Esophageal cancer often is asymptomatic until it has advanced or metastasized to distant organs, limiting treatment options. The 2 most common forms are squamous cell carcinomas that appear in the upper or midesophagus and esophageal adenocarcinomas that tend to occur lower in the esophagus or at the gastroesophageal junction. Since the 1980s higher rates of esophageal adenocarcinomas have been reported. Radiation therapy has emerged as a standard treatment and palliative therapy for esophageal cancer. This article introduces readers to the biology, epidemiology, diagnosis, staging, and treatment of these most common forms of esophageal cancer.

This article is a Directed Reading. Your access to Directed Reading quizzes for continuing education credit is determined by your membership status and CE preference.

After completing this article, the reader should be able to:

- Discuss trends in the histology, imaging, and treatment of esophageal cancer.
- Identify components of esophageal anatomy relevant to diagnostic imaging of cancer.
- Compare the available evidence bases for adjuvant and neoadjuvant radiation therapy.
- List risk factors for the 2 leading types of esophageal cancer.
- Discuss the definitive, neoadjuvant, and palliative roles for external-beam radiation therapy.

Squamous cell carcinoma (SCC) was the predominant form of esophageal cancer until the 1980s, and remains so in most of the world and among certain patient populations. But since the 1980s, for reasons that are not entirely clear, the United States, England, and Australia have seen a dramatic shift in the etiology of esophageal cancers, to a predominance of esophageal adenocarcinomas. Because esophageal cancers tend to be asymptomatic until tumors are advanced and have invaded adjacent organs, regional lymph nodes, and frequently, distant organs such as the brain and lungs, these malignancies tend to be diagnosed at advanced and highly lethal stages.

Radiation therapy is playing an evolving and expanding role in managing esophageal cancers, and now is widely considered to be a definitive treatment modality and alternative to radical surgery in some cases. The risk of cardiopulmonary toxicities associated with radiation fields that include nontarget cardiac and respiratory tissue has prompted development of more tumor-contoured radiation therapy techniques such as 3-D conformal radiation therapy and intensity-modulated radiation therapy (IMRT) that help to minimize irradiation of healthy tissues while delivering therapeutic radiation doses to tumors and involved lymph nodes.

Functional Anatomy

The esophagus appears to be simply a muscle-lined tube that connects the pharynx to the stomach (see Figure 1). Approximately 18 cm to 26 cm long in adults, its extent is functionally demarcated by muscular upper and lower esophageal sphincters that control the entry of food and liquid into the esophagus, and their exit from the esophagus into the stomach.

The esophagus is not a uniform, straight tube; it is subtly curved in the coronal and anteroposterior planes, and has 3 constrictions at approximately 15, 23, and 40 cm from the incisor teeth. Some of these landmarks correspond with other structures through which
Abdominal esophagus – the portion between the diaphragmatic hiatus (T10) and the stomach (at T11), adjacent to the liver, where smooth muscle fibers predominate.1,2 The endoscopically visible boundary between the abdominal esophagus and stomach mucosa is called the Z-line.1 The lumen of the cervical and thoracic esophagus usually is compressed or collapsed but expands to accommodate swallowed boluses of food.1 The lumen wall of the abdominal esophagus is open and round, even in the resting state.1

The esophageal sphincters are made up of cartilage and 3 layers of muscle fibers with complex nerve supplies.1,2 Normally, the sphincters play important roles in preventing stomach acid from reaching the esophagus, pharynx, and mouth.1 However, sphincter dysfunction can lead to the upward migration of stomach bile and acid into the esophagus, a condition known as gastroesophageal reflux disease (GERD). Chronic GERD-associated tissue damage to the esophageal mucosa can contribute to tissue and cell changes that might lead to esophageal adenocarcinoma tumorigenesis.1 Disease-related upper esophageal sphincter dysfunction is known as oropharyngeal dysphagia and is associated with difficulty swallowing.1 The lower esophageal sphincter is made up of esophageal muscle fibers and diaphragm muscle, which normally helps to raise the pressure within the esophagus and help prevent backflow of stomach contents into the upper esophagus.1

The esophageal wall is made up of muscle strata sandwiched between an external adventitia layer and...
internal mucosa and submucosa tissue layers. A thin layer of connective tissue known as the lamina propria is situated immediately beneath the epithelial cells of the lumen surface. The epithelium and lamina propria are collectively referred to as the mucosa. A layer of muscle cells known as the muscularis mucosae separates the lamina propria from the submucosa. A serosa membrane layer that lines the stomach and distal gastrointestinal (GI) tract does not exist in the esophagus, and the absence of the membrane could contribute to the rapid spread of tumors in esophageal tissues and to complications in treating esophageal cancer. The innermost lumen-facing mucosa typically is made up of squamous epithelial cells.

Esophageal musculature, referred to as the muscularis propria, is made up of a thin outer layer of longitudinally oriented muscle fibers and an internal layer of laterally oriented muscle fibers that circumvent the mucosa and submucosa of the esophagus. The inner muscle fibers of the muscularis propria perform the swallowing motion as a tightly coordinated sequence of peristaltic contractions moving food from the pharynx to the stomach. Accessory muscle fibers also anchor the esophagus to adjacent structures such as the left respiratory bronchus. Close anatomic associations between the esophagus and adjacent structures allow esophageal tumors to spread not only through the blood and lymph systems but also directly into neighboring organs including the aorta and heart, vertebrae, trachea, bronchi, and lungs.

Various arteries supply blood to the cervical, thoracic, and abdominal esophagus. Similarly, esophageal blood drains from the submucosal tissues into different veins. The extensively interconnected immune lymphatic node and drainage system of the esophagus is situated in the mucosa, which can hasten the spread of tumor cells along the length of the esophagus and to distant organs.

Pathobiology

Esophageal cancer is one of the most aggressive and lethal types of cancer. Although benign esophageal neoplasms are fairly common, they rarely are symptomatic, and therefore seldom diagnosed. The vast majority of symptomatic esophageal neoplasms are malignant. These tumors appear to be associated with sources of chronic tissue inflammation. Chronic inflammation of the squamous epithelium triggers cellular dysplasia and tumorigenesis. Inflammation of esophageal tissues can be caused by repeated consumption of swallowed toxic, caustic, or scalding agents—or in the case of esophageal adenocarcinomas, by chronic GERD.

Malignancies of the esophagus typically begin in the mucosa and then grow to invade underlying layers of the esophagus and other tissues and organs. In addition to direct invasion of adjacent tissues and organs, esophageal tumors can spread via the lymph system and the bloodstream, causing metastatic tumors to emerge in the liver, lungs, bone, brain, iris of the eye, and other organs. Primary tumors in the esophagus also can invade the aorta, respiratory system, and vertebrae. Patients with these invasive tumors are not considered candidates for surgical tumor resection.

Esophageal malignancies can be histologically diverse and genetically heterogeneous. The most common types of esophageal cancers are epithelial malignancies: SCC, which also is called epidermoid esophageal carcinoma, and esophageal adenocarcinoma. There are histological variants of SCC including spindle-cell carcinoma, verrucous carcinoma, squamous papilloma, and basaloid squamous cell carcinoma. About 1% of esophageal cancers are neuroendocrine neoplasms. Other rare nonepithelial malignancies of the esophagus include the smooth-muscle tumors called leiomyomas, along with leiomyosarcoma, lymphoma, melanoma, and neurofibroma. SCC usually begins in the cervical or thoracic esophagus but can occur in the abdominal esophagus as well. Conversely, 75% of esophageal adenocarcinoma cases originate in the abdominal esophagus.

Untreated chronic GERD can lead to Barrett esophagus, a condition in which normal, flat squamous epithelial cells are replaced by a columnar morphology epithelium. Columnar epithelial cells are more rectangular than typical flat, squamous cells. For reasons not yet well understood, chronic GERD can cause epithelial cells to undergo metaplasia and become less organized and more abnormal in appearance. In Barrett esophagus, metaplasia leads to the formation of goblet cells, a process sometimes called intestinalization. Whether the presence of goblet cells is required to confirm a diagnosis of Barrett esophagus is controversial, but the cells’ presence in a biopsy...
sample is widely considered a diagnostic criterion.\textsuperscript{16} Barrett metaplasia, in turn, can evolve through progressively severe stages of dysplasia and tumorigenesis.\textsuperscript{17} Histologically assessed dysplasia is believed to reflect underlying genetic or genomic changes.\textsuperscript{14}

Dysplasia is an indicator of esophageal adenocarcinoma risk, but its endoscopic assessment is subjective and can be problematic. Up to 3% of patients with low-grade esophageal dysplasia develop esophageal adenocarcinoma tumors each year, although estimates vary, partly because of the poor reliability of identifying low-grade dysplasia in patients with Barrett esophagus.\textsuperscript{14} Interobserver agreement among pathologists is lower than 50%.\textsuperscript{14} Among patients with low-grade dysplasia confirmed by expert pathologists, the annual risk of progression to high-grade dysplasia or esophageal adenocarcinoma has been reported at 9%.\textsuperscript{14} Esophageal adenocarcinoma incidence rates are higher among those patients who develop high-grade dysplasia, who have Barrett esophagus longer than 10 years, or who have esophagitis and Barrett esophagus.\textsuperscript{14} In more than half of cases, initial endoscopic findings of low-grade dysplasia are not confirmed with follow-up endoscopy, but it is unclear if this is due to a biological reversal of dysplasia or simply an ongoing failure to detect dysplasia.\textsuperscript{14} The resulting uncertainty has complicated efforts to develop screening protocols.

High-grade dysplasia is believed to be an intermediate step between low-grade dysplasia and tumorigenesis.\textsuperscript{11} Patients with high-grade dysplasia face a risk of developing esophageal adenocarcinoma that averages up to 11.8% per year, or 59% over 5 years, according to one study.\textsuperscript{11} However, meta-analysis of data pooled from multiple studies found lower incidence rates (6% per year) of esophageal adenocarcinoma associated with high-grade dysplasia.\textsuperscript{18,19} Authors of one of the meta-analyses found that men with high-grade dysplasia and Barrett esophagus are twice as likely as women to have the condition progress to esophageal cancer.\textsuperscript{14}

The anatomic extent of Barrett esophageal metaplasia, particularly in the abdominal esophagus, is associated with increased risk of esophageal adenocarcinoma.\textsuperscript{6} However, most patients with esophageal cancer have no medical history of Barrett esophagus at the time of cancer diagnosis.\textsuperscript{6}

Epidemiology

Esophageal carcinomas emerge in the tissues of the esophagus but can spread to distant organs throughout the body. Because early-stage esophageal cancers are frequently asymptomatic, diagnosis commonly is made only after tumors are at an advanced stage and patients have a poor prognosis.\textsuperscript{13} As a result, esophageal cancers are highly lethal malignancies, and are associated with a 5-year survival rate following diagnosis of only 17.9%.\textsuperscript{9} The National Cancer Institute combines statistics on esophageal cancers of different histologic types, but other research indicates that survival rates are higher for patients in the United States with esophageal adenocarcinoma than they are for esophageal SCC.\textsuperscript{3}

The age-adjusted incidence rate for esophageal cancer is 4.4 per 100 000 Americans, and mortality rates are 4.2 per 100 000.\textsuperscript{9} In the United States, nearly 17 000 new cases of esophageal cancer are diagnosed each year, and more than 15 000 people die from esophageal cancer in the United States annually, representing approximately 1% of all cancer diagnoses and 2.6% of all cancer deaths.\textsuperscript{9} In 2012, an estimated 35 781 people with esophageal cancer were living in the United States.\textsuperscript{8} Overall, an estimated 0.5% of people living in the United States will receive a diagnosis of esophageal cancer in their lifetimes.\textsuperscript{9}

Most (59.9%) of the esophageal cancers occurring in the United States are adenocarcinomas, and an estimated 85% of patients with this cancer are men.\textsuperscript{8,20} SCC was the most common form of esophageal carcinoma in the United States, as it still is in most of the world outside of Australia and the United Kingdom.\textsuperscript{5} However, beginning in the 1980s, the incidence rate of esophageal adenocarcinomas has increased and the cancer subtype has overtaken SCC in the United States, United Kingdom, and Australia.\textsuperscript{11} This shift has been geographically uneven, with SCC remaining the most common form of esophageal cancer in most of the rest of the world and among black men in the United States.\textsuperscript{9} The epidemiology of this shift from SCC to esophageal adenocarcinoma predominance in these countries remains unclear.\textsuperscript{5}

Most patients learn of an esophageal cancer diagnosis during mid- or late adulthood, after age 44 years, and the median age of those with the disease at death is 69 years.\textsuperscript{9} Rates are markedly higher among men than women, at 7.6 cases per 100 000 men vs 1.7 cases per
100,000 women. Hispanics, Asian/Pacific Islanders, and American Indians tend to have lower rates than whites or blacks (see Figure 2). At diagnosis, approximately 21% of patients with esophageal cancer have tumors that are localized at their primary site; 31% have already spread to regional lymph nodes; and 38% have metastasized to distant organs. Another 11% are of undetermined state at diagnosis. The corresponding 5-year relative survival rates for patients based on stage of the cancer at diagnosis are:  
- Localized esophageal cancer – 40.4%.  
- Regional lymph node involvement – 21.6%.  
- Metastatic disease – 4.2%.

**Risk Factors**

Tobacco smoking is a major risk factor for both esophageal SCC and esophageal adenocarcinomas. The combination of alcohol use and tobacco smoking is believed to underlie 90% of SCC cases. Although alcohol and tobacco use each independently increase the risk of esophageal SCC, there is some evidence that heavy consumption of both tobacco and alcohol has a synergistic effect on SCC risk—an effect that multiples rather than simply adds to overall risk. This could be because alcohol is a solvent and increases epithelial cell uptake of tobacco carcinogens such as nitrosamines, aldehydes, phenols, and polycyclic hydrocarbons. Dietary intake of nitrosamines such as those found in some canned vegetables and fish also is associated with SCC.

Certain bacterial or viral infections appear to modulate esophageal cancer risk, as well. Chronic infection with the bacteria *Helicobacter pylori*, which has been confirmed to increase risk of gastric cancers, is associated with a doubling of risk of developing esophageal SCC. *Helicobacter pylori* appears to have an inverse relationship with some esophageal disease, however, actually decreasing risk of developing Barrett esophagus and esophageal adenocarcinomas.

**Number of New Cases Per 100,000 People by Race/Ethnicity & Sex: Esophageal Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>All Races</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>8.0</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7.6</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>3.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>4.9</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>5.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>7.9</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

SEER 18 2008-2012, Age-Adjusted

Some studies, but not others, suggest that Epstein-Barr virus might be associated with esophageal cancers. Despite a significant role for oncogenic human papillomavirus (HPV) in SCC incidence in parts of Asia, Africa, and South America, HPV infections appear to play a negligible role in esophageal cancers in the United States.

Diet also might play a role in SCC risk. Malnourishment and low body mass index (BMI) are associated with increased esophageal SCC risk worldwide. Eating high levels of dietary fats might increase esophageal SCC risk. Consumption of fruits and vegetables appears to be associated with a reduced risk of both esophageal SCC and adenocarcinoma. Regular consumption of hot teas or beverages containing alcohol could increase SCC risk through chronic thermal damage to the esophageal mucosa. The International Agency for Research on Cancer has identified regular consumption of extremely hot yerba mate tea, a traditional drink in South America, as “probably carcinogenic.”

Risk factors for esophageal adenocarcinomas are less well understood but include GERD and Barrett esophagus. However, because the incidence of esophageal adenocarcinomas is relatively low, even seemingly dramatic associations between a risk factor such as Barrett esophagus and esophageal adenocarcinoma can affect relatively few patients. Accordingly, although the risk of esophageal adenocarcinoma is up to 100 times higher among people with a history of Barrett esophagus than for those who have not had the condition, fewer than 5% of patients diagnosed with esophageal adenocarcinomas have a history of Barrett esophagus.

Whereas reduced BMI is associated with increased risk of SCC, increased BMI is considered to be a risk factor for esophageal adenocarcinoma. For example, obesity is associated with up to 7 times the risk for esophageal adenocarcinoma compared with individuals who fall in the lowest quartile of BMI calculation, possibly because obesity can contribute to the development of GERD. The association between esophageal adenocarcinoma and obesity is strongest for abdominal obesity. Fat cells and inflammatory cells within fat deposits secrete proinflammatory cytokines that might contribute to tissue inflammation in other organs.

Some occupational exposures might contribute to esophageal cancer risk, particularly SCC. For example, esophageal SCC also could be associated with occupational exposures to asbestos, carbon black (eg, among chimney sweeps or dockyard workers), sulfuric acid, textile dye work-associated perchloroethylene exposure, and polycyclic aromatic hydrocarbons associated with asphalt work. Esophageal adenocarcinoma risk appears to be elevated for people who are exposed to lead and sulfur-containing chemicals in the occupational setting. Based on limited available evidence, the International Agency for Research on Cancer has classified occupation in the dry cleaning and rubber industries as a risk factor for esophageal cancers.

Elevated risks of esophageal SCC are reportedly associated with exposure to ionizing radiation, including exposure among Japanese survivors of atomic bomb fallout, and among patients who have undergone radiation therapy for the treatment of breast cancer or ankylosing spondylitis. Breast radiation therapy has not been found to increase the risk of esophageal adenocarcinoma, however.

Genetic and Epigenetic Risk Factors

The advent of high-throughput, rapid genetic sequencing and genome-wide DNA sequencing is revolutionizing the understanding of the molecular epidemiology of cancers and tumor formation, progression, and metastasis. For example, alterations in the gene-encoding enzymes involved in alcohol metabolism appear to increase esophageal SCC risk, and SCC tumors frequently have mutations in the RFI, CDKN2A, PIK3CA, NOTCH1, and NFE2L2 genes. SMAD family member 4 (SMAD4) mutations are found in high-grade esophageal dysplasia and esophageal adenocarcinoma cells.

Genome-wide sequencing also should hasten the identification of molecular biomarkers that will help identify patients at particular risk for poor prognosis or who are likely to benefit from a particular type of treatment. Although no candidate biomarker for esophageal cancer risk or prognosis has yet been validated, aberrant expression of the tumor protein p53 (TP53) gene appears to show promise as a biomarker of progression from nondysplastic epithelia, or low-grade dysplasia, into high-grade dysplasia and esophageal adenocarcinoma. Both overexpression and underexpression of TP53 increase the risk of progression to malignancy from low-grade dysplasia. Other biologically plausible candidate gene mutations and
molecular pathways have been implicated in esophageal cancers and are undergoing further study.\textsuperscript{11} Genomic alterations other than genetic mutations can contribute to esophageal cancer processes. For example, aneuploidy, which is having an abnormal number of chromosomes in a cell, and epigenetic changes to certain genes, a condition called hypermethylation, appear to drive progression of Barrett esophagus to high-grade dysplasia and esophageal adenocarcinoma.\textsuperscript{13} Epigenetic changes do not entail mutations in the DNA sequence of a gene, but instead involve the attachment of chemicals on a genetic sequence to up-regulate or down-regulate expression of that gene.

\textbf{Prevention}

Avoiding tobacco and alcohol reduces the risk of esophageal cancers.\textsuperscript{4} Regular consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin is associated with a modest chemopreventive effect against the risk of both esophageal SCC and adenocarcinoma.\textsuperscript{4} The potential benefits of NSAIDs must be balanced, however, with increased risk of GI tract bleeding, myocardial infarction, heart failure, and stroke.\textsuperscript{7} Despite the relationship between GERD, Barrett esophagus, and esophageal adenocarcinoma, the evidence base is not yet robust enough to determine whether surgical or pharmacologic management of GERD would reduce the risk of esophageal adenocarcinoma.\textsuperscript{4}

According to an assessment from the National Cancer Institute, radiofrequency ablation of Barrett esophagus with high-grade dysplasia can help eradicate both dysplasia and intestinal metaplasia and reduce the risk that the diseases will progress to esophageal adenocarcinoma.\textsuperscript{9} However, the effect of the preventive measure on patient survival has not been established and radiofrequency ablation entails potential harms such as esophageal stricture and upper GI tract hemorrhage.\textsuperscript{4}

\textbf{Screening}

Esophageal cancer and Barrett esophagus screening and surveillance efforts are controversial.\textsuperscript{4,16,26} The National Cancer Institute has concluded that balanced evidence suggests screening would have little to no effect on U.S. mortality rates from esophageal cancer.\textsuperscript{4} No screening protocol is in use for esophageal adenocarcinoma among patients diagnosed with Barrett esophagus, and 93% of esophageal adenocarcinoma cases are not detected by current screening strategies.\textsuperscript{6,21} With the rise in esophageal adenocarcinoma incidence rates beginning in the 1980s, attempts have been made to institute screening for Barrett esophagus among patients diagnosed with GERD, along with surveillance endoscopy of patients with Barrett esophagus for early detection of esophageal adenocarcinoma; however, these screening efforts have not led to earlier detection of esophageal adenocarcinoma.\textsuperscript{22}

Mucosal high-grade dysplasia is associated with an elevated risk of esophageal adenocarcinoma, but high-grade dysplasia is not always extensive enough or readily differentiated from low-grade dysplasia in Barrett esophagus for reliable detection during surveillance endoscopy.\textsuperscript{4,17} Effective detection of dysplastic areas often requires examination of much of the internal luminal surface area of the esophagus.\textsuperscript{17} By the time dysplasia is extensive enough to be detected with endoscopy, malignancies are frequently already present, limiting the opportunity for prevention or early intervention.\textsuperscript{14}

Sampling error during endoscopy has led to promulgation of the Seattle biopsy protocol recommendations.\textsuperscript{14} Adherence to the Seattle protocols would dramatically improve detection rates for high-grade dysplasia and esophageal adenocarcinoma, but adherence rates appear to be low (51%) where the protocols have been implemented.\textsuperscript{14}

Various endoscopic imaging methods have been proposed to better detect epithelial dysplasia, including chromoendoscopy with contrast or stain agents such as methylene blue, indigo carmine, or Congo red, to differentiate normal esophageal mucosa from intestinalized epithelia.\textsuperscript{17} Narrowband endoscopy and autofluorescence imaging methods also are under investigation. Narrowband endoscopy uses nonwhite light sources to detect columnar and dysplastic epithelia.\textsuperscript{7} Despite efforts to develop alternative endoscopic modalities such as these, traditional white-light-based endoscopy remains the standard for assessment of the esophageal mucosa, including endoscopic surveillance and screening efforts.

Authors of a meta-analysis of the progression of dysplasia to esophageal adenocarcinoma in patients with Barrett esophagus have cautioned that the cost-effectiveness of surveillance will remain uncertain until patients with the highest cancer risk can be reliably identified for targeted...
surveillance. With the advent of genome-wide DNA sequencing and epigenetic characterization of patient and tumor genetics, however, it is widely anticipated that the genetic mutations and molecular pathways of esophageal adenocarcinoma and SCC tumorigenesis, disease progression, and metastasis will become much better understood in the future. This technology will allow the development of clinically meaningful diagnostic and prognostic molecular and genomic biomarkers for patient risk stratification. Such tools are expected to improve early detection of dysplasia and tumorigenesis associated with Barrett esophagus, as well as differentiation of high-risk and low-risk dysplasia. Biomarkers also can help identify which patients are likely to benefit from particular targeted therapies.

**Diagnosis**

Progressive difficulty or discomfort in swallowing, or dysphagia, is the most common clinical presentation for patients who are ultimately diagnosed with esophageal adenocarcinoma and SCC; dysphagia typically emerges rapidly over just a few months. Swallowing food often is more difficult than swallowing liquids for patients with dysphagia, at least initially. In advanced cases, however, even swallowing liquids can be challenging. Dysphagia in esophageal cancer usually is related to tumor mass in the abdominal esophagus vs oropharyngeal dysphagia, which is associated with upper esophageal sphincter dysfunction.

Patients also frequently present with fatigue and less commonly with upper GI tract pain or bleeding. In patients with SCC, recent weight loss and history of tobacco and alcohol use are common; weight loss is not a common clinical presentation among patients with esophageal adenocarcinoma.

Differential diagnosis of dysphagia involves excluding caustic or radiation injury, tuberculosis, esophagitis, scleroderma, hiatal hernia, aortic aneurysms, or nonepithelial malignancies such as lung cancer or lymphoma. Confirmation of a diagnosis of esophageal cancer involves endoscopy with biopsy. Upper GI endoscopy is the initial diagnostic procedure for suspected esophageal cancer. Esophagogastroduodenoscopy or endoscopic biopsy with ultrasonographic guidance leads to definitive diagnosis of esophageal cancer from histopathological analysis of tumor tissue. The biopsy tissue sample also provides important tumor staging information, such as proximal and distal tumor extent and involvement of adjacent organs. Bronchoscopy can help assess respiratory tissue involvement of tumors in the thoracic esophagus. Endoscopy can be complicated by disease-related esophageal strictures and obstructions of the esophageal lumen by tumor mass.

**Staging**

Treatment options for esophageal cancer depend on how advanced the malignancy is at diagnosis. Therefore, tumors are staged following endoscopic biopsy and diagnosis of esophageal cancer. At the time of diagnosis, only approximately 25% of patients with esophageal adenocarcinoma have localized tumors; most patients already have advanced-stage disease; in 50% of cases the advanced disease includes distant metastases.

The American Joint Committee on Cancer has endorsed the tumor, node, and metastasis (TNM) staging system to assess prognosis and treatment options for patients with esophageal cancer (see Figure 3). In this system, the T stage represents the extent of primary tumor invasion of the esophageal wall and, in more advanced T stages, through the esophageal wall into adjacent structures. N stage refers to the involvement of tumor cells in the regional lymph nodes (see Figure 4). M stage refers to the spread of esophageal tumors to distant organs; M0 means no distant organ or bone metastatic tumors exist, whereas M1 represents metastatic disease being detected in one or more distant organs.

An updated seventh edition of the TNM staging system for esophageal cancer was released in 2009, reflecting advances in diagnostic imaging and treatment planning, and an improved evidence base regarding treatment outcomes (see Table 1). For example, the updated system differentiates T4a, or surgically resectable, tumors from T4b tumors, which are not resectable; these 2 types of tumors previously had been grouped together as T4. Lymph node (N) staging was updated from reflecting the presence (N1) or absence (N0) of tumor involvement in regional lymph nodes to reflecting how many nodes are involved (N0-N3) to indicate the prognostic significance of this information. Finally, the update has simplified metastatic disease (M) staging to exclude regional lymph node status criteria and instead to
Figure 4. Regional lymph nodes according to the seventh edition of the staging manual for esophageal cancer. The posterior mediastinal lymph node (3P) is not shown here. Reprinted with permission from Hong SJ, Kim TJ, Nam KB, et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. Radiographics. 2014;34(6):1729.

Abbreviations: 1L, left supraclavicular; 1R, right supraclavicular; 2L, left upper paratracheal; 2R, right upper paratracheal; 4L, left lower paratracheal; 4R, right lower paratracheal; 5, aortopulmonary; 6, anterior mediastinal; 7, subcarinal; 8L, lower paraesophageal; 8M, middle paraesophageal; 9, pulmonary ligament; 10L, left tracheobronchial; 10R, right tracheobronchial; 15, diaphragmatic; 16, paracardial; 17, left gastric; 18, common hepatic; 19, splenic; 20, celiac.
reflect only metastatic spread of esophageal cancer to distant organs (see Figures 5 and 6).\textsuperscript{3,9}

The updated staging system has reportedly improved postsurgical prognostic risk-stratification of patients.\textsuperscript{30} However, noninvasive preoperative staging remains challenging and can be imprecise.\textsuperscript{31} The accuracy of computed tomography (CT) chest image tumor depth staging is 50% to 80%, according to the National Cancer Institute.\textsuperscript{31} Endoscopic ultrasonography is more accurate (85%-90%) at tumor staging because it

### Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Sixth Edition</th>
<th>Seventh Edition</th>
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<tbody>
<tr>
<td>Tumor (T)</td>
<td>Tis: carcinoma in situ</td>
<td>Tis: high-grade dysplasia</td>
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<tr>
<td></td>
<td>T1: invasion of lamina propria, muscularis mucosae, or submucosa</td>
<td>T1: invasion of lamina propria, muscularis mucosae (T1a), or submucosa (T1b)</td>
</tr>
<tr>
<td></td>
<td>T2: invasion of muscularis propria</td>
<td>T2: invasion of muscularis propria</td>
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<td></td>
<td>T3: invasion of the adventitia</td>
<td>T3: invasion of the adventitia</td>
</tr>
<tr>
<td></td>
<td>T4: invasion of adjacent structures</td>
<td>T4: invasion of adjacent structures</td>
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<tr>
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<td></td>
<td>T4a: resectable (pleura, pericardium, or diaphragm)</td>
</tr>
<tr>
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<td>T4b: unresectable (aorta, vertebral body, or trachea)</td>
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<td>N1: present (any number)</td>
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<td>N2: 3-6 regional lymph nodes</td>
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<td></td>
<td></td>
<td>N3: $\geq$7 regional lymph nodes</td>
</tr>
<tr>
<td>Metastasis (M)</td>
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<td>M0: absent</td>
</tr>
<tr>
<td></td>
<td>M1a: cervical lymph node (in upper esophageal cancer) or celiac lymph node (in lower esophageal cancer)</td>
<td>M1: present</td>
</tr>
<tr>
<td></td>
<td>M1b: all other distant metastases</td>
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</tbody>
</table>

**Figure 5.** T4b tumor with tracheobronchial invasion. Axial contrast-enhanced CT image at the level of the tracheal bifurcation and the main-stem bronchi shows diffuse wall thickening in the midesophagus (*), a finding later confirmed to be esophageal cancer. Direct tumor extension into the left main bronchus is seen (arrow). Reprinted with permission from Hong SJ, Kim TJ, Nam KB, et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. Radiographics. 2014;34(6):1728.
Fine-needle aspiration with endoscopic ultrasonography guidance for lymph node (N) staging can offer highly-accurate N staging and, unlike radiographic images, cytologic confirmation of the presence of metastatic tumor tissue within nodes. Reports have shown up to 93% sensitivity, or true-positive rate, and 100% specificity, or true-negative rate, for use of the fine-needle biopsy technique.

Fludeoxyglucose (FDG) 18 positron emission tomography (PET)-CT shows promise in metastatic disease staging. FDG 18 PET-CT also is used widely for post-treatment restaging and monitoring. However, CT and PET-CT can miss small metastatic tumors in the liver and lungs. For that reason, some institutions still use minimally invasive surgical thoracoscopy or staging laparoscopy to assist in tumor staging for some patients.
To optimize the strengths of each of these diagnostic imaging modalities, preoperative staging typically is multimodality in nature, using images acquired with CT, endoscopic ultrasonography, and FDG 18 PET-CT (see Figure 7). For example, on CT, a wall of a distended esophagus with asymmetric thickening to greater than 5 mm might indicate the presence of a T1- or T2-stage esophageal tumor; however, these tumors frequently must be evaluated using follow-up endoscopic ultrasonography or PET-CT.

Histological cell type and grade also are relevant to a patient’s prognosis and treatment options. Esophageal adenocarcinoma and SCC tumors can be difficult to distinguish from one another with structural diagnostic imaging, but their location in the esophagus can provide an important diagnostic indication. SCC tends to occur in the cervical or thoracic esophagus, whereas esophageal adenocarcinoma usually occurs in the abdominal esophagus. Physicians determine the location of a tumor in the esophagus by its upper extent or periphery, not the center of its volume or mass.

The updated TNM staging system includes biologic activity, or namely histologic tumor grade, to help differentiate SCC from esophageal adenocarcinoma. Grade 1 refers to tumors with good histologic differentiation, grade 2 to moderate differentiation, and grade 3 to poor differentiation. Grade 4 is reserved for undifferentiated tumors. Tumor grades correlate with stage. For example, a T1a tumor is likely to be grade 1,

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**Figure 7.** Imaging modalities have different strengths in staging esophageal cancers, so staging typically involves several modalities. These CT, endoscopic ultrasonography, and axial PET-CT images of a T1a esophageal tumor illustrate the strengths of a multimodality imaging strategy. A. Axial contrast-enhanced CT image at the level of the right pulmonary artery shows a suspicious small nodular lesion in the midesophagus (arrow), a finding that is not easily substantiated without endoscopy. The lesion was later confirmed to be squamous cell carcinoma. B. Endoscopic ultrasonogram shows an irregularly shaped nodule (arrow) and preservation of the hyperechoic third layer (submucosa; arrowheads). C. Axial PET-CT image at the same level as figure A shows no definite FDG uptake in the primary tumor. Reprinted with permission from Hong SJ, Kim TJ, Nam KB, et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. Radiographics. 2014;34(6):172S.
whereas a T1b tumor is likely to be grade 2 or grade 3. As with tumor stage, increasing tumor grade is associated with poorer patient prognoses. 

Treatment

Esophageal cancer treatment depends on disease stage and patient history. Treatment recommendations can involve surgery only, chemotherapy, external-beam radiation therapy, or a combination of these therapies. In contemporary clinical practice, treatment planning usually involves an interdisciplinary and multimodal approach, with individual patients’ treatment plans designed for their particular esophageal cancer subtype.

Traditionally, surgical resection (esophagectomy) with lymphadenectomy was the primary esophageal cancer treatment, with chemotherapy and radiation therapy in adjuvant and palliative roles. Although several surgical techniques have been used, survival and tumor recurrence rates remain comparably poor among these approaches, prompting development of alternative treatment strategies. Minimally invasive esophagectomy appears to be associated with a lower patient mortality rate and improved postsurgical quality of life compared with conventional open esophagectomy.

Chemotherapy typically includes cisplatin or carboplatin plus 5-fluorouracil. The evidence base for adjuvant chemotherapy in treating esophageal cancer is relatively scant and equivocal, leading some researchers to recommend that the therapy be used primarily when histology and other clinical signs suggest a high likelihood of metastatic disease. The National Comprehensive Cancer Network (NCCN) does not recommend adjuvant chemotherapy for patients diagnosed with SCC, and recommends adjuvant chemotherapy for patients with esophageal adenocarcinoma only if they have received induction radiation therapy. The NCCN recommends neoadjuvant concurrent external-beam radiation therapy (for a total of 45-50.4 Gy) and chemotherapy for patients undergoing resection for locally advanced esophageal adenocarcinoma.

In recent years, neoadjuvant combined chemotherapy and radiation therapy have become more widely used, particularly for patients with locally advanced, or stage T1-T3, esophageal cancer. Neoadjuvant chemotherapy and radiation therapy are associated with superior patient survival times compared with surgery alone, and although toxicities vary among studies, this approach has been shown to result in comparable patient morbidity and mortality compared to neoadjuvant chemotherapy alone.

For stages Tis and T1a esophageal SCC or stage N0/M0 esophageal adenocarcinomas, endoscopic tumor resection or ablation alone now is preferred to open surgical resection, particularly when tumors are grade 1 or grade 2 and smaller than 3 cm in diameter. Endoscopic mucosal resection of foci is performed for these early-stage tumors; tumor tissue is removed, along with adjacent Barrett esophagus and regions of high-grade dysplasia that could become foci of progression to tumorigenesis and tumor recurrence. Endoscopic submucosal dissection is appropriate for tumors at stage T1b or more advanced. Patients undergoing endoscopic tumor resection who have residual Barrett esophagus or high-grade dysplasia frequently (in up to 30% of cases) have tumor recurrence. Therefore, endoscopic eradication therapy is sometimes recommended following endoscopic tumor resection to remove residual Barrett esophagus that might conceal high-grade, tumorigenesis-prone dysplasia. These patients also are candidates for periodic endoscopic surveillance to detect recurrences.

Surgical resection with or without neoadjuvant chemotherapy with radiation therapy generally is preferred for stage T1b, T2, T3, and T4a tumors. For patients with cervical esophageal tumors, the larynx is removed along with the esophagus, which means that patients permanently lose their ability to speak. Combined chemotherapy and radiation therapy is preferred for patients with nonmetastatic (M0) T4b-stage tumors. By definition, patients with any distant metastases (M1) are candidates only for palliative therapy. The therapy might include modalities that treat or destroy the tumor, but with the goal of easing symptoms and improving quality of life rather than prolonging a patient’s life. Endoscopic ablative laser therapy sometimes is included in a palliative care plan.

In addition to standard chemotherapy drugs, a newer targeted therapy aimed at the erb-b2 receptor tyrosine kinase 2 (ERBB2) has shown promise against some metastatic (M1) esophageal cancers. The targeted therapy involving trastuzumab (Herceptin), is used along with palliative chemotherapy regimens.
Radiation Therapy

Radiation therapy is an important component of the interdisciplinary treatment of esophageal cancers, playing 4 potential roles for patients:

- Primary or definitive radiation therapy and chemotherapy, with or without surgery, intended to cure. 43
- Neoadjuvant radiation therapy with or without chemotherapy, delivered before surgery to potentially improve the surgery’s effectiveness. 41,45
- Adjuvant radiation therapy, with or without chemotherapy, delivered after surgery to destroy micrometastatic tumor cells not removed during surgery. 41
- Palliative radiation therapy as short-course radiation therapy or brachytherapy, with or without chemotherapy, to ease pain or other symptoms that can degrade the quality of a patient’s life, administered to patients with incurable, metastatic cancer. 43

Surgery remains the preferred treatment for curative therapy when esophageal tumors are resectable. 41 However, combined radiation therapy and chemotherapy has emerged as a viable treatment alternative with curative potential for patients with unresectable, locally advanced esophageal cancer, or patients who are otherwise not deemed candidates for definitive surgical treatment. 43,45

A meta-analysis of trial data has shown similar survival times and nearly similar mortality rates for patients who received surgery or chemotherapy and radiation therapy for esophageal SCC. 41 Definitive chemotherapy and radiation therapy also is an emerging treatment option, even for patients with resectable esophageal cancers when patients wish to preserve esophageal function. It has been found that required salvage surgery for persisting or recurrent tumors following the combination therapy offers similar patient outcomes to surgery. 41

Radiation therapy without chemotherapy also is a treatment option, particularly among patients with metastatic disease or elderly patients with advanced-stage cancers and poor performance status. 41

Photodynamic therapy with the photosensitizing agent porfirmer sodium (Phototorin) has been approved by the FDA for palliative treatment of symptoms arising from Barrett esophagus or obstructive esophageal tumors. 44

Photodynamic therapy has shown promise in early clinical trials against gastroesophageal adenocarcinoma as well as other types of cancer. 43

The evidence base for neoadjuvant and adjuvant therapy for resectable esophageal cancer is evolving. 5,34,37,38 Neoadjuvant chemotherapy and radiation therapy followed by surgical resection is a standard of care for locally advanced esophageal cancer. 37 Long-term results from the neoadjuvant chemoradiotherapy for esophageal cancer followed by surgery study (CROSS) clinical trial were published in August 2015 in The Lancet Oncology and showed that 5-year overall survival rates among patients with esophageal SCC and esophageal adenocarcinomas undergoing neoadjuvant chemotherapy and radiation therapy are superior to those for patients who have surgery alone. 38

The CROSS study’s 23-day therapy regimen involved chemotherapy with intravenous carboplatin and paclitaxel, delivered concurrently with external-beam radiation therapy delivered in 23 daily fractions of 1.8 Gy, 5 days per week for a total dose of 41.4 Gy. 37 The authors reported that local-regional and distant disease progression were significantly reduced by neoadjuvant chemotherapy and radiation therapy, with prolonged local-regional control. 37 The CROSS regimen was associated with a better toxicity profile than the popular regimen of 45 Gy plus 5-FU and cisplatin, but most of the patients in the study had distal abdominal-esophageal tumors or tumors at the gastroesophageal junction, which means radiation fields included less nontarget respiratory tissue than has been the case in previous studies, which included a higher proportion of cervical-esophageal and thoracic-esophageal cancers. 37

Despite the promising CROSS study findings, it remains unclear whether neoadjuvant chemotherapy and radiation therapy is beneficial in early-stage esophageal cancer; only 17% of CROSS study participants had stage T1 or T2 tumors, and a separate randomized trial has found increased risks of postoperative deaths associated with neoadjuvant chemotherapy and radiation therapy among these patients. 41,46 Furthermore, other researchers

(Cyramza), another targeted agent, sometimes is used as a second-line therapy after tumor recurrence in patients whose primary tumors occurred at the gastroesophageal junction. 44 Both targeted agents have been approved by the U.S. Food and Drug Administration (FDA) for patients with esophageal cancer. The investigational targeted agent alisertib also has shown promise in previous studies, which included a higher proportion of cervical-esophageal and thoracic-esophageal cancers. 38

Despite the promising CROSS study findings, it remains unclear whether neoadjuvant chemotherapy and radiation therapy is beneficial in early-stage esophageal cancer; only 17% of CROSS study participants had stage T1 or T2 tumors, and a separate randomized trial has found increased risks of postoperative deaths associated with neoadjuvant chemotherapy and radiation therapy among these patients. 41,46 Furthermore, other researchers
have noted that not all CROSS study participants received benefit from the neoadjuvant therapy, showing that, to date, there is no single accepted neoadjuvant approach to treating early-stage esophageal cancer.14

**Radiation Therapy Planning**

Radiation therapy involves planning based on imaging to deliver therapeutic doses of external beam radiation to destroy malignant cells while minimizing irradiation of healthy, nontarget tissues near tumors or along radiation beam pathways to minimize toxicity and morbidity. Imaging is used to delineate radiation therapy target volumes.14,47 Treatment planning involves CT, endoscopic ultrasonography, and PET-CT.

CT scans for radiation therapy planning simulation are acquired with the patient in supine or prone position on the table, and protocols typically require CT slice acquisitions of less than 5 mm.14 The supine position is preferred for patients with pulmonary comorbidities such as chronic obstructive pulmonary disease, and entails use of a mold or other patient immobilization device.14 The patient should be instructed to raise his or her arms if the tumors are located in the gastroesophageal junction or thoracic esophagus.14

The ongoing challenge for developing a treatment plan is ensuring the best dose conformity to target volumes, while minimizing dose to healthy tissue. Theoretically, all tumor cells could be eradicated with the use of radiation, but only if no radiation is subsequently delivered to healthy tissues. It is inevitable that some degree of healthy tissue is included when devising treatment plans. This requires the total prescribed therapeutic dose for the treatment volume to be divided and administered in smaller doses over the course of multiple fractions. For example, instead of delivering a total prescribed treatment dose of 60 Gy to 70 Gy in a single treatment, the dose is administered in 1.8 Gy to 2.0 Gy daily fractions until the full dose is administered.14

Radiation therapy planning target volumes are commonly delineated using diagnostic imaging. For patients with esophageal cancer who are being treated with radiation, the data obtained from esophagogastrroduodenoscopy, endoscopic ultrasonography, CT, FDG PET-CT, or a combination of imaging examinations is used to delineate the treatment planning target volumes.14 Planning traditionally involves the delineation of 3 treatment planning volumes specific to each patient: the gross tumor volume (GTV), clinical target volume (CTV), and the planning target volume (PTV). These 3 volumes make up a portion of the total irradiated volume; however, the total irradiated volume is defined as the entire tissue volume receiving a significant amount of the prescribed radiation dose, usually 50% of the target dose (see Table 2).

The GTV commonly used for esophageal treatment includes the primary tumor (GTVp) of the esophagus and also can include regionally involved lymph nodes (N1), referred to as GTVn.41,47 For planning purposes, any unresectable enlarged nodes usually are included in the GTV as well.14 Radiation oncologists might elect to include any subclinical regional nodes, or nodes of uncertain status, in the planning volumes.14 Elective radiation field coverage beyond the GTVp and GTVn is intended to ensure adequate coverage of possible, but unconfirmed, micrometastasis.14 However, little evidence supports including the regional lymph node bed in the treatment field.14 In one systematic review, the authors concluded that for patients with cervical esophageal cancer, lymph node irradiation fields should be extended to include the tracheal bifurcation.14

The CTV includes a region of presumed microscopic malignant spread around the margins of the discernable

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**Table 2**

**Typical Target Volumes for Treatment Planning of Esophageal Lesions**41,47,48,50

<table>
<thead>
<tr>
<th>Volume</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross tumor volume</td>
<td>( \text{GTV}_p = \text{primary esophageal lesion} )</td>
</tr>
<tr>
<td>(GTV)</td>
<td>( \text{GTV}_n = \text{GTV}_p + \text{regionally involved lymph nodes} )</td>
</tr>
<tr>
<td>Clinical target volume</td>
<td>( \text{CTV}_p = \text{GTV} + 2-4 \text{ cm proximal and distal margins} )</td>
</tr>
<tr>
<td>(CTV)</td>
<td>( \text{CTV}_{n+s} = \text{GTV} + \text{subclinical regional lymph nodes} )</td>
</tr>
<tr>
<td>Planning target volume</td>
<td>( \text{PTV} = \text{CTV} + 1-2 \text{ cm proximal and distal + 0.5-1 cm laterally} )</td>
</tr>
<tr>
<td>Irradiated volume</td>
<td>( \text{GTV} + \text{CTV} + \text{PTV} ) and any tissue receiving a significant amount of the prescribed dose</td>
</tr>
</tbody>
</table>

Abbreviations: \( _p \) includes primary lesion; \( _n \) includes regionally involved lymph nodes; \( _s \) includes subclinical regional lymph nodes.
lesion, or GTV. Margin definitions vary; however, one published standard defines the CTV as the GTV plus 2-cm to 4-cm proximal and distal margins. An alternate definition of the volume is based on data that suggests that microscopic disease spread can be captured within the CTV in 94% of patients when 3-cm margins are used. While the inclusion of regional lymph nodes is dependent on the location of the esophageal lesion, CTV , is defined as the GTV plus up to 0.5-cm circumferential margins. For esophageal SCC, elective irradiation of involved subclinical regional lymph nodes, or CTV , is defined for every primary lesion. The regional lymph nodes included in CTV vary depending on the esophageal location of the target tumors (see Figure 4). Residual tumor outside the CTV following neoadjuvant chemotherapy and radiation therapy is a proposed prognostic factor that can predict patient survival in esophageal cancer.

Patient immobilization techniques are used to minimize respiratory and other patient motion issues; however, a safe margin is added to the CTV to account for respiration and other patient motion, setup errors, and internal target volume (ITV) or the interfraction changes in tumor and nontarget anatomy that occur during treatment (eg, trachea, bronchi, stomach, vessels). This additional margin is added to the CTV, which defines the PTV. For patients with esophageal cancer, the PTV is defined as CTV plus 1-cm to 2-cm proximal and distal margins, and 0.5-cm to 1-cm margins laterally.

The total irradiated volume encompasses all of these volumes (GTV + CTV + PTV), and represents any amount of tissue that receives a significant amount of the prescribed radiation dose, usually 50%. Any dose to tissues that qualify as the irradiated volume should be recorded.

**Adverse Effects**

Even with fractionation, however, planning must accommodate radiation dose constraints. Radiation and combined chemotherapy and radiation therapy toxicities often are dose limiting, resulting in disruption or discontinuation of therapy. Patients undergoing radiation therapy or combined therapy for esophageal cancers frequently experience diarrhea, nausea, and vomiting.

Radiation esophagitis also is common, typically starting 2 to 4 weeks after initiation of therapy begins. Radiation esophagitis frequently leads to dysphagia, dehydration, and malnutrition, necessitating intubation and nutritional support. Radiation-induced strictures also are common, typically beginning 4 weeks after initiation of therapy, and often can be treated with endoscopic dilation.

When esophageal tumors have directly invaded adjacent structures such as the trachea or bronchus, irradiation and necrosis of the tumors can cause the worsening of fistulas between the esophagus and the respiratory system. This sometimes leads to discontinuation of esophageal radiation therapy and necessitates surgical intervention or intubation.

Radiation pneumonitis might occur 6 weeks following the initiation of radiation therapy when radiation fields include lung tissue. Recording FDG uptake levels in PET-CT before initiating therapy recently was proposed as a prognostic biomarker that could help stratify risk in patients who are under consideration for esophageal radiation therapy.

Another emerging and serious concern is late radiation-associated heart disease, particularly for patients with radiation fields that include the cardiac ventricles, namely those targeting distal abdominal esophageal tumors or tumors of the gastroesophageal junction. Up to 10.8% of patients having radiation therapy for esophageal cancer develop cardiac toxicities including pericardial effusion, ischemic heart disease, and heart failure. Radiation-induced myocardial fibrosis has been noted among patients undergoing definitive radiation therapy for primary tumors and involved regional lymph nodes when the patients received total radiation doses of 60 Gy to 70 Gy with a median total dose of 66 Gy.

**Radiation Therapy Technique**

Using conformal radiation therapy (CRT), usually 3-D CRT and intensity-modulated radiation therapy (IMRT) treatment techniques, for esophageal cancer radiation therapy minimizes the total irradiated volume to exclude respiratory and cardiac tissues as much as possible and reduces cardiopulmonary toxicities. A multi-leaf collimator often is used to shape the radiation beams using small leaves; in IMRT, these leaves can be adjusted between and during delivery of treatment fields varying beam intensity to different components of the irradiated volume. Combination external-beam and intraluminal
brachytherapy also has been proposed and validated in small, preliminary patient cohort studies as an alternative to combined chemotherapy and radiation therapy.  

Three-dimensional CRT treatment planning allows direct target-volume identification and delineation using CT scan images, with CT scan data transferred directly from the scanner to treatment planning software. Scan data are used to identify and delineate the radiation therapy volumes using 3-D CRT planning software. Once the volumes are defined and contoured, the radiation oncologist and medical dosimetrist collaboratively determine optimal beam-path arrangements to achieve planned contours and radiation doses—a process called forward planning. In contrast, IMRT planning employs inverse planning software to determine beam path arrangements given the desired tumor dose and goals for sparing healthy tissue outlined by the radiation oncologist in the radiation therapy prescription.

Neoadjuvant combined chemotherapy and radiation therapy delivers a median total dose of 50.4 Gy. IMRT treatment plans are associated with significantly lower rates of weight loss and high-grade toxicities, compared with 3-D CRT. Contouring guidelines for esophageal and gastroesophageal junction cancer IMRT were published in 2015. Despite a relatively young evidence base for these newer techniques (especially IMRT), researchers have concluded that whenever possible, 3-D CRT or IMRT should be employed for radiation therapy components of esophageal cancer treatment to minimize healthy tissue irradiation.

Proton beam therapy is an emerging radiation therapy modality still in research and clinical evaluation stages for patients with esophageal cancer. Because of the energy-deposition profile of protons, this therapy should be able to better spare healthy nontarget tissues in external radiation beam paths than photon beam radiation therapy techniques. Preliminary studies of neoadjuvant proton beam conformal radiation therapy with a total dose of 50.4 Gy suggest a low rate of serious toxicity, but this approach to esophageal cancer radiation therapy remains investigational as of fall 2015 and awaits additional prospective studies involving larger numbers of patients.

Palliative Radiation Therapy

Palliative radiation therapy helps alleviate dysphagia, hematemesis, and other symptoms among patients with metastatic or unresectable esophageal cancer, and usually is recommended when endoscopic ablation has been unsuccessful or is not an option. Other indications for palliative radiation therapy include painful metastatic tumors; brain metastases causing neurologic signs and symptoms such as headache, seizure, or weakness; airway obstruction; and shortness of breath.

Palliative radiation therapy regimens vary; published total radiation doses range from 20 Gy to 64 Gy, delivered in fractionation schedules ranging from 5 to 20 fractions. For example, one published palliative radiation therapy regimen for elderly patients with dysphagia involves a total dose of 20 Gy delivered in 5 fractions. The exact prescribed dose reflects patient performance status, prognosis, comorbidities, and tumor location. The CTV for palliative external beam radiation therapy typically includes a 5-cm longitudinal margin on both ends of the esophagus from the tumor margins and 2-cm lateral margins.

Careful clinical monitoring of the patient throughout the course of palliative radiation therapy is important, with particular attention to the possibility that irradiation could worsen rather than relieve dysphagia. This treatment is associated with radiation esophagitis and tissue edema around the target tumors.

For palliative radiation therapy after tumor recurrence, when treatment has been unsuccessful—or when a patient’s life expectancy is considered to be less than 6 months—endoscopic placement of tumor-conformal radioactive brachytherapy seeds also can be attempted to deliver a sustained radiation dose to tumor tissue. Brachytherapy is used to treat well-delineated, small-volume lesions situated close to radiosensitive nontarget tissues; large irradiated or treated volumes require external-beam radiation therapy. Self-expanding metal stent placement followed by brachytherapy can provide rapid relief from dysphagia, compared with 2 or more weeks from brachytherapy seed placement to symptom relief in the absence of stents. Placement of self-expandable stents combined with brachytherapy shows promise in early studies on palliative therapy for dysphagia. However, hemorrhages occurred in some patients who had previous esophageal radiation therapy.

Conclusion

As the population ages, the number of cases of esophageal cancer will climb. Genome-wide and epigenetic
sequencing tools are leading to new insights into the molecular pathways and risk factors for esophageal tumor- igenesis, progression, and metastasis. As these pathways become better understood, new prognostic biomarkers and therapies will emerge that can better assist in developing treatment strategies unique to patients and their tumors’ biology. Ongoing clinical research also will help identify which diagnostic, staging, and treatment techniques are best suited for different patient populations. Technological innovation, including advanced radiation therapy equipment and planning software, also likely improves the targeting and optimization of therapeutic radiation dose that can be delivered to tumors while better sparing healthy, nontarget tissues, reducing adverse effects of radiation.

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References


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Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. Gastroesophageal reflux disease (GERD) can result from dysfunction of the esophageal:
   a. sphincter.
   b. mucosa.
   c. submucosa.
   d. serosa.

2. Esophageal malignancies appear to be associated with which of the following?
   1. chronic inflammation
   2. caustic agents
   3. chronic GERD
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

3. Malignancies of the esophagus typically begin in the:
   a. sphincter.
   b. mucosa.
   c. submucosa.
   d. serosa.

4. Patients with esophageal cancer often have a poor prognosis because:
   a. the cancer is so difficult to treat.
   b. patients fail to report symptoms.
   c. early-stage disease is typically asymptomatic and therefore undetected.
   d. the tumors are difficult to detect on existing medical imaging.

5. Esophageal cancers are associated with a 5-year postdiagnosis survival rate of ______%.
   a. 6.7
   b. 12.4
   c. 17.9
   d. 24.3
6. Esophageal adenocarcinoma has overtaken squamous cell carcinoma (SCC) as the predominant form of esophageal cancer among which populations?
   a. U.S. black men  
   b. Australian residents  
   c. Hispanic women  
   d. most of the world

7. The combination of ______ and ______ is believed to underlie 90% of SCC cases.
   a. tobacco smoking; diet  
   b. tobacco smoking; alcohol use  
   c. alcohol use; obesity  
   d. obesity; diet

8. Which of the following might reduce the risk of disease progression of Barrett esophagus with high-grade dysplasia but has not been established to affect patient survival?
   a. surgery  
   b. endoscopic mucosal resection  
   c. radiofrequency ablation  
   d. brachytherapy

9. ______ is the initial diagnostic procedure for suspected esophageal cancer.
   a. Abdominal computed tomography (CT)  
   b. Positron emission tomography–CT  
   c. Upper gastrointestinal endoscopy  
   d. Open surgical biopsy

10. SCC tends to occur in the ______ esophagus.
    1. cervical  
    2. thoracic  
    3. abdominal
    a. 1 and 2  
    b. 1 and 3  
    c. 2 and 3  
    d. 1, 2, and 3

11. The evidence base for ______ is scant and equivocal.
    a. adjuvant chemotherapy  
    b. brachytherapy  
    c. intensity-modulated radiation therapy (IMRT)  
    d. chemoradiotherapy

12. Neoadjuvant ______ is associated with superior patient survival times compared with surgery alone.
    a. chemotherapy  
    b. brachytherapy  
    c. IMRT  
    d. chemoradiotherapy

13. According to the article, the U.S. Food and Drug Administration has approved which targeted agents for treating patients with esophageal cancer?
    1. trastuzumab  
    2. alisertib  
    3. ramucirumab
    a. 1 and 2  
    b. 1 and 3  
    c. 2 and 3  
    d. 1, 2, and 3

14. Radiation therapy without chemotherapy potentially is an option for patients with:
    1. advanced age and cancer stage.  
    2. metastatic disease.  
    3. advanced age and poor performance status.
    a. 1 and 2  
    b. 1 and 3  
    c. 2 and 3  
    d. 1, 2, and 3

continued on next page
15. CT scans for radiation therapy planning simulation for esophageal cancer typically are acquired with patients in the supine or prone position in slices of less than ______ mm.
   a. 2
   b. 5
   c. 7
   d. 10

16. Radiation pneumonitis can occur ______ week(s) following the initiation of radiation therapy when radiation fields include lung tissue.
   a. 1
   b. 2
   c. 4
   d. 6
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