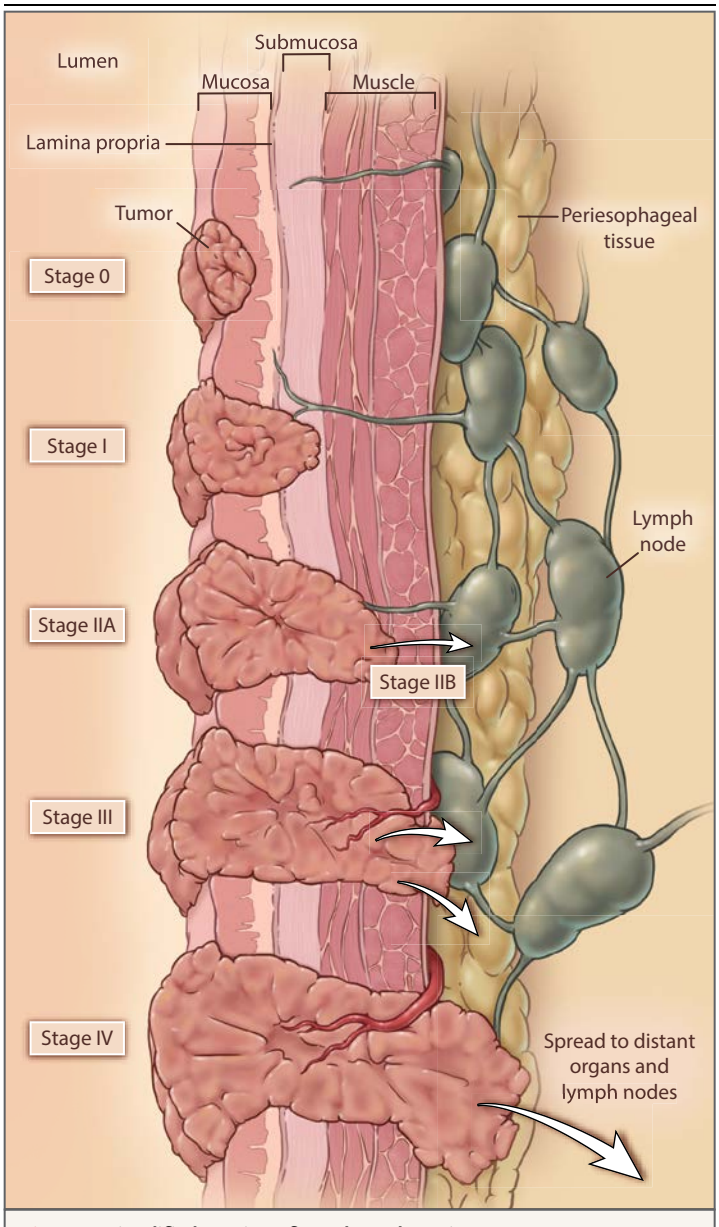

Figure 2. Simplified Staging of Esophageal Carcinoma.

Stages 0 through IV are used to classify carcinoma characterized by different degrees of tumor invasion, lymph-node involvement, and metastasis. Stage 0 tumors are intramucosal tumors that do not invade the lamina propria. Stage I tumors invade the lamina propria without lymph-node or distant involvement. Stage II tumors extend to the muscle layer either without (IIA) or with (IIB) lymph-node involvement. Stage III tumors invade through the muscular layer and involve lymph nodes or other adjacent structures. Stage IV tumors spread to distant organs or lymph nodes. For detailed information, see Table S2 in the Supplementary Appendix.

fine-needle aspiration to endoscopic ultrasonography further improves the sensitivity of lymph-node staging.[77] Endoscopic ultrasonography is particularly helpful for staging in patients with no obvious regional or distant spread seen on imaging of the chest and abdomen; in such cases, endoscopic mucosal resection offers improved staging as well as an opportunity for cure. PET scanning identifies occult distant metastases, which are most common in the supraclavicular and retroperitoneal lymph nodes, and leads to establishment of a more advanced stage in 10 to 20% of cases.

MUCOSAL TUMORS

The introduction of endoscopic mucosal resection with or without ablation has been a major advance in treating Barrett's esophagus with high-grade dysplasia or adenocarcinoma that is limited to the epithelial portion of the mucosa (category T1a), particularly for small tumors (<2 cm in diameter) that are asymptomatic and noncircumferential. This approach is usually supplemented by endoscopic ablation of the remaining Barrett's esophagus lesions (Fig. 3). The risk of lymph-node metastasis is correlated with the depth of tumor invasion; the risk is close to zero among patients with Barrett's esophagus who have high-grade dysplasia and is only 1 to 2% among patients with stage I tumors.[78] There are no data from randomized trials comparing endoscopic therapies with surgical approaches,[79] but several observational studies have suggested that cure and survival rates associated with endoscopic treatments are equivalent to the rates with surgical resection.[80] Endoscopic therapy should be considered as first-line therapy for patients with stage 0 or I esophageal adenocarcinoma who do not have contraindications or major coexisting conditions.[81] In patients with category T1b tumors that have penetrated the muscularis mucosae and entered the submucosa, the risk of lymph-node spread is as high as 20%, and radical esophagectomy may be the preferred method of treatment, although some treatment centers have expanded the indications for endoscopic therapy to include low-risk submucosal tumors.[82]

LOCALLY ADVANCED TUMORS

Locally advanced tumors, defined as category T3N1, are best treated with esophagectomy. Although cure through definitive chemoradiotherapy alone has been reported, especially in patients with squamous-cell carcinoma,[83] that approach is not supported by evidence from randomized, controlled trials and should be restricted to pa-

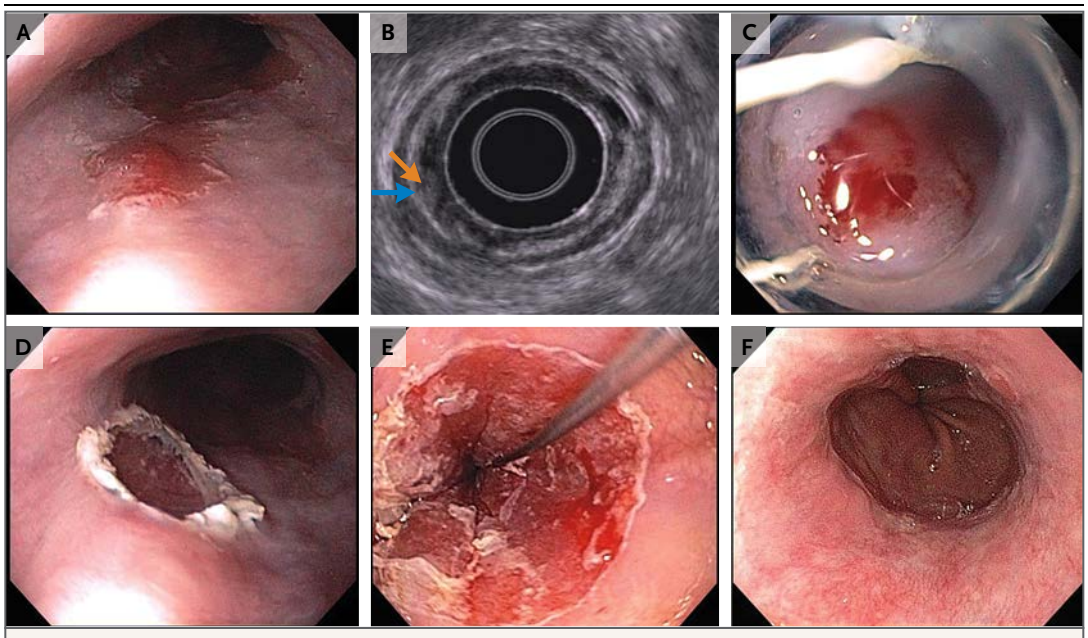

Figure 3. Endoscopic Images.

Panel A shows intramucosal adenocarcinoma in the background of Barrett's esophagus at the lower end of the esophagus. Panel B is an endoscopic ultrasound image showing esophageal mucosa thickening (orange arrow) and intact submucosa (blue arrow). Panel C shows endoscopic mucosal resection with the use of a suction cap, followed by band application and resection with a thermal snare. Panel D is the view after endoscopic mucosal resection, showing exposed clean submucosa. Panel E is the view after radiofrequency ablation of the remaining Barrett's esophagus, showing superficial circumferential ulceration and denuding of the Barrett's esophagus. Panel F shows the healed esophagus approximately 3 months later. Follow-up biopsy results showed normal squamous epithelium with no metaplasia, dysplasia, or cancer.

tients whose condition is declining or who are not healthy enough to undergo esophagectomy. Unfortunately, esophagectomy alone is associated with a high rate of recurrence and low 5-year survival rates (5 to 34%). The main advance in treating patients who undergo esophagectomy has been the adoption of neoadjuvant treatment. Randomized, controlled trials have shown a survival benefit with neoadjuvant chemoradiotherapy or chemotherapy, as compared with esophagectomy alone, in both types of esophageal carcinoma.[83-85] Chemoradiotherapy with carboplatin and paclitaxel[84] or cisplatin and fluorouracil[85] is becoming the standard treatment in the United States[86]; in Europe, neoadjuvant chemotherapy alone is the preferred approach. There may be a small advantage to neoadjuvant chemoradiotherapy over chemotherapy alone. A meta-analysis showed a pooled hazard ratio for death from any cause of 0.78 (95% confidence interval [CI], 0.70 to 0.88) for neoadjuvant chemoradiotherapy and 0.87 (95% CI, 0.79 to 0.96) for neoadjuvant chemotherapy, with a greater benefit in adenocarcinoma than in squamous-cell carcinoma.[87] Chemotherapy before and after resection may have a small additional benefit in patients with squamous-cell carcinoma.[88] There is no reliable test apart from histologic examination of the resected specimen to confirm the response to neoadjuvant therapy, and esophagectomy therefore remains necessary. Patients with adenocarcinoma who have residual, node-positive, completely resected disease after neoadjuvant therapy have poor outcomes, and the benefits of adjuvant chemotherapy or chemoradiotherapy are unclear in such patients. However, adjuvant chemotherapy is used for node-positive patients with squamous-cell carcinoma; this approach has been shown to have benefits in several randomized trials in Japan.[89]

Surgical outcomes appear to be better in high-volume centers and with experienced surgeons, a benefit apparently related to the incidence and management of postoperative complications.[90] Two-field lymphadenectomy in the abdomen and tho-

rax is standard practice in most centers in Europe and North America, and additional dissection of lymph nodes of the neck is performed in some countries where squamous-cell carcinoma is common. Minimally invasive esophagectomy may have equivalent safety and a similar rate of complications, but it is technically challenging, even when performed in specialized centers.[91]

ADVANCED TUMORS

Obstructive symptoms related to unresectable disease can be palliated with endoscopic esophageal stenting (see Fig. S2 in the Supplementary Appendix) or high-dose intraluminal brachytherapy.[92] Endoscopic placement of self-expanding metal stents has become the first-line palliative option for dysphagia. Randomized, controlled trials have shown higher symptomatic relief, as well as less need for reintervention due to complications, with self-expanding metal stents than with locoregional treatment. The addition of high-dose brachytherapy to stenting may result in a modest prolongation of survival.[93] Other methods of treatment, such as endoscopic dilation or ablation, placement of plastic stents, bypass surgery, or chemoradiotherapy, are not recommended because of their low efficacy and high rates of complications.

Palliative chemotherapy for the prolongation of survival is also commonly used to treat patients with unresectable, metastatic, or recurrent disease. Treatment with cisplatin or oxaliplatin combined with either infusional fluorouracil or capecitabine achieves response rates of 35 to 45% and a few months of prolonged survival, especially among patients with squamous-cell carcinoma. The addition of a third drug may increase response rates by an additional 5 to 10 percentage points but is associated with higher toxicity. Second-line chemotherapy remains investigational. The use of gefitinib as a second-line treatment for unselected patients does not improve overall survival.[94] Promising results are emerging with docetaxel (which interferes with cell division by stabilizing microtubules)[95] and ramucirumab (which targets vascular endothelial growth factor receptor 2). Trastuzumab, a biologic agent in which ERBB2 is amplified, confers a modest 2.7-month increase in overall survival and a 1.7-month increase in progression-free survival among patients with advanced esophageal adenocarcinomas.[96]

PROGNOSIS

The overall 5-year survival rate for patients with esophageal adenocarcinoma in the United States is approximately 17%, which is slightly higher than the rate for patients with squamous-cell carcinoma (Fig. 1). There has been a progressive improvement in overall survival and a marked improvement in progression-free survival among patients who undergo surgical resection. In spite of the fact that the ability to detect early-stage esophageal adenocarcinoma has improved, most tumors are found when regional metastasis (in 30% of cases) or distant metastasis (in 40% of cases) has already occurred, at which point the 5-year survival rate declines from 39% in cases of localized disease to 4% in cases with distant metastasis. Furthermore, 60 to 70% of patients with esophageal cancer have not been receiving guideline-concordant treatment. The management of esophageal cancer appears to be improved by discussion with a multidisciplinary tumor board.

SUMMARY

The main risk factors for esophageal adenocarcinoma are GERD, obesity, and cigarette smoking; *H. pylori* infection is associated with a reduced risk. Cigarette smoking and alcohol consumption constitute the main risk factors for esophageal squamous-cell carcinoma. Endoscopic screening allows for the identification of Barrett's esophagus, which in turn allows for periodic surveillance of Barrett's esophagus for the detection of dysplasia and early-stage esophageal adenocarcinoma. Endoscopic ablative therapy has been shown to be efficacious for the treatment of dysplasia and may have an important role in the treatment of intramucosal adenocarcinoma. Identification of certain genomic regions and genes might provide insights into the underlying pathogenesis of esophageal cancer and may have translational implications for biomarker identification and development of novel therapies.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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