New TNM Staging System for Esophageal Cancer: What Chest Radiologists Need to Know[1]

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Esophageal cancer is a leading cause of cancer-related deaths worldwide, and the 5-year relative survival rate remains less than 20% in the United States. The treatment of esophageal cancer should be stage specific for better clinical outcomes. Recent treatment paradigms tend to involve a multimodality approach to management, which includes surgical resection and preoperative or definitive chemoradiation therapy. Accurate pretreatment staging of esophageal cancer is integral for assessing operability and determining a suitable treatment plan. The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) have published the seventh edition of the staging manual for cancer in the esophagus and esophagogastric junction. Unlike the sixth edition, the revised staging manual is data driven and harmonized with the staging of stomach cancer. Improvements include new definitions for the anatomic classifications Tis, T4, regional lymph node, N, and M and the addition of nonanatomic cancer characteristics (histopathologic cell type, histologic grade, and cancer location). Given the recent increase in the incidence of adenocarcinoma of the distal esophagus, esophagogastric junction, and gastric cardia, the staging of tumors in the esophagogastric junction has been addressed. Radiologists must understand the details of the seventh edition of the AJCC-UICC staging system for esophageal cancer and use appropriate imaging modalities, such as computed tomography (CT), endoscopic ultrasonography, and positron emission tomography/CT, for initial staging.

Abbreviations: AJCC = American Joint Committee on Cancer, FDG = fluorodeoxyglucose, UICC = Union for International Cancer Control, WECC = Worldwide Esophageal Cancer Collaboration

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See discussion on this article by Leavitt (pp 1740–1741).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the important differences between the sixth and seventh editions of the AJCC-UICC TNM staging system for esophageal cancer.
- Discuss stage grouping with nonanatomic cancer characteristics, including histopathologic cell type, histologic grade, and cancer location.
- Recognize the diagnostic imaging features of esophageal cancer at CT, endoscopic US, and PET/CT.

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TEACHING POINTS

See last page

Introduction

Esophageal cancer is the fifth most common cause of cancer-related deaths in men and the eighth leading cause of cancer mortality in women worldwide (1). In the United States, the 5-year relative survival rate remains less than 20%, and the death rate for esophageal cancer in men is increasing, particularly in the 5th–8th decades of life (2). The treatment of esophageal cancer should be stage specific for better clinical outcomes. Recent treatment paradigms tend to evolve into a multimodality approach to management, which includes surgical resection and preoperative or definitive chemoradiation therapy (3). Consequently, precise pretreatment staging of esophageal cancer is integral for assessing operability, determining a suitable treatment plan, and minimizing inappropriate treatment (4).

The internationally used staging system is the TNM classification system maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). It includes the depth of local invasion by the primary tumor (T), the extent of regional lymph node involvement (N), and the presence or absence of distant metastasis (M) and provides a stage grouping on the basis of T, N, and M (5). The staging system for cancer in the esophagus and esophagogastric junction has been revised in the seventh edition, published in 2009. Unlike the sixth edition, the revised staging system is data driven and is harmonized with the staging of stomach cancer (6,7). Currently, multimodality-assessed preoperative staging of esophageal cancer is advocated to determine a treatment plan and includes the use of computed tomography (CT), endoscopic ultrasonography (US), and positron emission tomography (PET)/CT with fluorodeoxyglucose (FDG) (8). With the increasing role of imaging in the staging of esophageal cancer, radiologists must understand the foundations, clinical-radiologic implications, and limitations of the revised TNM staging system.

In this article, we review the revisions to the TNM staging system for esophageal cancer and identify important changes from the sixth edition. In addition, we discuss and illustrate the imaging features of esophageal cancer at CT, endoscopic US, and PET/CT. We also briefly describe the stage-based management of esophageal cancer.

Background for the Revisions in TNM Staging

The previous AJCC-UICC staging system for esophageal cancer (sixth edition) was neither data driven nor harmonized with the staging of stomach cancer (9). Stage grouping was empirical and was determined on the basis of a simple, orderly arrangement of increasing the T, N, and M classifications. A growing interest in factors associated with survival, including both anatomic and nonanatomic cancer characteristics, led to a new emphasis on revisions to the previous staging system (10). Additionally, the previous N classification of esophageal cancer was not determined by the number of cancer-positive nodes, unlike the N classification of stomach cancer. For tumors at the esophagogastric junction, the previous system produced different stage groupings depending on whether esophageal or stomach cancer stage groupings were used (7).

At the request of the AJCC, the Worldwide Esophageal Cancer Collaboration (WECC) assembled multi-institutional international data from five countries and three continents. The data were used to construct a database of 4627 patients with esophageal or esophagogastric junction cancer who underwent esophagectomy without preoperative or postoperative adjuvant therapy. Researchers then analyzed cancer characteristics and patient survival rates. Analyses were also performed on the relationship between cancer characteristics and patient survival to produce stage groupings for which survival was *(a)* monotonic (decreasing with increasing stage group), *(b)* distinctive between groups, and *(c)* homogeneous within groups (11,12).

The seventh edition of the AJCC-UICC cancer staging manual for the esophagus and esophagogastric junction is data driven and is harmonized with stomach cancer staging. Improvements include new definitions of the anatomic classifications Tis, T4, regional lymph node, N, and M and the addition of nonanatomic cancer characteristics (ie, histopathologic cell type, histologic grade, and cancer location) (13).

Figure 1a provides a schematic of the seventh edition of the TNM staging system for esophageal cancer. Table 1 compares the sixth and seventh editions of the TNM cancer staging system for the esophagus and esophagogastric junction.

Anatomic Classifications

Primary Tumor

The degree of primary tumor invasion is represented by the T classification, which provides details regarding local tumor invasion into the esophageal wall and advanced invasion into adjacent structures. The T classification is one of the important prognostic factors in patients with esophageal cancer because a higher T category is associated with a greater likelihood of nodal metastatic disease (14,15). Furthermore, in general practice, the T classification is crucial to determining suitability for surgical resection and establishing a treatment plan (16).

In the seventh edition of the cancer staging manual, the Tis classification is now defined as high-grade dysplasia and includes all noninvasive neoplastic epithelium previously called carcinoma in situ. The T1–T3 classifications have remained the same as in the sixth edition, while the T4 classification has been subcategorized into T4a and T4b according to surgical resectability (6,13).

T1–T3 Classifications.—T1 tumors invade the lamina propria or muscularis mucosae (T1a) (Fig 2) or submucosa (T1b). T2 tumors invade the muscularis propria, and T3 tumors involve the adventitia of the esophageal wall.

CT is one of the noninvasive imaging modalities used for staging esophageal cancer. Normal esophageal wall thickness at CT is usually less

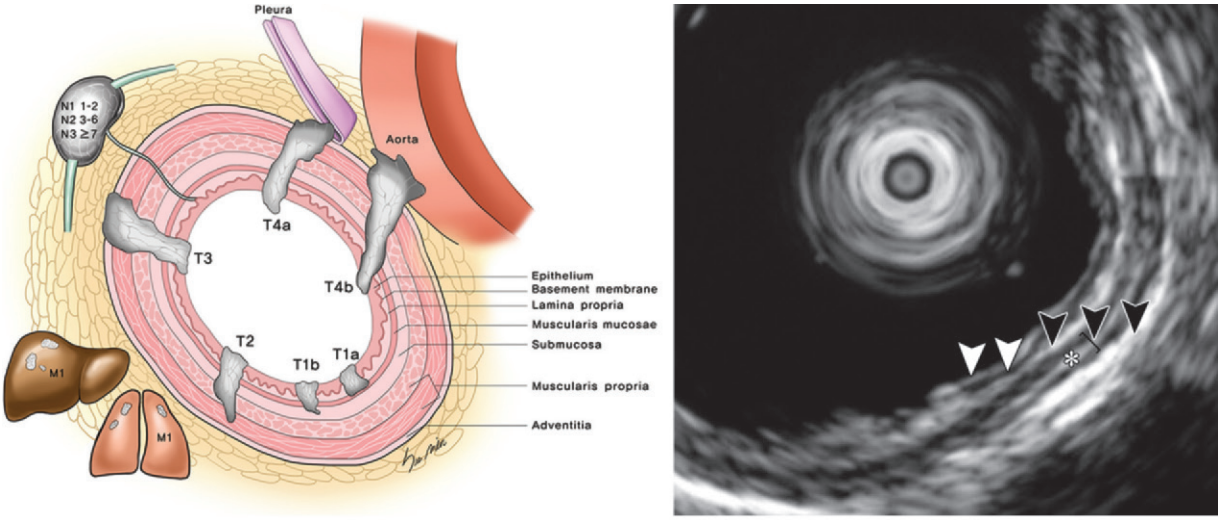


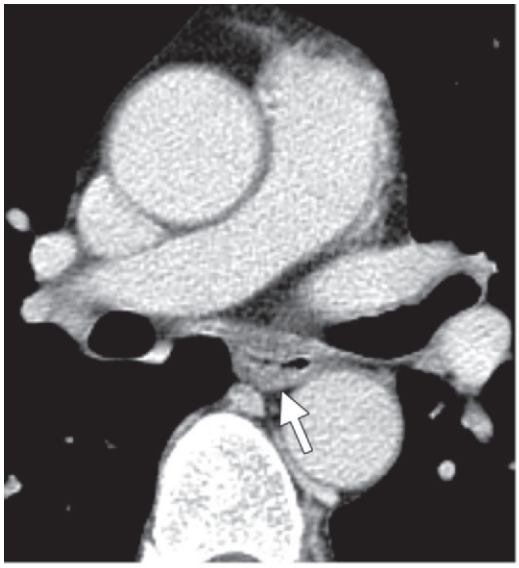
Figure 1. **(a)** Drawing illustrates the revised TNM staging system for esophageal cancer (seventh edition). **(b)** Endoscopic US image shows the normal esophageal wall, with five alternating hyper- and hypoechoic layers (arrowheads). The hyperechoic layer between the hypoechoic inner and outer muscularis propria (*) is the inner muscular connective tissue layer and is sometimes seen prominently. (Courtesy of Cheol-Min Shin, MD, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.)

Table 1: Comparison of Sixth and Seventh Editions of TNM Staging System for Esophageal Cancer

Category	Sixth Edition	Seventh Edition
Tumor	Tis: carcinoma in situ	Tis: high-grade dysplasia
	T1: invasion of lamina propria, muscularis mucosae, or submucosa	T1: invasion of lamina propria, muscularis mucosae, or submucosa
	T2: invasion of muscularis propria	T2: invasion of muscularis propria
	T3: invasion of adventitia	T3: invasion of adventitia
	T4: invasion of adjacent structures	T4: invasion of adjacent structures
	…	T4a: resectable (pleura, pericardium, or diaphragm)
	…	T4b: unresectable (aorta, vertebral body, or trachea)
Node	N0: absent	N0: absent
	N1: present	N1: 1–2 regional LNs
	…	N2: 3–6 regional LNs
	…	N3: ≥7 regional LNs
Metastasis	M0: absent	M0: absent
	M1a: cervical LN (in upper esophageal cancer) or celiac LN (in lower esophageal cancer)	M1: present
	M1b: all other distant metastases	…

Note.—LN = lymph node.

than 3 mm when the esophagus is distended, and any thickness greater than 5 mm is considered abnormal (17). Although T1 or T2 esophageal cancer is usually seen as an asymmetric thickening of the esophageal wall (Fig 3a), it is not easy to detect tumors in routine practice without the use of endoscopic US or PET/CT. In contrast, esophageal cancer that appears as an intraluminal mass at CT can be easily detected (Fig 4a). T3 esophageal cancer can be seen at CT as definite wall thickening or as an esophageal mass that causes luminal obstruction. In some cases, adventitial penetration by the tumor may appear as ill-defined abnormal soft tissue around the tumor (Fig 5a) (18), and this finding can be considered T3 disease if the fat planes between the esophageal cancer and adjacent structures are preserved. However, the use of CT is limited for determin-



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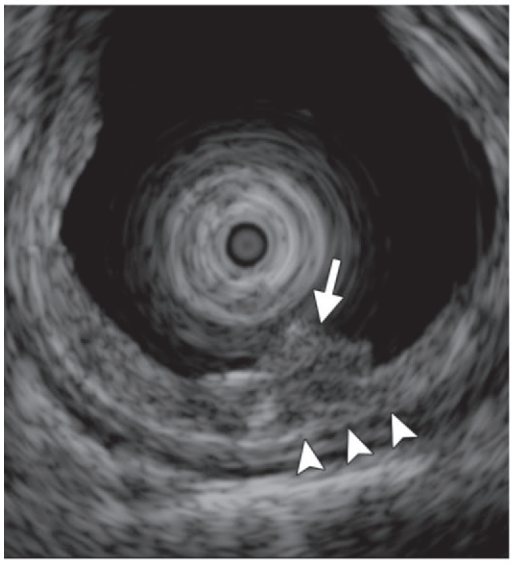

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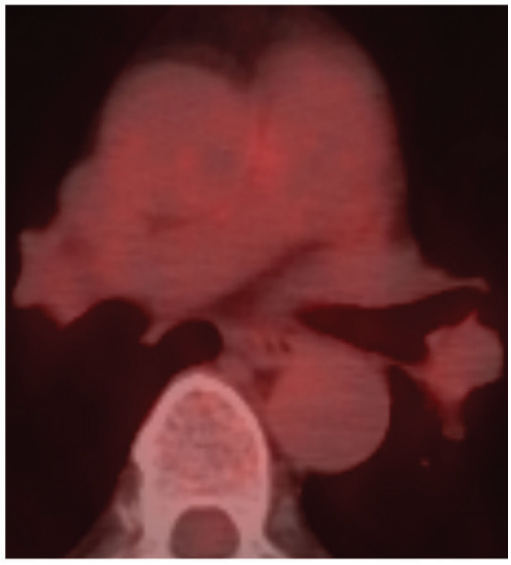
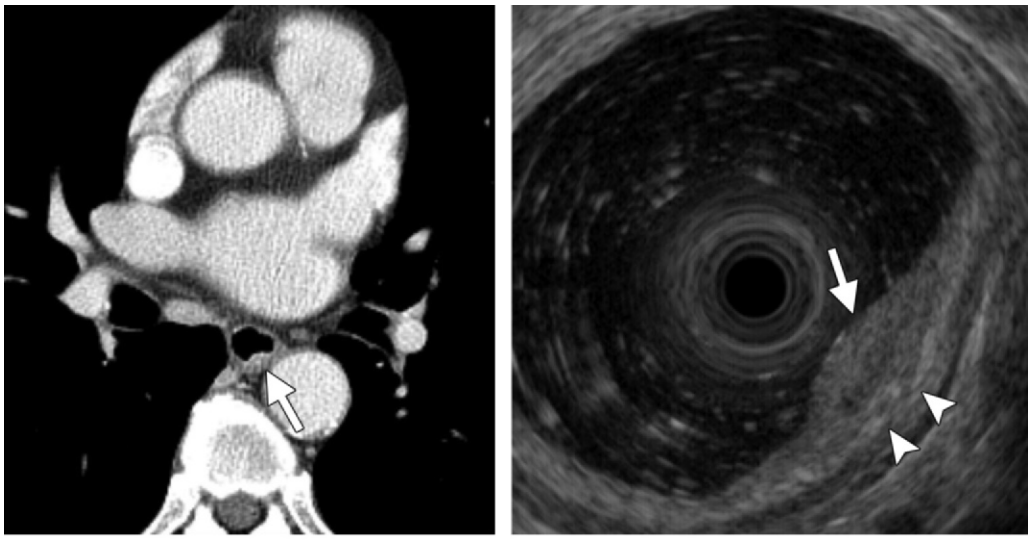


c.

Figure 2. T1a tumor. **(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 easy to detect without endoscopy. The lesion was later confirmed to be squamous cell carcinoma. **(b)** Endoscopic US image 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 **a** shows no definite FDG uptake in the primary tumor.

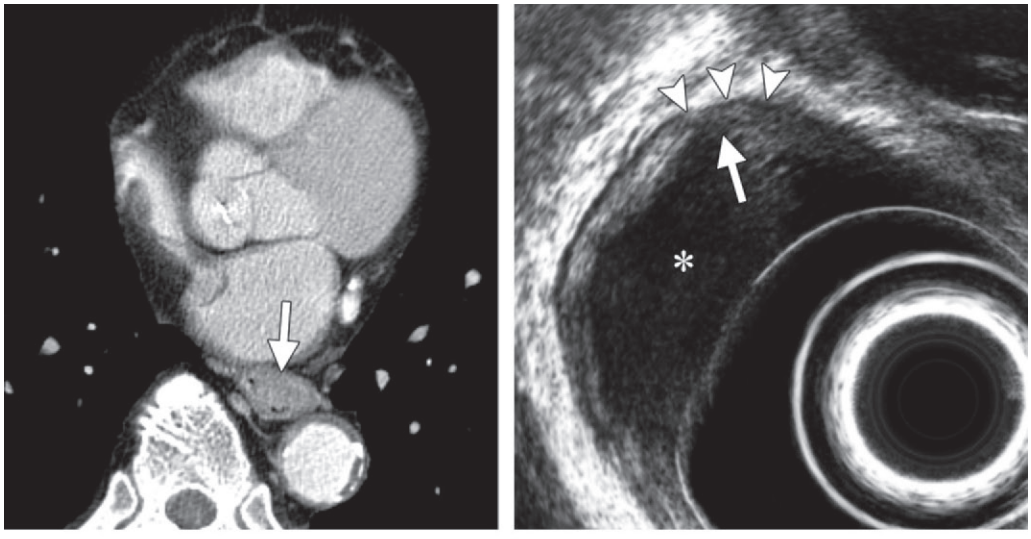
ing the exact depth of tumor invasion into the esophageal wall, and the accuracy of CT for specific T staging is lower than that of endoscopic US (19,20).

Endoscopic US is considered the most accurate imaging modality for the T staging of esophageal cancer because it can be used to define the layers of the esophageal wall and thereby differentiate T1, T2, and T3 tumors. The normal esophageal wall has five alternating layers of differing echogenicity (Fig 1b). The innermost, third, and fifth layers are hyperechoic, while the second and fourth layers are hypoechoic. The first layer represents the interface between the balloon and the superficial mucosa, and the second layer represents the lamina propria and muscularis mucosae. The third layer represents the submucosa, and the fourth layer represents the muscularis propria. The fifth layer represents the interface between the adventitia and surrounding tissues (21). It is important to identify the third and fifth hyperechoic layers because preservation of the third hyperechoic layer indicates T1a disease, while obliteration of this layer indicates T1b disease. Preservation of the fifth hyperechoic layer indicates T2 disease, while obliteration of this layer indicates T3 disease (Figs 2–5). Preservation of the fat plane between the aorta or left atrium and a tumor rules out T4 disease at endoscopic US (Fig 5b). Particularly in T1a tumors that are amenable to local ablative therapy (eg, endoscopic mucosectomy or photodynamic destruction), endoscopic US with high-frequency probes (15 and 20 MHz) can be used to more accurately differentiate mucosal (T1a) from submucosal (T1b) tumor invasion (22).



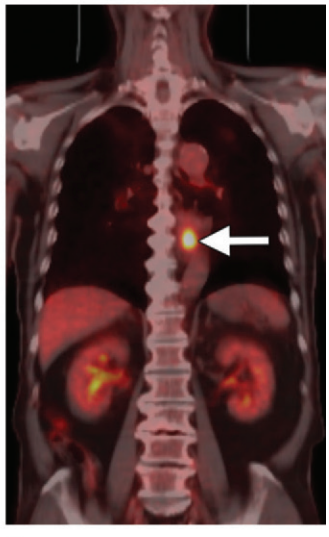
a. b.

Figure 3. T1b tumor. **(a)** Axial contrast-enhanced CT image at the level of the left atrium shows asymmetric wall thickening in the midesophagus (arrow), a finding later confirmed to be squamous cell carcinoma. **(b)** Endoscopic US image shows smooth, marginated, eccentric wall thickening (arrow), with focal obliteration of the hyperechoic third layer (submucosa) (arrowheads).



a. b.

Figure 4. T2 tumor. **(a)** Axial contrast-enhanced CT image at the level of the left atrium shows an intraluminal mass in the midesophagus (arrow), a finding later confirmed to be squamous cell carcinoma. **(b)** Endoscopic US image shows an eccentric nodular lesion (*), with penetration into the hypoechoic fourth layer (muscularis propria) (arrow) and preservation of the hyperechoic fifth layer (adventitia) (arrowheads). **(c)** Coronal PET/CT image shows intense FDG uptake in the primary tumor (arrow).



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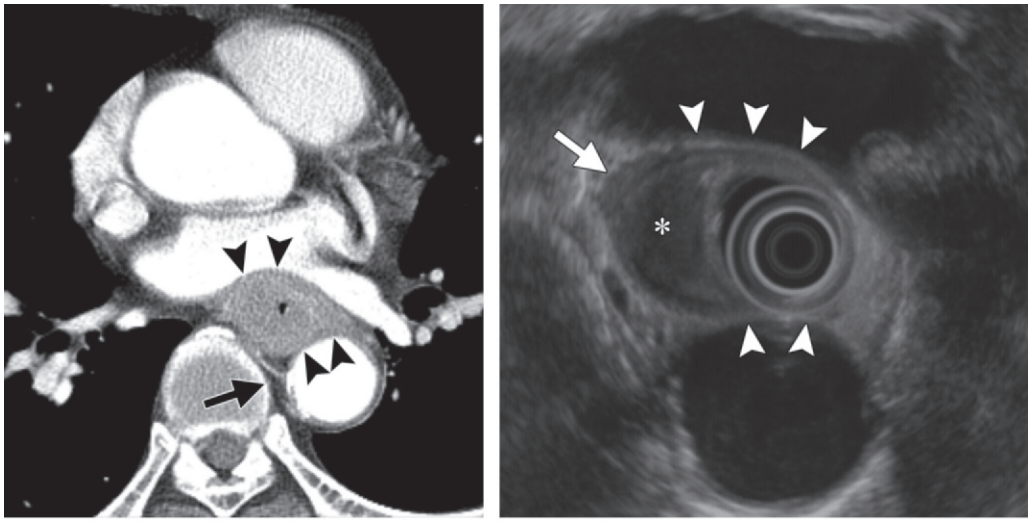


Figure 5. T3 tumor. **(a)** Axial contrast-enhanced CT image at the level of the left inferior pulmonary vein shows diffuse wall thickening in the lower esophagus and periesophageal fat infiltration, findings later confirmed to be squamous cell carcinoma. Obliteration of the fat plane between the mass and the left atrium or descending thoracic aorta is equivocal (arrowheads), and the triangular fat space is preserved (arrow). **(b)** Endoscopic US image shows an eccentric mass (*), with focal obliteration of the hyperechoic fifth layer (adventitia) (arrow). The normal fat plane between the mass and the left atrium or descending thoracic aorta is clearly identified (arrowheads).

Although a meta-analysis of 27 primary articles has reported the accuracy of endoscopic US for T staging of esophageal cancer as 89% (23), endoscopic US has several limitations for use in T staging. Endoscopic US is an operator-dependent procedure, and different experience levels among investigators create interobserver variation. Peritumoral edematous changes may lead to overstaging, while limited tumor penetration below the resolution of endoscopic US may lead to understaging (24). In patients with stenotic tumors in whom the endoscope cannot be passed through the lumen, it may be difficult to evaluate the entire tumor by using endoscopic US (25).

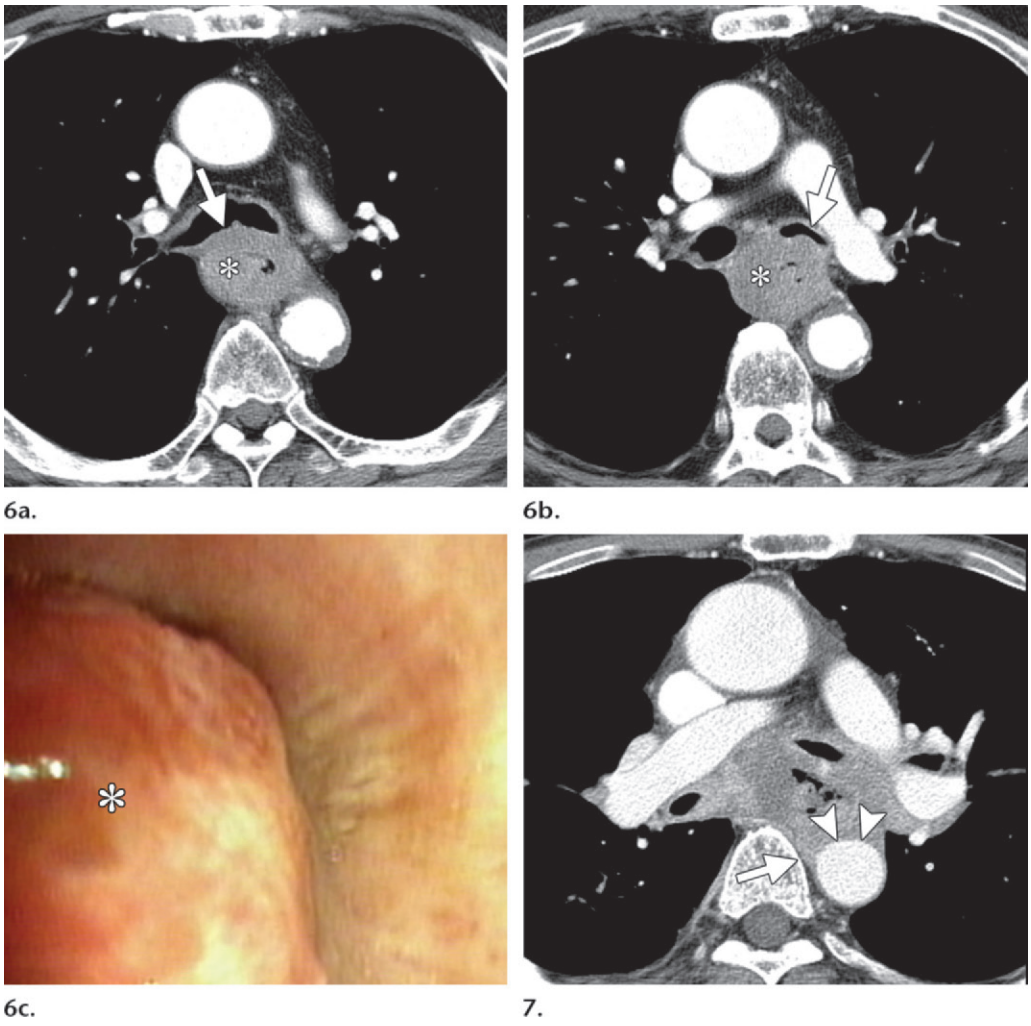
FDG PET/CT is useful for detecting esophageal primary tumors (Fig 4c). Its sensitivity ranges from 78% to 95%, with most false-negative results occurring in patients with T1 or small T2 tumors (Fig 2c) (26,27). On the other hand, false-positive results can occur as a result of FDG uptake from esophagitis or gastroesophageal reflux disease (28,29). PET/CT has little role in helping determine the specific T classification because it provides limited information about the depth of tumor invasion (30).

T4 Classification.—In the seventh edition of the TNM staging system, T4 tumors that invade adjacent structures include the new subcategorizations of T4a and T4b, which are based on tumor resectability. T4a tumors are resectable cancers that invade adjacent structures such as the pleura-peritoneum, pericardium, or diaphragm. T4b tumors are unresectable cancers that invade other adjacent structures such as the aorta, carotid vessels, azygos vein, trachea, left main bronchus, or vertebral body.

CT is considered the most accurate imaging tool for depicting local invasion to adjacent structures, which helps determine suitability for surgical resection. CT criteria for local invasion include loss of the fat planes between the tumor and adjacent structures in the mediastinum and displacement or indentation of adjacent mediastinal structures (8). However, it frequently is impossible to delineate normal fat planes at CT, particularly in the midesophageal area, in severely underweight patients and in patients who have undergone radiation therapy or surgery (31,32).

Pericardial invasion is suspected if CT images show obliteration of the fat plane between the esophageal mass and pericardium, pericardial thickening, pericardial effusion, or indentation of the heart with a concave deformity (33). A tracheobronchial fistula or direct extension into the lumen is an unequivocal finding of airway invasion by the tumor (Figs 6, 7). Tracheobronchial invasion is also suspected if there is a discrete indentation on the posterior wall or displacement of the trachea or bronchus by the tumor (34,35). Aortic invasion is suggested if the contact area between the tumor and aorta is greater than 90° or if there is obliteration of the triangular fat space between the esophagus, aorta, and spine adjacent to the

Teaching Point



Figures 6, 7. **(6)** T4b tumor with tracheobronchial invasion. **(a, b)** Axial contrast-enhanced CT images at the level of the tracheal bifurcation and main-stem bronchi show diffuse wall thickening in the midesophagus (*), a finding later confirmed to be squamous cell carcinoma. Direct tumor extension into the carina and left main bronchus is seen as carinal blunting (arrow in **a**) and luminal narrowing of the left main bronchus (arrow in **b**). **(c)** Bronchoscopic image of the left main bronchus shows mucosal elevation and irregular mucosal markings in the posterior wall (*), findings consistent with mucosal involvement of esophageal cancer. **(7)** T4b tumor with aortic and bronchial invasion. Axial contrast-enhanced CT image at the level of the right main pulmonary artery shows diffuse irregular wall thickening in the midesophagus. The tumor contacts the descending thoracic aorta at greater than 90° (arrowheads) and obliterates the triangular fat space between the esophagus and thoracic aorta (arrow). Surgery confirmed squamous cell carcinoma.

primary tumor (Fig 7) (36,37). The reported sensitivity of CT for detecting aortic and tracheobronchial involvement is almost 100%, and the reported specificity is 52%–97% (38).

Endoscopic US has limited utility for evaluating T4 tumors whose outer borders may be outside the field of view, especially stenotic tumors. PET/CT has little value for depicting the local invasion of adjacent mediastinal structures because its spatial resolution is lower than that of CT.

Regional Lymph Nodes

The N classification, which considers regional lymph node involvement, is the most important prognostic factor in esophageal cancer because patients without lymph node involvement have a better prognosis than those with nodal involvement (39). The extensive submucosal lymphatic network of the esophagus allows early regional lymph node metastases from esophageal cancer by longitudinal spread along the esophageal wall (40). Hence, the N classification influences the establishment of multimodality treatment and helps determine the suitability of surgical resection and the use of preoperative or definitive chemoradiation therapy.

The sixth edition of the TNM cancer staging manual defined lymph node metastasis as regional

Table 2: Esophageal Cancer Staging of Lymph Node Metastases in the Sixth and Seventh Editions

Location of Lymph Node Metastases	Sixth Edition	Seventh Edition
Cervical and supraclavicular	N1 (CE), M1a (UE), M1b (ME, LE)	N1–N3
Mediastinal and perigastric	N1 (UE, ME, LE), M1b (CE)	N1–N3
Celiac	M1a (LE), M1b (CE, UE, ME)	N1–N3
Distant	M1b	M1

Note.—CE = cervical esophagus, LE = lower esophagus, ME = middle esophagus, UE = upper esophagus.

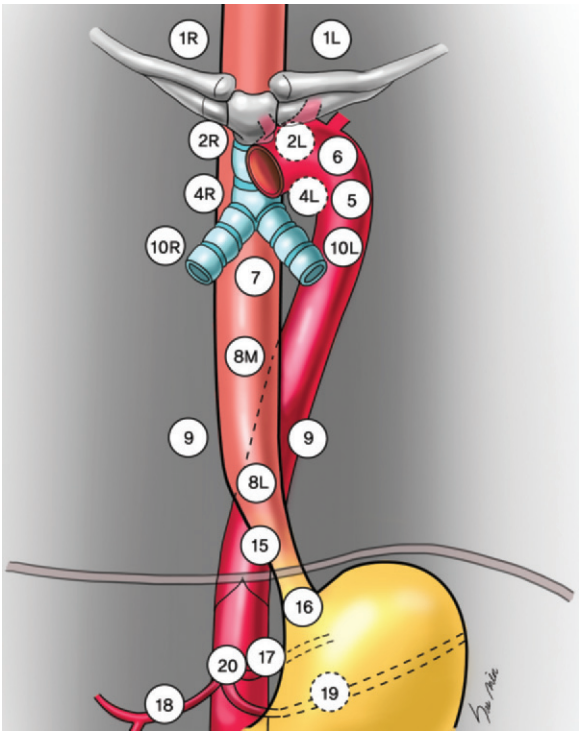


Figure 8. Regional lymph nodes according to the seventh edition of the staging manual for esophageal cancer. *1L* = left supraclavicular, *1R* = right supraclavicular, *2L* = left upper paratracheal, *2R* = right upper paratracheal, *4L* = left lower paratracheal, *4R* = right lower paratracheal, *5* = 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. The posterior mediastinal lymph node (3P) is not shown.

or distant metastasis, depending on the anatomic location of the primary tumor, and the N classification was determined by the absence (N0) or presence (N1) of histologic involvement (9) (Table 2). However, because of the longitudinal nature of lymphatic drainage, the revised manual defines regional lymph nodes to include any paraesophageal lymph nodes from the cervical nodes to the celiac nodes (Fig 8). The new N classification comprises N0 (no cancer-positive nodes), N1 (one or two cancer-positive nodes), N2 (three to six cancer-positive nodes), and N3 (seven or more cancer-positive nodes) (Figs 9–11) and is derived from data analyses that support convenient coarse groupings of the number of cancer-positive nodes. Cervical or celiac axis lymph node metastases are no longer classified as M1a or M1b disease (Figs 9, 10). Consequently, the new N classification is similar to that used in stomach cancer staging, where N describes the number of cancer-positive nodes.

Teaching Point

At CT, normal lymph nodes are usually smaller than 1 cm in short-axis diameter and have a smooth well-defined border, uniform homogeneous attenuation, and a central fatty hilum (32). Detection of pathologic lymph nodes at CT depends primarily on size criteria. Intrathoracic and abdominal lymph nodes larger than 1 cm and supraclavicular lymph nodes larger than 5 mm in short-axis diameter are considered metastatic lymph nodes (41,42). However, normal-sized lymph nodes that contain microscopic metastatic foci cannot be differentiated from nonmetastatic lymph nodes at CT and can lead to understaging, and benign, enlarged, inflammatory lymph nodes seen at CT may lead to overstaging (43). In addition, metastatic lymph nodes adjacent to esophageal cancer may not be detected because they are inseparable from the primary tumor (34). If there are conglomerated lymph nodes, the number of lymph node metastases cannot be accurately measured, and determining the N category can be difficult (Fig 12).

Endoscopic US shows higher accuracy rates (72%–80%) for assessing lymph node metastases than does CT (46%–58%) (44,45) because endoscopic US relies not only on the size criterion of a short-axis diameter greater than 1 cm but also on the internal echo characteristics of individual nodes. Nodes that are round, have a hypoechoic central echo pattern, and have sharply demarcated borders are more likely to represent malignancy. Although the accuracy

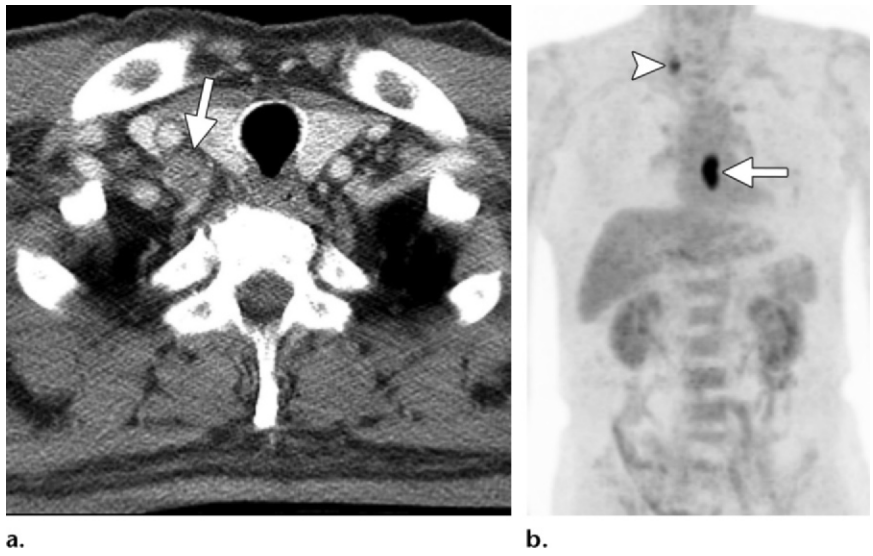


Figure 9. N1 disease. **(a)** Axial contrast-enhanced CT image shows an enlarged right supraclavicular lymph node (arrow) measuring 11 mm in short diameter. **(b)** Coronal PET image shows FDG uptake in the primary tumor in the midesophagus (arrow) and in the right supraclavicular lymph node (arrowhead). Surgery confirmed squamous cell carcinoma with a malignant lymph node (N1 disease), which was considered M1b disease in the sixth edition of the TNM staging system.

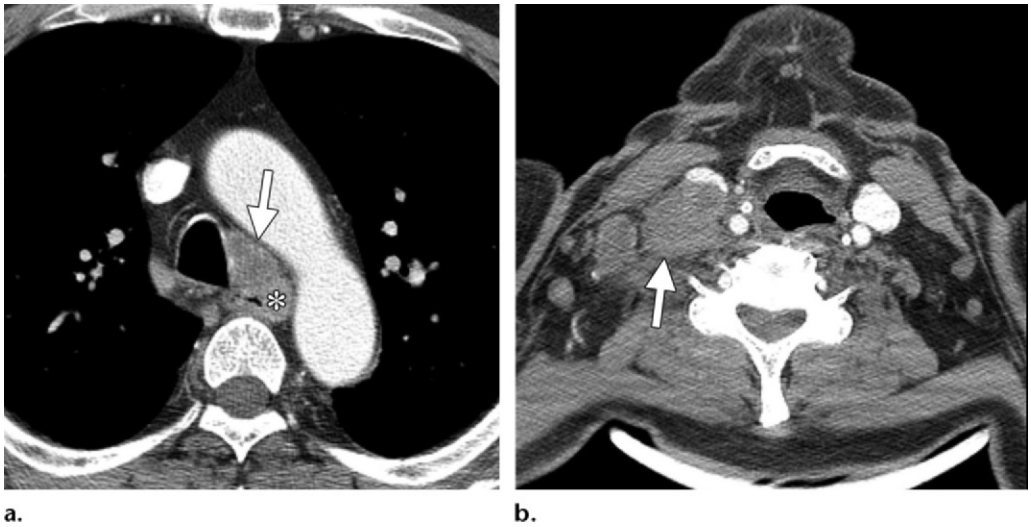


Figure 10. N2 disease. **(a)** Axial contrast-enhanced CT image at the level of the aortic arch shows asymmetric wall thickening (*) in the upper esophagus and an enlarged paraesophageal lymph node (arrow). Another small paraesophageal lymph node was also seen (not shown). **(b)** Axial contrast-enhanced CT image shows an enlarged right supraclavicular lymph node (arrow) measuring 32 mm in short diameter. Surgery confirmed squamous cell carcinoma with three malignant lymph nodes (N2 disease), which was considered M1a disease in the sixth edition of the TNM staging system.

of endoscopic US for predicting lymph node metastases has been reported as 100% if all four features of malignancy are present, only a small number of metastatic lymph nodes demonstrate all four features, especially in the paraesophageal region (46–48).

Additionally, endoscopic US–guided fine-needle aspiration (FNA) can allow cytologic confirmation of lymph node metastases, including mediastinal and even abdominal lymph nodes along the left gastric artery and celiac axis, and can help distinguish metastatic nodes from reactive hyperplasia or inflammatory nodes. However, FNA of peritumoral lymph nodes should be avoided because the needle would have to pass through the primary tumor in the esophageal wall, which could lead to a false-positive result (32).

PET/CT is also superior to CT for detecting lymph node metastases and can depict metastases in normal-sized lymph nodes through the uptake of FDG (34). In a meta-analysis of 12 previous studies, the sensitivity of PET/CT (51%) was significantly lower than that of CT (63%–87%), but the specificity of PET/CT (84%) was relatively higher than that of CT (14%–43%). The lower sensitivity of PET/CT may result from the difficulty in differentiating the primary tumor from peritumoral lymph nodes because of intense FDG uptake by the tumor, as well as from false-positive findings due to inflammatory enlarged

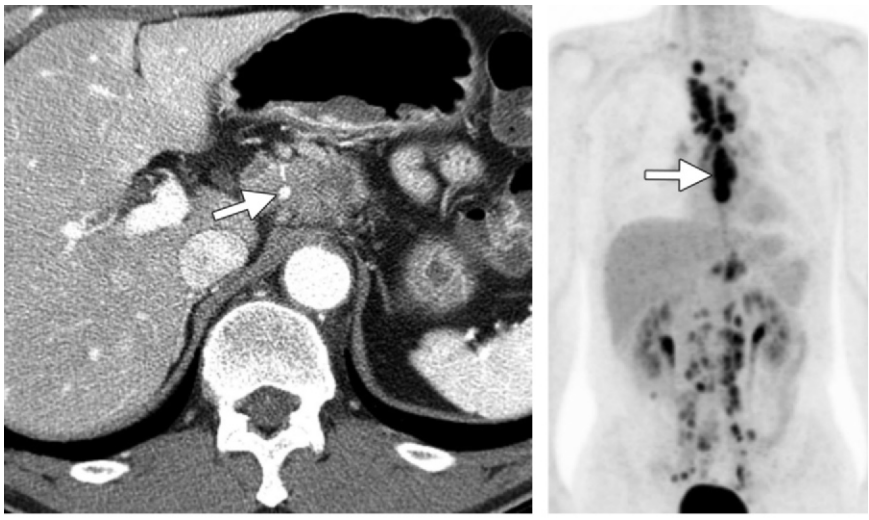


Figure 11. N3 disease. **(a)** Axial contrast-enhanced CT image shows conglomerated lymph nodes with encasement of the left gastric artery (arrow). **(b)** Coronal PET image shows FDG uptake in the primary tumor in the midesophagus (arrow), a finding confirmed to be squamous cell carcinoma at endoscopic biopsy. FDG uptake is also seen in multiple lymph nodes in the mediastinum, left gastric area (consistent with N3 staging), retroperitoneum, and both iliac areas (consistent with M1 staging).

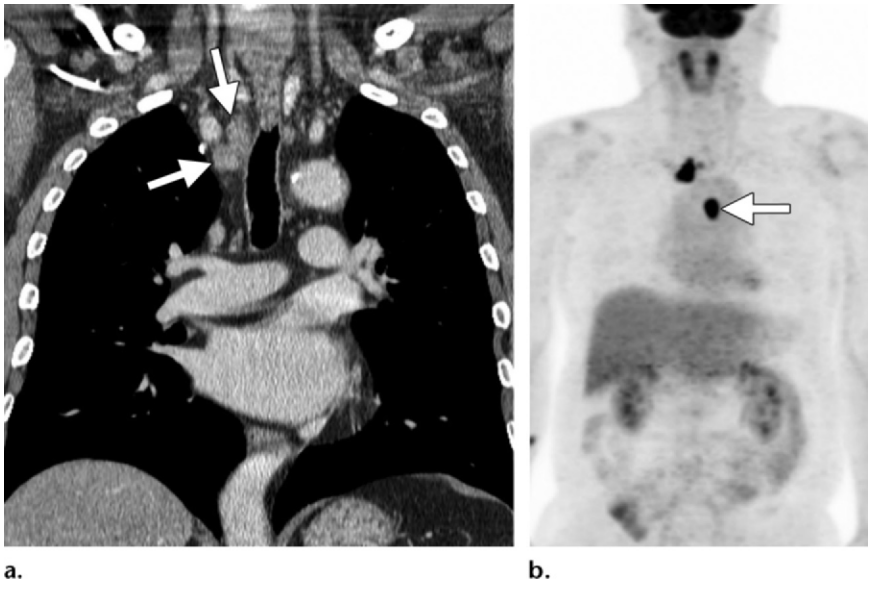


Figure 12. Pitfalls in N staging at CT and PET. **(a)** Coronal CT image shows two enlarged lymph nodes in the right upper paratracheal area (arrows). **(b)** Coronal PET image shows FDG uptake in the primary tumor in the upper esophagus (arrow) and right upper paratracheal area. However, it is difficult to count the number of enlarged lymph nodes on the PET image, and the findings were considered N1 disease on the basis of the CT and PET images. Surgery confirmed squamous cell carcinoma with three malignant lymph nodes (N2 disease).

lymph nodes (49,50). In a recent study comparing PET/CT and endoscopic US, endoscopic US was superior to PET/CT for identifying local-regional lymph node metastases (51).

Distant Metastases

Tumor involvement through hematogenous metastases to distant organs is defined as the M classification and is an important factor in determining operability (8). Distant metastases have been reported at initial presentation in 20%–30% of patients with esophageal cancer and are most commonly diagnosed in the liver (35%), followed by the lungs (20%), bones (9%), adrenal glands (5%), and, rarely, peritoneum and brain (52,53).

In the seventh edition of the TNM staging system, the previous M1a and M1b subclassifications have been eliminated. M1a indicated metastases to the cervical or celiac axis lymph nodes, and M1b indicated metastases to distant sites. The new M classification is simply designated M0 or M1 according to the absence or presence of distant metastasis, respectively (13).

CT has been widely used for detection of distant metastases in the initial staging of newly diagnosed esophageal cancer. Liver metastases usually appear at CT as hypoattenuating ill-defined lesions that are best visualized during the portal venous phase of liver enhancement (54,55). Pulmonary metastases usually are round, smooth-bordered, and noncalcified at CT. In the case of bone metastases, CT has a lower sensitivity than radionuclide bone scans, PET/CT, or magnetic resonance (MR) imaging (which is especially useful for evaluation of the spine) (3). Adrenal metastases may be seen at CT as focal heterogeneous enlargement of the adrenal gland, a finding that must be differentiated from benign adrenal adenomas (30).

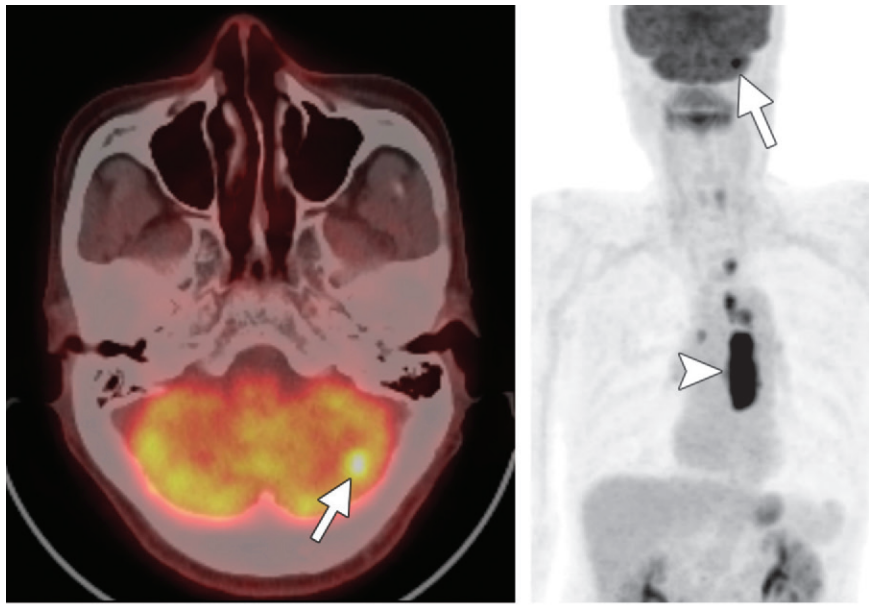


Figure 13. Unexpected M1 disease. Axial PET/CT **(a)** and coronal PET **(b)** images show unexpected focal FDG uptake in the left cerebellum (arrow). FDG uptake is also seen in the primary tumor in the midesophagus (arrowhead in **b**), a finding later confirmed to be squamous cell carcinoma, and in the mediastinal lymph nodes in **b** (fewer than seven nodes, a finding consistent with N2 disease).

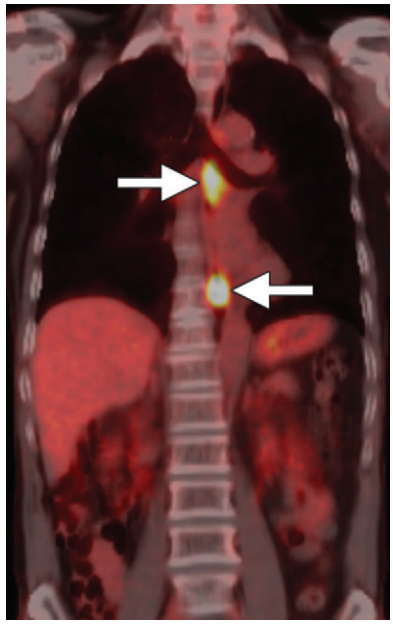


Figure 14. Synchronous multiple esophageal cancers. Coronal PET/CT image shows FDG uptake in the midesophagus and lower esophagus (arrows). At surgery, the midesophageal lesion was confirmed to be moderately differentiated squamous cell carcinoma, and the lesion in the lower esophagus was confirmed to be differentiated squamous cell carcinoma.

Endoscopic US has limited value for assessing distant metastases because of the small field of view, in contrast to its higher accuracy for assessing depth of tumor invasion and local-regional lymph node metastases (8).

PET/CT has the advantage of allowing total body coverage, and its primary role is to depict distant sites of metastatic disease (25). Previous reports have shown that PET/CT is superior to CT for depicting distant metastases (26,56). The most common sites of distant metastases detected at PET (but frequently missed at CT) are the bones and liver (57). Furthermore, PET/CT can depict metastases in unusual and unexpected locations, including the brain, skeletal muscles, subcutaneous tissues, thyroid gland, and pancreas (Fig 13) (58).

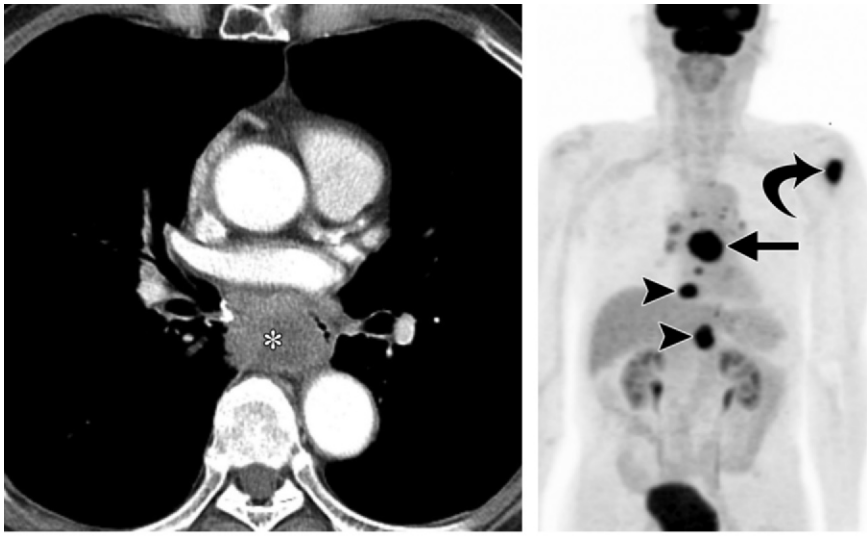
Given the gradually increasing incidence of multiple primary cancers that are associated with esophageal cancer, the use of PET/CT and CT has become more important in detecting synchronous cancer. According to previous reports, synchronous cancer in another location in the esophagus or in another organ (eg, head and neck, stomach, or lungs) has been associated with smoking or alcohol use and the concept of field cancerization (Fig 14) (59–61).

Teaching Point

Nonanatomic Cancer Characteristics

Histopathologic Cell Type

Histologically, most esophageal cancers are either squamous cell carcinomas or adenocarcinomas. Squamous cell carcinoma arises from the squamous epithelium and usually occurs in the middle or upper one-third of the esophagus. Smoking and alcohol consumption are the most important risk factors and are synergistic in contributing to the development of squamous cell carcinoma. Other predisposing conditions include genetic risk factors, such as tylosis and Plummer-Vinson syndrome, and environmental



a. b.

Figure 15. Adenocarcinoma. **(a)** Axial contrast-enhanced CT image at the level of the left atrium shows an eccentric mass in the midesophagus (*). The lesion involves periesophageal fat, and the fat plane between the mass and the pericardium of the left atrium is not preserved, findings suggestive of T4a disease that were later confirmed to be adenocarcinoma. **(b)** Coronal PET image shows intense FDG uptake in the primary tumor in the midesophagus (straight arrow) and in the right retrocrural and left gastric lymph nodes (arrowheads). Unexpected intense FDG uptake is seen in the left humeral head (curved arrow), a finding consistent with M1 disease.

exposures, including lye ingestion and therapeutic irradiation (62).

Adenocarcinoma is most commonly found in the distal esophagus and esophagogastric junction and generally develops in association with Barrett syndrome. This is a columnar metaplasia of the squamous epithelium of the esophagus that is related to gastroesophageal reflux disease, which is usually associated with overweight and obesity (63). In the past few decades, the incidence of squamous cell carcinoma has been decreasing because of long-term reductions in smoking and alcohol consumption in several Western countries, whereas that of adenocarcinoma has been increasing because of increases in the prevalence of known risk factors such as overweight and obesity (Fig 15) (1).

Recently, Siewert et al (64) found that the overall 5-year survival rate was 46% for patients with esophageal adenocarcinoma versus 37% for patients with esophageal squamous cell carcinoma. The results of an extensive retrospective study of data assembled by the WECC indicate that the histopathologic cell type is important in groups with the best survival rates (10). Therefore, squamous cell carcinoma and adenocarcinoma should be managed with separate stage groupings, specifically for stage I and stage II cancers (Tables 3, 4) (7). If the histopathologic type is mixed or not otherwise specified, the tumor should be recorded as squamous cell carcinoma (6).

Histologic Grade

In the seventh edition of the TNM staging system, another newly included cancer characteristic is the biologic activity of the tumor (ie, histologic grade), which is categorized as well differentiated (G1), moderately differentiated (G2), or poorly differentiated (G3). This subclassification follows the traditional histologic differentiation of squamous cell carcinoma from adenocarcinoma (Fig 16). If the histologic grade of an esophageal cancer cannot be assessed, the tumor is considered G1 cancer for stage grouping. If the histologic grade is undifferentiated, the tumor is considered G3 cancer (6).

According to a study that used the WECC data, an increasing histologic grade of the primary tumor was associated with an incrementally decreasing survival rate, especially for early-stage cancers. Consequently, the stage groupings of T1–T3 N0M0 cancers in squamous cell carcinoma and T1–T2 N0M0 cancers in adenocarcinoma are influenced by these histologic grades (Tables 3, 4) (10,13).

Cancer Location

The esophagus is classically divided into four regions: cervical, upper thoracic, middle thoracic, and lower thoracic. Compared with the sixth edition, the newly defined divisions in the seventh edition of the staging system include changes in the boundaries of the esophageal segments (Fig

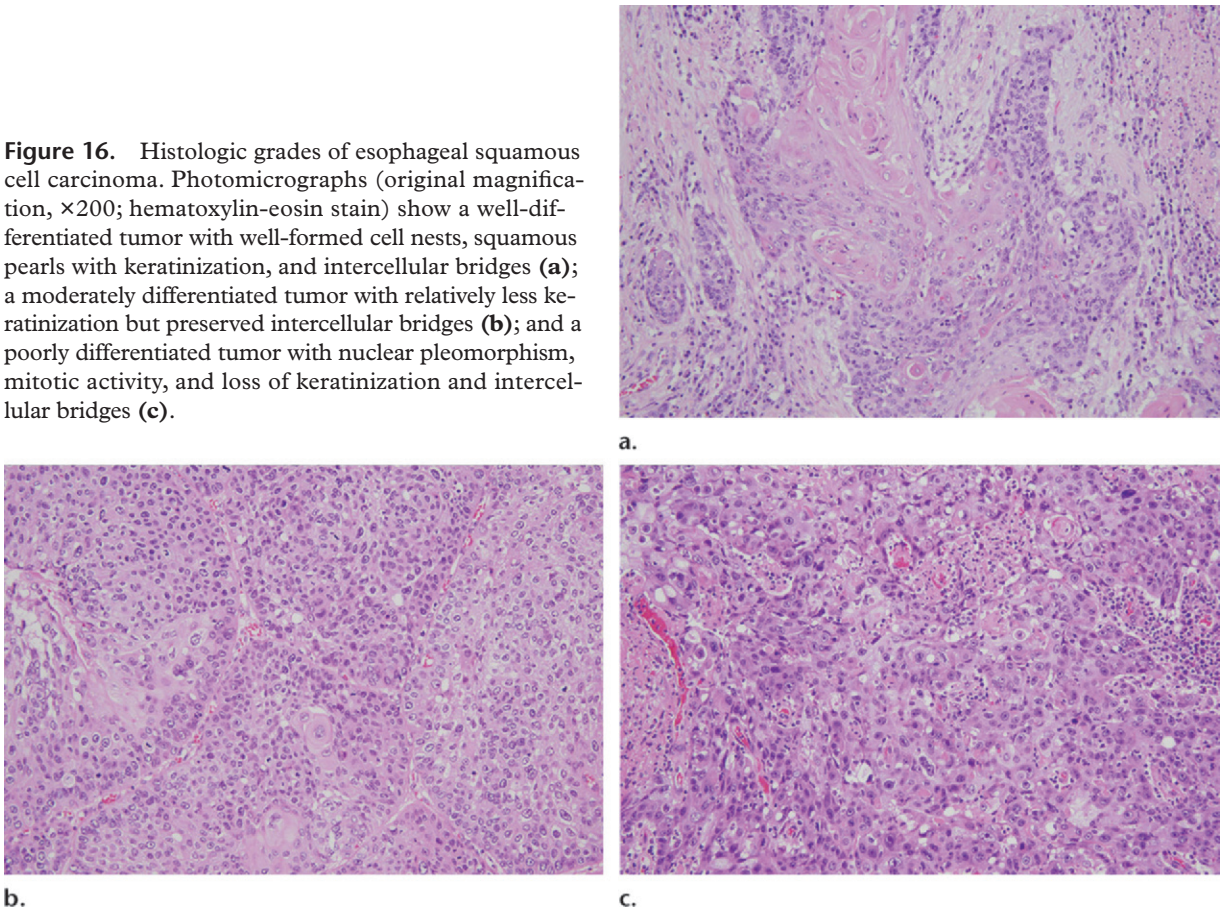


Figure 16. Histologic grades of esophageal squamous cell carcinoma. Photomicrographs (original magnification, ×200; hematoxylin-eosin stain) show a well-differentiated tumor with well-formed cell nests, squamous pearls with keratinization, and intercellular bridges **(a)**; a moderately differentiated tumor with relatively less keratinization but preserved intercellular bridges **(b)**; and a poorly differentiated tumor with nuclear pleomorphism, mitotic activity, and loss of keratinization and intercellular bridges **(c)**.

Table 3: Stage Groupings for Squamous Cell Carcinoma

	Stage				
	N0				
TM Category	G1	G2–G3	N1	N2	N3
T1M0	IA	IB	IIB	IIIA	IIIC
T2M0			IIB	IIIA	IIIC
LE	IB	IIA			
UME	IIA	IIB			
T3M0			IIIA	IIIB	IIIC
LE	IB	IIA			
UME	IIA	IIB			
T4M0			IIIC	IIIC	IIIC
T4a	IIIA	IIIA			
T4b	IIIC	IIIC			
Any T, M1	IV	IV	IV	IV	IV

Note.—G = histologic grade, LE = lower esophagus, UME = upper and middle esophagus.

17). The cervical esophagus, which is 15–20 cm from the incisors at esophagoscopy, begins at the level of the cricopharyngeus muscle and ends at the level of the sternal notch (Fig 18). The upper thoracic esophagus, which is 20–25 cm from the incisors, is bounded superiorly by the sternal notch and inferiorly by the azygos arch. The middle thoracic esophagus, which is 25–30 cm from the incisors, extends from the level of the azygos arch to the level of the inferior pulmonary vein.

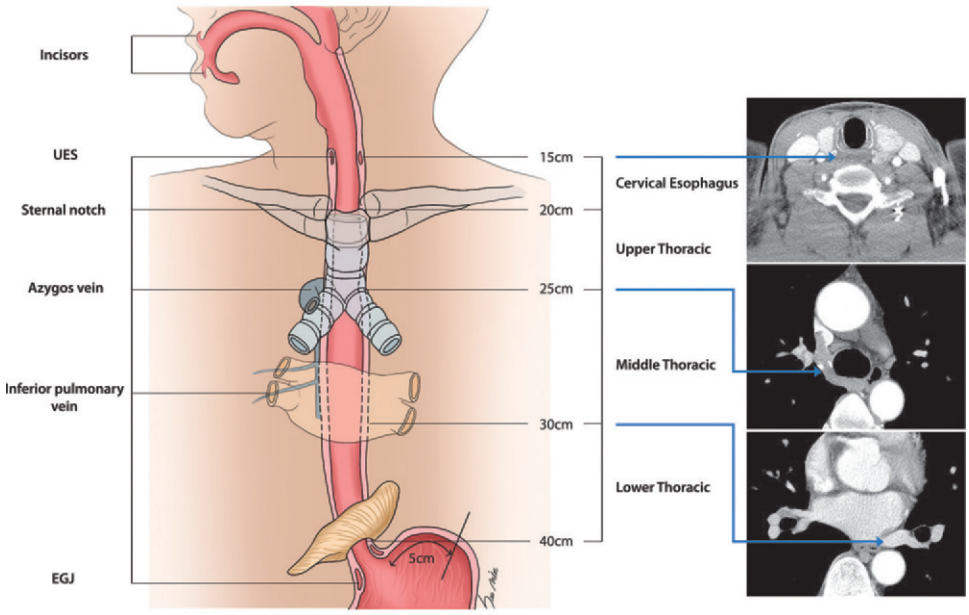


Figure 17. Drawing and axial CT images show the locations of esophageal cancer as described in the seventh edition of the TNM staging manual. *EGJ* = esophagogastric junction, *UES* = upper esophagus.

Table 4: Stage Groupings for Adenocarcinoma

	Stage				
	N0				
TM Category	G1–G2	G3	N1	N2	N3
T1M0	IA	IB	IIB	IIIA	IIIC
T2M0	IB	IIA	IIB	IIIA	IIIC
T3M0	IIB	IIB	IIIA	IIIB	IIIC
T4M0			IIIC	IIIC	IIIC
T4a	IIIA	IIIA			
T4b	IIIC	IIIC			
Any T, M1	IV	IV	IV	IV	IV

Note.—G = histologic grade.

The lower thoracic esophagus is 30–40 cm from the incisors and extends from the level of the inferior pulmonary vein to the lower esophageal sphincter (6).

Whereas the cancer location of the primary tumor was indirectly considered when determining the N and M1a classifications in the sixth edition, cancer location has been directly included in the stage grouping of T2–T3 N0M0 squamous cell carcinoma in the seventh edition, on the basis of data-driven analysis (Table 3) (7). An important factor in assessing cancer location is to determine the position of the upper edge of the tumor in the esophagus, not the position where the tumor occupies the largest volume (13).

Teaching Point

Additionally, the new concept of tumors that occur in the esophagogastric junction has been addressed in the seventh edition. Tumors in this region have caused much confusion about whether they arise from esophageal cancer or proximal gastric cancer. Given the recent significant increase in the incidence of adenocarcinomas of the distal esophagus, esophagogastric junction, and gastric cardia, precise localization of these tumors is important for accurate staging and appropriate management (65,66).

Consensus meetings and parallel analysis with the Digestive Cancer Task Force have shown that patients with adenocarcinoma of the esophagogastric junction and gastric cardia have lower survival rates than patients with other gastric cancers (10). Additionally, the International Gastric Cancer Association (IGCA) and International Society for Diseases of the Esophagus (ISDE) define adenocarcinomas of the esophagogastric junction as tumors that have their center within 5 cm proximal and distal to the anatomic cardia (67).

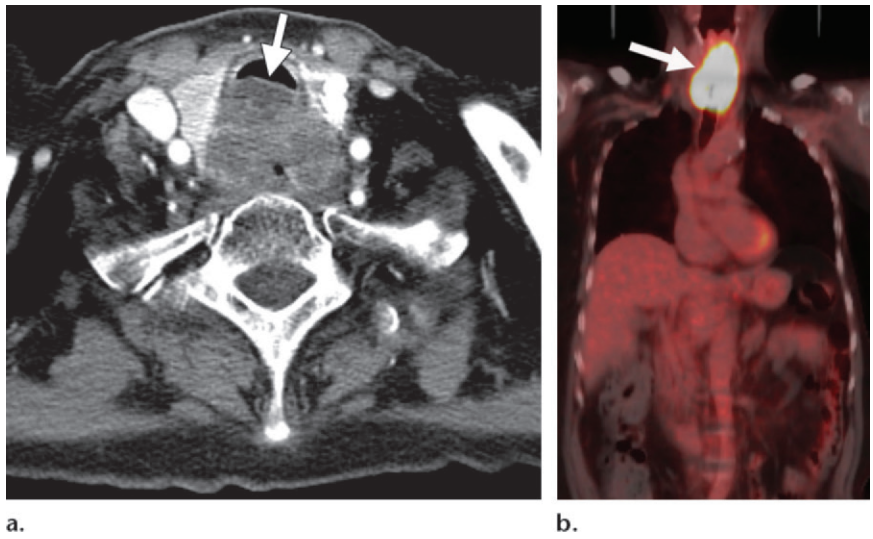


Figure 18. Cervical esophageal cancer. **(a)** Axial contrast-enhanced CT image at the level of the thyroid gland shows irregular circumferential wall thickening in the cervical esophagus, with direct tumor extension into the posterior wall of the trachea (arrow). The lesion was later confirmed to be squamous cell carcinoma. **(b)** Coronal PET/CT image shows intense FDG uptake in the primary tumor (arrow).

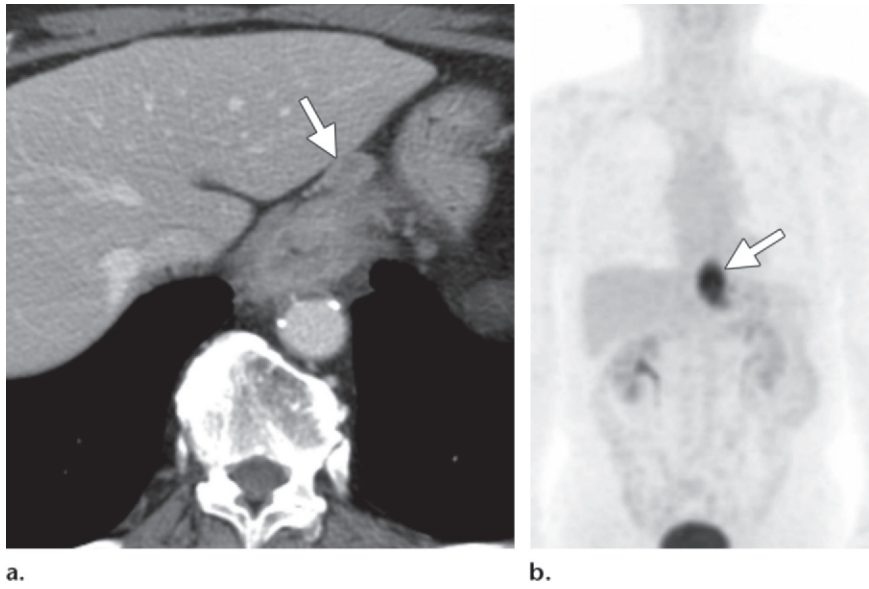


Figure 19. Involvement of the esophagogastric junction. **(a)** Axial contrast-enhanced CT image shows diffuse wall thickening around the esophagogastric junction and an equivocal paracardial lymph node measuring 10 mm in short-axis diameter (arrow). **(b)** Coronal PET image shows intense FDG uptake in the primary tumor (arrow), which involves the esophagogastric junction. At surgery, the findings were confirmed to be squamous cell carcinoma with a malignant lymph node.

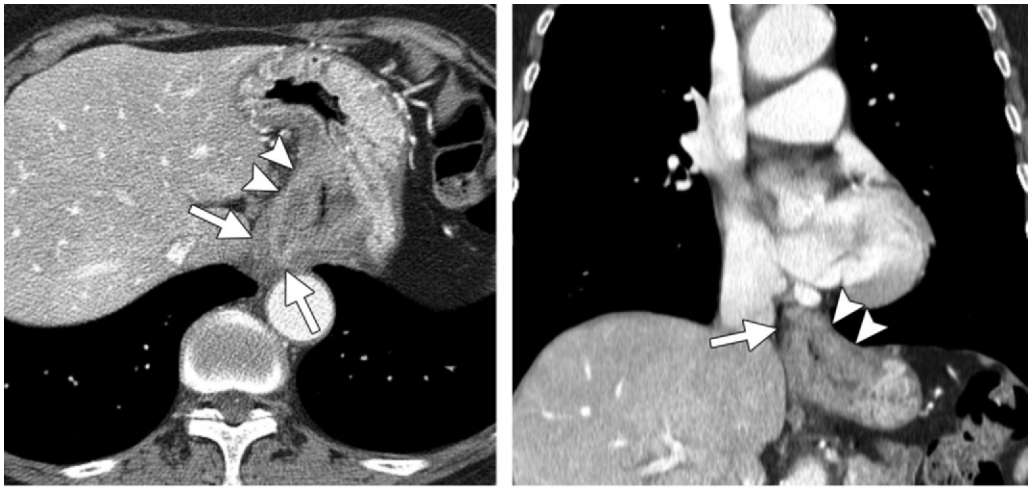
Teaching Point

Therefore, tumors in the esophagogastric junction are staged as esophageal cancer if *(a)* the tumor's epicenter is within the lower thoracic esophagus or at the esophagogastric junction or *(b)* the epicenter is within the proximal 5 cm of the stomach and the tumor extends into the esophagus (Figs 19, 20) (13). Tumors with an epicenter within 5 cm of the stomach without extension into the esophagus and those with an epicenter in the stomach that is more than 5 cm from the esophagogastric junction are classified and staged as stomach cancer (68).

Stage Groupings and Limitations

While previous stage groupings in the sixth edition were made according to the T, N, and M classifications only, the new stage groupings in the seventh edition are made according to the anatomic T, N, and M classifications and also nonanatomic cancer characteristics, including histopathologic cell type, histologic grade, and cancer location. These stage groupings are consistent with data-driven analysis and correspond to risk-adjusted curves (7). For lymph node–negative esophageal cancers, the risk-adjusted 5-year survival rate is affected by the T classification and nonanatomic cancer characteristics. For lymph node–positive esophageal cancers, the 5-year survival rate is affected by the number of cancer-positive lymph nodes (10,13). Tables 3 and 4 show the stage groupings from the seventh edition for squamous cell carcinoma and adenocarcinoma.

A limitation of this data-driven approach is that staging is determined by the cancer characteristics of esophageal cancers that were treated by esophagectomy alone, without preoperative or postoperative chemotherapy or radiation therapy. The T4 and M1 classifications may be underrepre-



a. b.

Figure 20. Involvement of the gastric cardia. Axial **(a)** and coronal **(b)** CT images show diffuse wall thickening in the proximal 5 cm of the stomach (arrowheads), a finding that extends into the esophagogastric junction (arrows). In the seventh edition of the staging manual, this tumor is classified as esophageal cancer rather than as gastric cancer.

Table 5: Treatment of Esophageal Cancer According to Seventh Edition of TNM Staging System

T	N	M	Treatment
T1a	N0	M0	Endoscopic tissue ablation (preferred) or surgical resection
T1b	N0	M0	Surgical resection
T1b T2 T3 T4a	Any N	M0	Surgical resection with or without preoperative chemoradiation therapy; definitive chemoradiation therapy for patients who decline surgery
T4b	Any N	M0	Definitive chemoradiation therapy
Any T	Any N	M1	Palliative therapy

sented or not represented at all. Moreover, cervical esophageal cancer, which is sometimes treated as a head and neck tumor, is poorly represented (6).

Stage-based Management

Because management of esophageal cancer usually requires a multidisciplinary approach, determination of optimal treatment is complicated and often varies according to the preference of the institution or clinician. Traditionally, surgical resection that includes esophagectomy and lymphadenectomy is an important component of therapy. However, because of the high rates of local recurrence and poor long-term survival rates, well-designed preoperative or definitive chemoradiation therapy has become an essential part of therapy (16,69).

For superficial T1a tumors of squamous cell carcinoma or adenocarcinoma, tissue ablation at esophagoscopy (eg, endoscopic mucosectomy or photodynamic destruction) is preferred, although surgical resection is possible. For T1bN0 tumors, surgical resection is the treatment of choice. For locally advanced cancers (T1b with N1–N3, T2–T4a with N0–N3) other than T1bN0 tumors, surgery alone may be inadequate, and treatment may require supplemental preoperative chemoradiation therapy. For patients who decline surgery, definitive chemoradiation therapy may be needed. In localized adenocarcinoma of the thoracic esophagus or esophagogastric junction, preoperative chemotherapy is the preferred approach. T4b tumors may require definitive chemoradiation therapy. For M1 tumors (stage IV), palliative therapy is all that can be offered (Table 5) (12,70).

Conclusions

Precise pretreatment staging of esophageal cancer is important in the initial evaluation and assessment of patients to determine appropriate stage-specific treatment options. Radiologists must understand the details of the seventh edition of the AJCC-UICC staging system for esophageal cancer, which includes changes in the TNM classifications and the addition of nonanatomic cancer characteristics.

In addition, CT, endoscopic US, and PET/CT should be considered complementary imaging modalities for the staging of esophageal cancer.

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New TNM Staging System for Esophageal Cancer: What Chest Radiologists Need to Know

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Page 1727
T4a tumors are resectable cancers that invade adjacent structures such as the pleura-peritoneum, pericardium, or diaphragm. T4b tumors are unresectable cancers that invade other adjacent structures such as the aorta, carotid vessels, azygos vein, trachea, left main bronchus, or vertebral body.

Page 1729
The revised manual defines regional lymph nodes to include any paraesophageal lymph nodes from the cervical nodes to the celiac nodes. The new N classification comprises N0 (no cancer-positive nodes), N1 (one or two cancer-positive nodes), N2 (three to six cancer-positive nodes), and N3 (seven or more cancer-positive nodes) and is derived from data analyses that support convenient coarse groupings of the number of cancer-positive nodes.

Page 1732
Synchronous cancer in another location in the esophagus or in another organ (eg, head and neck, stomach, or lungs) has been associated with smoking or alcohol use and the concept of field cancerization.

Page 1735
An important factor in assessing cancer location is to determine the position of the upper edge of the tumor in the esophagus, not the position where the tumor occupies the largest volume.

Page 1736
Tumors in the esophagogastric junction are staged as esophageal cancer if *(a)* the tumor's epicenter is within the lower thoracic esophagus or at the esophagogastric junction or *(b)* the epicenter is within the proximal 5 cm of the stomach and the tumor extends into the esophagus.