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18

Esophageal Tumors

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ESOPHAGEAL CANCER

Demographics & Epidemiology

Esophageal cancer is a gastrointestinal malignancy with an insidious onset and a poor prognosis. The disease predominantly affects older age groups with a peak incidence between 60 and 70 years of age; it is rarely seen in children or young adults. There is also a predilection toward men with a ratio of at least 4:1. By far, the most common esophageal cancer worldwide is squamous cell carcinoma. Adenocarcinoma accounts for less then 15% of all esophageal cancers. Other malignant tumors of the esophagus, such as sarcomas, lymphoma, primary malignant melanoma, and small cell carcinoma, are very rare (Table 18-1). Although considered relatively uncommon, esophageal cancer is the seventh most common cause of cancer-related deaths in men in the United States and has ranked among the top 10 causes of cancer-related deaths worldwide.

Squamous cell cancer
Adenocarcinoma
Sarcoma
Epidermoid carcinoma (carcinosarcoma and pseudo-sarcoma)
Leiomyosarcoma
Fibrosarcoma
Rhabdomyosarcoma
Kaposi's sarcoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Endocrine cell tumor (small cell carcinoma)
Lymphoma
Adenosquamous carcinoma
Primary malignant melanoma
Primary esophageal carcinoid tumor

Table 18-1. Malignant tumors of the esophagus.

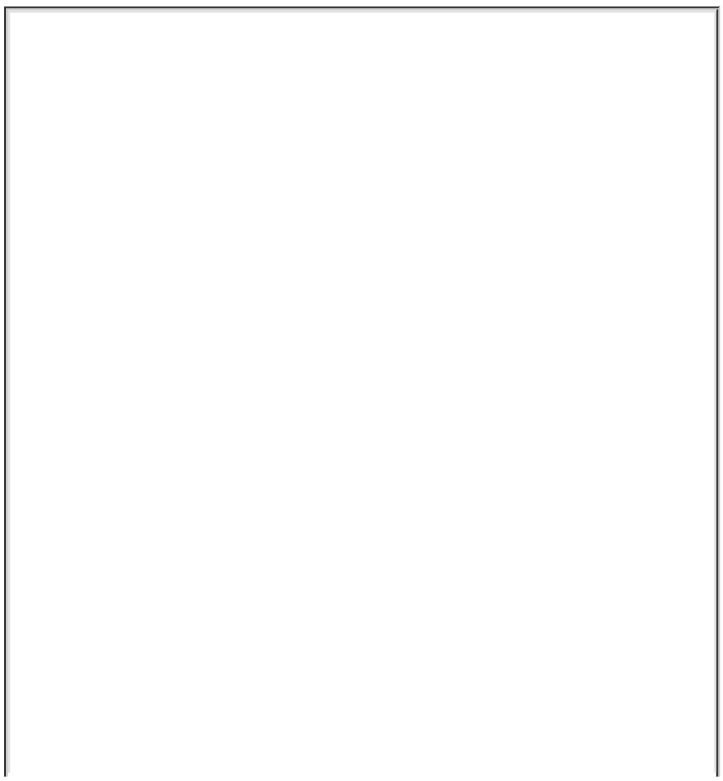
The incidence of esophageal cancer also differs significantly by geographic region and race. The rates can vary between regions in a given country, demonstrating an important role for environmental and possibly dietary/nutritional factors. Worldwide, the

highest incidence of esophageal cancer is observed in Linxian, China, with an annual rate of more than 130 per 100,000 population. Other regions with high incidences of esophageal cancer include areas of Iran, Russia, Colombia, and South Africa. In the Western Hemisphere, the incidence is approximately 5–10 per 100,000 population. In the United States, the estimated number of new cases of esophageal cancer for the year 2000 was 12,300, with estimated deaths of 12,100.

Over the past two decades, the patterns of esophageal cancer have changed dramatically in the United States. Parallel changes are also seen in other Western countries. The incidence of adenocarcinoma of the esophagus has risen sharply, especially among white males, whereas the rates of squamous cell carcinoma have remained essentially unchanged or have declined slowly. By the early 1990s, adenocarcinoma surpassed squamous cell carcinoma to become the most common type of esophageal cancer among white males, accounting for nearly 60% of all esophageal cancers, although squamous cell carcinoma remains the predominant cell type among African Americans. This change in the epidemiology of esophageal cancer is most likely multifactorial, involving a combination of factors and is not simply explained by the reclassification of gastric cardia carcinoma as esophageal adenocarcinoma or accounted for by the rising rate of Barrett's esophagus.

Etiology

Numerous studies have demonstrated that in developed countries cigarette smoking and alcohol consumption are the most important predisposing factors for esophageal cancer (Table 18-2). The carcinogenic effects of alcohol and tobacco are far more pronounced for squamous cell carcinoma than for adenocarcinoma of the esophagus. Although the mechanisms remain unclear, it is postulated that alcohol may act at several steps in the multiphase process of carcinogenesis, whereas the many tobacco-derived chemicals, such as nitrosamines, may affect the initiation of esophageal carcinoma or act as promotional agents.



Squamous cell carcinoma
Chronic tobacco use
Heavy alcohol consumption
History of head and neck malignancy
History of radiation therapy
Chronic esophagitis (most common in Asia and Africa)
Chronic stricture (lye ingestion and radiation)
Tylosis (palmar and plantar hyperkeratosis)
Plummer-Vinson syndrome
Achalasia
Dietary/nutritional
Deficiency in carotene, vitamins C and E, riboflavin, selenium, and zinc
Low intake of fruits and vegetables
High intake of red meat and nitrate-containing foods
Consumption of scalding hot beverages
Adenocarcinoma
Barrett's esophagus and GERD
Obesity
Cigarette smoking
Alcohol consumption
Scleroderma
History of colon cancer
Medications: theophylline and β-agonists (long-term use >5 years)

Table 18-2. Risk factors for esophageal cancer.

It was previously thought that the total lifetime consumption of alcohol and amount smoked correlated with the risk of esophageal cancer. However, recent studies have shown the contrary; alcohol consumption and tobacco use do not affect the risk of esophageal cancer in the same way. For alcohol consumption, it is the mean intake (>200 g/week) rather than the duration, and for tobacco smoking, it is the duration (>15 years) rather than the mean intake that is more closely associated with the risk of esophageal cancer. In other words, a high intake of alcohol during a short period of time carries a higher risk than a moderate intake for a long time; a moderate consumption of tobacco for a long period carries a higher risk than a high intake for a short period. The risk of esophageal squamous cell carcinoma can be significantly reduced once patients achieve long-term smoking cessation (>10 years); however, the risk of esophageal adenocarcinoma may remain elevated for up to 30 years from the time of smoking cessation

Whereas alcohol consumption and tobacco use are the most significant risk factors for esophageal squamous cell carcinoma, Barrett's esophagus is the most important risk factor for esophageal adenocarcinoma. Barrett's esophagus, a known premalignant

lesion, is a consequence of chronic gastroesophageal reflux disease (GERD) in which the squamous epithelium of the distal esophagus is replaced by intestinal-type columnar epithelium. Patients with GERD who develop Barrett's esophagus may have a certain degree of esophageal dysmotility. This usually results in a hypotensive or inappropriately relaxed lower esophageal sphincter (LES) allowing reflux of gastric

contents into the esophagus and ineffective peristalsis prolonging contact of refluxate with esophageal mucosa, thus causing esophageal epithelial damage. It is postulated that esophageal cancer evolves through a simliar temporal sequence of alterations seen in the dysplasia-to-carcinoma sequence in colonic neoplasm: metaplasia to low-grade dysplasia to high-grade dysplasia to adenocarcinoma. Barrett's esophagus is found in 10–15% of patients who undergo endoscopic evaluation for GERD. It is believed that this number probably underestimates the disease prevalence as many patients with Barrett's esophagus remain asymptomatic. The lifetime risk of esophageal adenocarcinoma in Barrett's esophagus is estimated to be 5%. In addition to its role in the pathogenesis of Barrett's esophagus, GERD is an independent risk factor for esophageal adenocarcinoma.

Recent epidemiologic studies have found that obesity (measured as body mass index) is another strong risk factor for esophageal adenocarcinoma. The elevated risk is mainly associated with excessive weight per se and is not related to weight changes over time. Although the mechanism by which obesity contributes to the increased risk of esophageal adenocarcinoma is unclear, it has been speculated that obesity promotes gastroesophageal reflux disease by increasing intraabdominal pressure, which in turn predisposes to developing a chronic GERD state and Barrett's esophagus. Other factors that may affect the cancer risk associated with obesity include body fat distribution, dietary practices, medications, and other conditions that may affect the severity of GERD.

Several esophageal motility disorders have been implicated in the development of esophageal cancer. Long-standing achalasia has been associated with increased risk of esophageal squamous cell carcinoma.

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On the other hand, scleroderma (systemic sclerosis) increases the risk of esophageal adenocarcinoma, perhaps through the development of Barrett's esophagus as the collagen deposits in the distal esophagus cause LES dysfunction. Other abnormalities or inflammatory lesions of the esophagus known to contribute to the development of esophageal squamous cell carcinoma include chronic esophagitis and strictures, tylosis, Plummer-Vinson syndrome, and lye ingestion.

In certain regions of the world, exceedingly high rates of esophageal cancer have been attributed to other environmental and dietary/nutritional factors. These include ingestion of hot foods and beverages, nitrate-containing preserved food, deficiencies in essential nutrients (carotene, riboflavin, vitamins C and E) and minerals (zinc and selenium), as well as infrequent consumption of fruits and vegetables. Human papillomavirus has also been implicated as a potential cause of esophageal squamous cell carcinoma.

Interestingly, colon cancer and breast cancer are found to be associated with an increased risk of esophageal cancer. More specifically, colon cancer is associated with adenocarcinoma, whereas breast cancer is associated with both adenocarcinoma and squamous cell carcinoma of the esophagus. The increased risk of esophageal squamous cell carcinoma in breast cancer is greater in those who have received radiation therapy as part of their treatment. Radiation may damage the genetic repair mechanisms or cause chronic esophagitis and strictures, both of which predispose to the development of squamous cell carcinoma.

Natural History

A. CLINICAL PRESENTATION

Approximately 15% of esophageal cancers arise in the upper one-third of the esophagus, 50% in the middle third, and 35% in the lower third and at the gastroesophageal junction. The presenting symptoms tend to correlate with the location of the tumor. Unfortunately, many of the symptoms experienced by patients with esophageal cancer occur late in the course of the disease, at which time the disease is already at an advanced stage, resulting in a very poor prognosis.

The most common presentation of esophageal cancer leading to its diagnosis is progressive dysphagia (Table 18-3). The esophagus is capable of accommodating to the partial obstruction initially because it lacks a serosal layer so that the smooth muscle can stretch. As a result, a patient may not manifest dysphagia until the lumen is more than 50–60% obstructed by the tumor mass. The narrowed esophageal lumen leads to solid food dysphagia first and later to liquid dysphagia with further disease progression and obstruction. Regurgitation may also occur as the enlarging tumor narrows the esophageal lumen.

Dysphagia (most common)—solids then liquid
Odynophagia/retrosternal discomfort
Back pain/chest pain
Anorexia
Weight loss
Regurgitation
Hoarseness/voice change
Aspiration/cough/recurrent pneumonia
Hematemesis

Table 18-3. Signs and symptoms of esophageal cancer.

Odynophagia is the second most common presenting symptom of esophageal cancer. It may be due to an ulcerated area in the tumor or involvement of mediastinal structures, although mediastinal invasion would more typically present as constant pain in the midback or midchest. Anorexia and weight loss often ensue with decreased nutritional intake. Hoarseness or voice change appears when the tumor invades the recurrent laryngeal nerve, causing vocal cord paralysis. Severe cough and aspiration are usually the result of tumor invasion into the airway or development of a fistula between the esophagus and the tracheobronchial tree.

Overt gastrointestinal bleeding as manifested by hematemesis or melena is rarely encountered. However, anemia is relatively common at presentation. Chronic subclinical bleeding is a major contributing factor for anemia. Massive hemorrhage can rarely occur and may require emergent surgical treatment if endoscopic therapy fails.

B. COMPLICATIONS

Esophageal cancer readily extends through the thin esophageal wall due to the absence of a serosa to invade adjacent structures. The vital mediastinal structures adjacent to the esophagus include the trachea, the right and left bronchi, the aortic arch and descending aorta, the pericardium, the pleura, and the spine. Tumor infiltration into these structures accounts for the most serious and, sometimes, life-threatening complications of esophageal cancer.

Most complications due to esophageal cancer are attributed to luminal obstruction and local tumor invasion. Patients often subconsciously adjust their diets to soft or liquid foods to avoid solid food dysphagia. The progressive inability to swallow solids leads to weight loss and nutritional deficiencies. Solid food impaction can result when there is severe stenosis, requiring endoscopic intervention for disimpaction. Regurgitation of food or oral secretions may also occur in the setting of significant luminal obstruction. Halitosis may be present due to food stasis and regurgitation.

Pulmonary complications from aspiration include pneumonia and pulmonary abscess. The tumor mass may cause compression and obstruction of the tracheobronchial tree, leading to dyspnea, chronic cough, and at times postobstructive pneumonia. Esophagoairway fistula may develop with tumor invasion of the trachea or bronchus. Airway fistulas are severely debilitating and are associated with significant mortality owing to the high risk of pulmonary complications such as pneumonia and abscess.

Although the aortic arch and descending aorta lie adjacent to the esophagus, extension into these structures is less frequent than airway invasion. Erosion through the aortic wall can result in severe hemorrhage and is often fatal. Tumor ingrowth of the pericardium has been reported as an infrequent cause of arrhythmias and conduction abnormalities. Pleural effusions are

usually small, but may signify pleural invasion when large effusions are present.

C. PROGNOSTIC FACTORS

1. Radiographic and endoscopic

Radiographic tests have been utilized to delineate the location and extent of esophageal involvement, as well as to stage the depth of tumor invasion, the presence of nodal involvement, and the presence of distant metastases. The length of esophageal involvement can be readily seen on barium esophagram and has been found to be a useful predictor of extraesophageal extension. Tumors measuring <5 cm are often confined to the esophageal wall whereas only 10% of those measuring >5 cm are localized. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest and abdomen are particularly useful in identifying distant metastases (most commonly to the liver and lung). The presence of metastases is a poor prognostic sign and is a contraindication to surgery.

For better evaluation of locoregional lymph node involvement and definition of depth of tumor penetration, endoscopic ultrasound (EUS) has emerged as the tool with the greatest accuracy (>80–90%). The primary advantage of EUS is as a staging modality. EUS is useful for identifying locally advanced disease after CT has ruled out metastatic disease. The presence of transmural invasion into adjacent organs such as the pericardium or trachea is associated with a poor prognosis. Evidence of lymph node

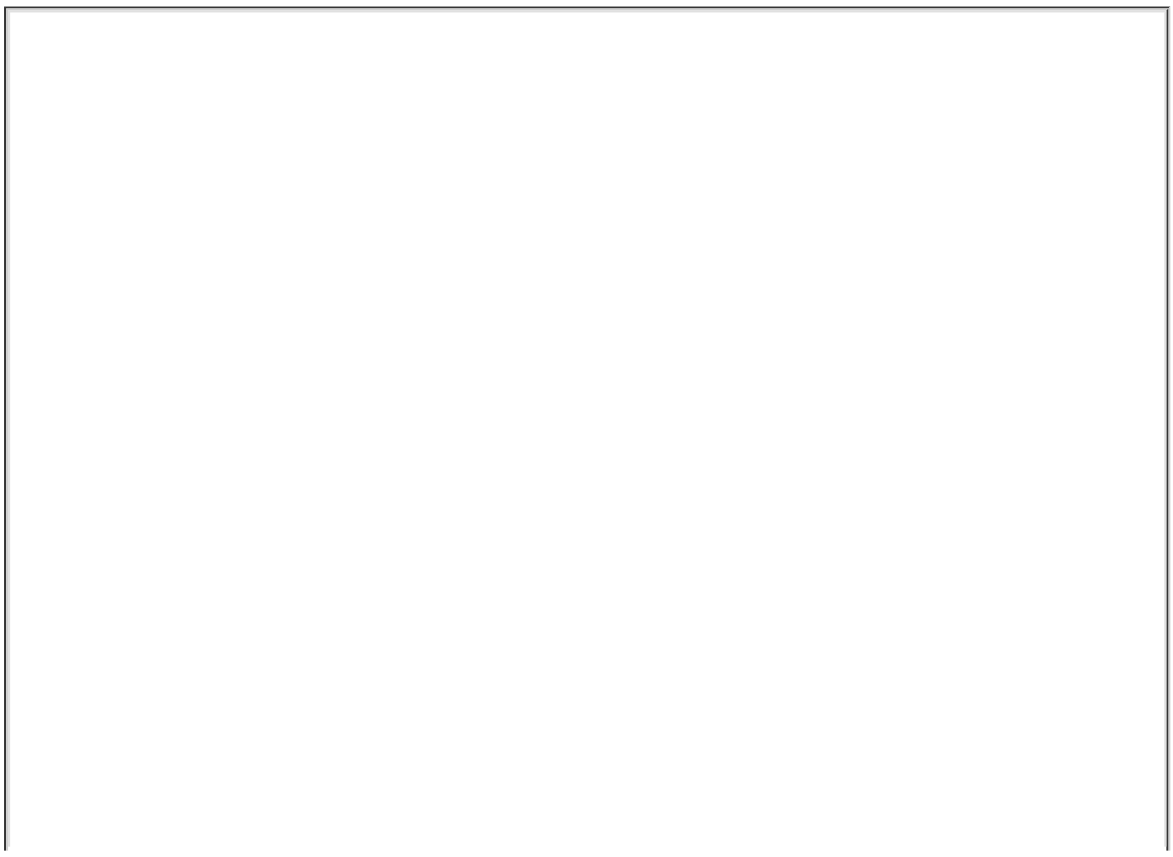
involvement is also associated with a poor overall 5-year survival (<20%).

2. Pathologic

Typically, the clinical prognosis of any malignant neoplasm depends on the histologic type and grade and the clinical stage. Esophageal cancer is no exception. The vast majority of esophageal tumors are either squamous cell carcinomas or adenocarcinomas. The former usually arise in the middle and the lower third of the esophagus whereas the latter are typically seen in the lower third. When compared stage to stage, there seems to be very little difference in the prognosis between the two. Rare esophageal malignancies associated with a poorer prognosis are small cell carcinoma and primary malignant melanoma. The overall prognosis of a poorly differentiated tumor is worse than that of a well-differentiated tumor.

3. Clinical stage

The revised tumor, nodes, metastasis (TNM) classification of 1997 is currently recommended for staging of esophageal cancer. The older classification system in which tumors were staged based on size, circumferential involvement, and extent of obstruction was abandoned. The new system recognizes five major prognostic stages (stage 0 to IV) of tumor extent and clearly defines the cancer stage based on local invasion of the tumor, nodal involvement, and presence of metastases (Table 18-4). According to the current classification, a T1 tumor is limited to the mucosa or submucosa. In stage T2, tumor invasion extends into but not through the muscularis propria. In stage T3, adventitia invasion is present. In stage T4, there is evidence of tumor invasion into adjacent structures such as the trachea, pericardium, or aorta. The 5-year survival rates associated with the depth of tumor invasion (T1 to T4) are approximately 80%, 45%, 25%, and <20%, respectively.



Primary tumor infiltration (T)

TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor limited to mucosa/submucosa
T2	Tumor involving muscularis propria
T3	Involvement of adventitia, no extraesophageal structures
T4	Extension into extraesophageal structures

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No nodal involvement
N1	Regional nodes involved

Distant metastasis (M)

MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases for tumors of the lower thoracic esophagus:
M1a	Metastases in celiac nodes
M1b	Other distant metastases for tumors of the cervical thoracic esophagus:
M1a	Metastases in cervical lymph nodes
M1b	Other distant metastases for tumors in the middle thoracic esophagus:
M1a	Not applicable
M1b	Nonregional lymph nodes or other distant metastases

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2–3	N0	M0
Stage IIB	T1–2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IV A	Any T	Any N	M1a
Stage IV B	Any T	Any N	M1b

[1]1997 revision.

Table 18-4. TNM staging system for esophageal cancers.[1]

In the present TNM system, all local lymph node involvement is classified as N1, whereas nodal metastases outside the regional nodes (eg, cervical or celiac) and distant organ metastases are classified as M1. Distant nodal involvement is less serious than the blood-borne metastases to distant organs such as liver or lung, although the higher the number of nodes involved the worse the prognosis.

The disadvantage of the current TNM system is the lack of reference to the presence of lymphatic or blood vessel invasion adjacent to the tumor mass. These are important independent adverse prognostic factors in esophageal squamous cell carcinoma. Blood vessel and lymphatic invasion should correlate with an advanced stage and presence of distant metastases.

Diagnosis

The initial diagnostic imaging test for most patients with dysphagia should be a barium esophagram (Figure 18-1). The study readily demonstrates narrowing of the esophageal

lumen at the tumor site and dilatation proximally. Typical features of malignant obstruction on the barium esophagram include irregular mass lesions, irregular mucosal relief, and abrupt angulation of the esophageal contour (so-called **tumor shelf**). Benign lesions of the esophagus are typically associated with a smooth outline of the mucosa and symmetric narrowing without angulation or extrinsic compression.

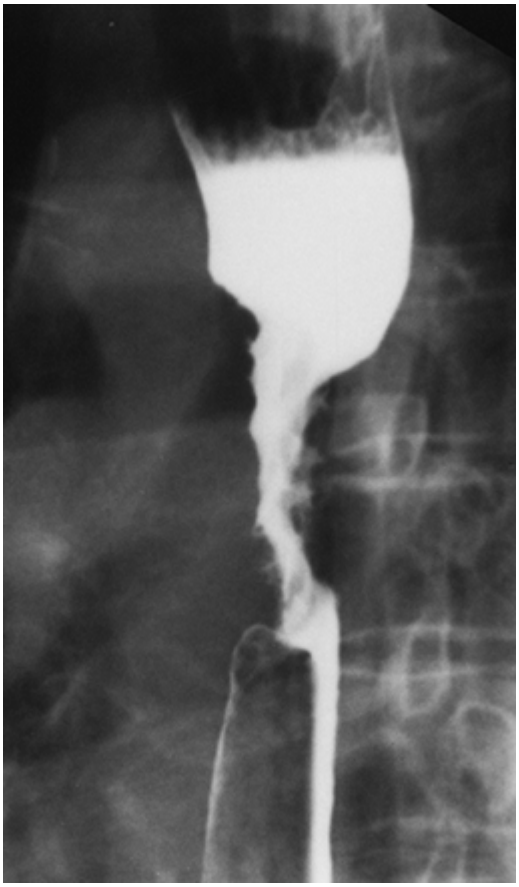


Figure 18-1. Barium esophagram showing mid-esophageal stricture. The abrupt change in caliber, irregular mucosa, and near circumferential narrowing are highly suggestive of an esophageal cancer.

All patients with abnormal barium esophagrams should undergo upper gastrointestinal endoscopy with biopsy to provide a definitive histologic diagnosis, assess the patency of the esophageal lumen, and confirm the endoscopic extent of the tumor. Endoscopy also offers important information regarding the feasibility of subsequent endoscopic therapeutic interventions such as dilation of a stenotic lumen, placement of prostheses (ie, stents), or ablation of an intraluminal tumor.

Routine chest x-ray may reveal an esophageal air-fluid level above the site of obstruction or a pulmonary infiltrate from aspiration. A pleural effusion or mediastinal mass may suggest mediastinal tumor extension. Electrocardiogram changes are unusual except in cases of advanced pericardial invasion in which the normal conduction pathways may be impaired.

Staging Techniques

Once the diagnosis is made, defining the stage of the esophageal cancer is the next essential step for further patient management. Previously, a significant number of patients with esophageal cancer went for exploratory surgery to attempt curative resection and/or for final staging. Unfortunately, this approach was disappointing as the majority of these patients were found to be inoperable due to extensive tumor invasion. At present, with advances in imaging techniques, the task of tumor staging is best accomplished by a combination of multiple imaging modalities, including EUS and CT or MRI. The current TNM classification for esophageal cancer was revised to reflect the improved preoperative staging available through these imaging studies.

Additional imaging for staging is necessary as contrast x-ray studies and endoscopy alone are often inaccurate for staging esophageal cancer because the extent of local invasion and presence of regional nodal and distant metastases cannot be determined. CT imaging has provided a nonoperative way to stage esophageal cancer. The standard CT imaging protocol for esophageal cancer involves the use of oral and intravenous contrast with examination from the upper chest to the upper abdomen, including the entire liver. The overall accuracy of CT for staging esophageal cancer is excellent for advanced disease. Liver metastases and findings consistent with adjacent organ invasion can be reliably noted on CT scan as well as by MRI. The sensitivity and specificity for detecting bronchotracheal and pericardial invasion exceed

90–95% in most series. However, CT imaging does not reliably detect local and regional lymph node metastases and “early” (T1–T2) tumors.

The advent of EUS offers the most significant advance in the preoperative staging of esophageal cancer. EUS is performed using a modified upper endoscope with an ultrasound transducer housed within the tip. At frequencies ranging from 7.5 to 12 MHz, EUS depicts five layers of the esophageal wall corresponding to its distinct histologic layers (Figure 18-2). Malignant tumors are identified as hypoechoic masses with irregular margins that disrupt the normal esophageal architecture. The depth of tumor invasion is defined by the outermost margin of the hypoechoic mass (Figure 18-3). Suspicious appearing lymph nodes are identified as hypoechoic rounded structures within the mediastinum and near the esophagus (Figure 18-4). Fine needle aspiration (FNA) biopsies of lymph nodes can be obtained through some EUS scopes for definitive diagnosis of malignant involvement (Figure 18-5). EUS can accurately diagnose early cancers, that is, those classified as T1–T2 (Figure 18-6 and Figure 18-7). The overall accuracy of EUS for predicting the extent of esophageal cancers approaches 80–90% for T and 70–80% for N classification.

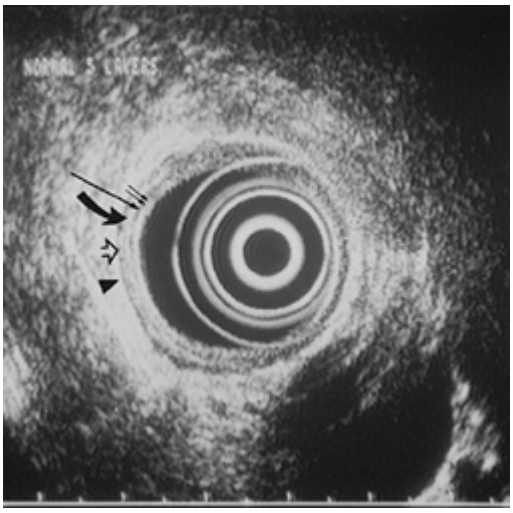


Figure 18-2. Endoscopic ultrasound image of the normal five-layered esophagus. ***Two small arrows:*** The inner-most layer corresponds to an interface echo and the mucosa. ***Single long arrow:*** The second layer corresponds to the mucosa (including the muscularis mucosa). ***Curved solid arrow:*** The third layer corresponds to the submucosa. ***Open arrow:*** The fourth layer corresponds to the muscularis propria. ***Solid arrowhead:*** The fifth outer-most layer corresponds to an interface echo and the adventitia (serosa equivalent). The five-layered appearance is essentially the same throughout the gastrointestinal tract. Because the esophagus lacks a serosa, the fifth echogenic layer in the esophagus represents the interface echo with the adventitia.

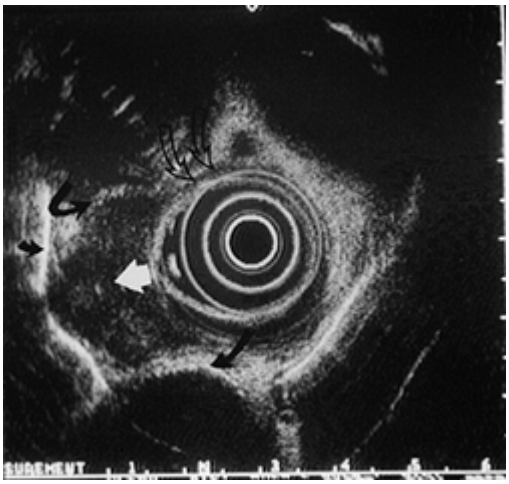


Figure 18-3. EUS image of an esophageal cancer in close proximity to mediastinal structures. ***Curved open black arrow:*** Muscularis propria, fourth hypoechoic layer. ***Solid white arrow:*** The tumor extending from the mucosa through the muscularis propria (T3). ***Angled arrow:*** Distinct fat plane between the tumor and right bronchus, indicating absence of bronchial invasion. ***Short curved arrow:*** Hyperechoic (bright white) plane between the tumor and right pleura. The tumor mass extends to the pleura but does not definitively invade. ***Curved arrow (bottom of image):*** Intact fat plane between the tumor and thoracic aorta.

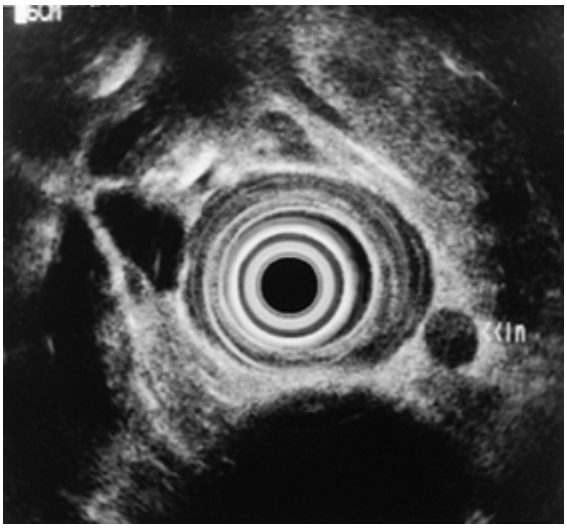


Figure 18-4. Suspicious appearing lymph nodes are identified as hypoechoic rounded structures within the mediastinum.

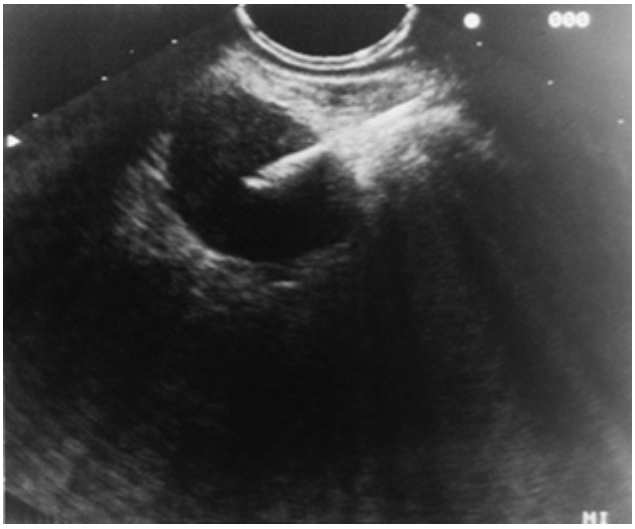


Figure 18-5. EUS-guided fine-needle aspiration biopsy of suspicious lymphadenopathy can be obtained during the staging process for definitive staging.

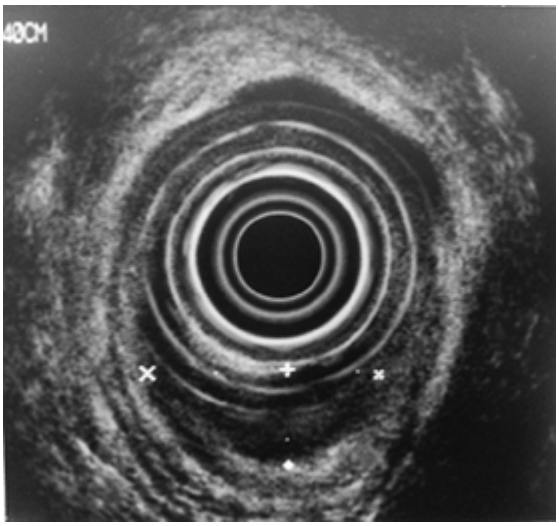


Figure 18-6. A T1 lesion is depicted. Note the hypoechoic focal mass that involves the mucosal and submucosal layers only.

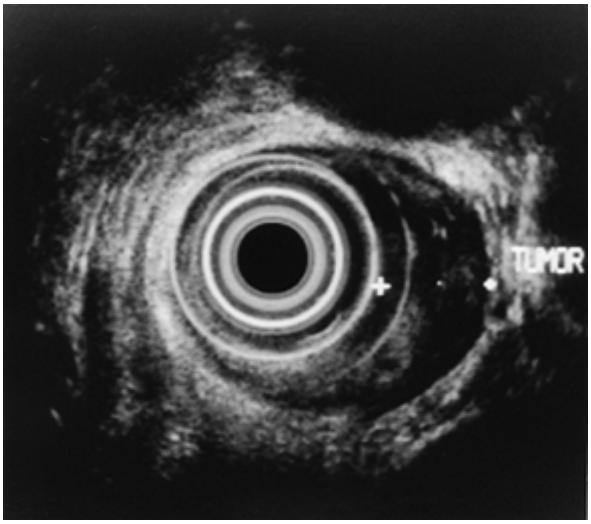


Figure 18-7. A T2 lesion is demonstrated here. This lesion is characterized by involvement of the mucosa and submucosa with invasion into the muscularis propria but not beyond the muscle layer.

There are several limitations of EUS for staging esophageal cancer that need to be recognized. Overstaging of a T2 lesion can sometimes happen when there is significant peritumoral inflammation, whereas understaging sometimes occurs largely due to microscopic invasion beyond the muscularis propria. EUS is also very reliable in diagnosing adjacent organ invasion (ie, invasion to pleura or aorta) (Figure 18-8 and Figure 18-9); however,

limited depth of penetration of EUS results in incomplete assessment for distant metastases. In addition, about 30% of esophageal cancers produce severe esophageal obstruction and cannot be traversed with the regular ultrasound endoscope at the time of presentation. Generally, these tumors can be accurately staged with EUS after dilation of the stricture; and when this occurs, they are almost always advanced tumors, that is, T3 or greater (Figure 18-10). Recently, the development of through-the-scope miniprobes and wire-guided small-diameter blind ultrasound probes has overcome the problems with tumor strictures in most cases. In addition, as these small caliber ultrasound probes utilize higher scanning frequencies (12–20 MHz), the detection and accuracy of staging for T2 tumors has improved significantly.

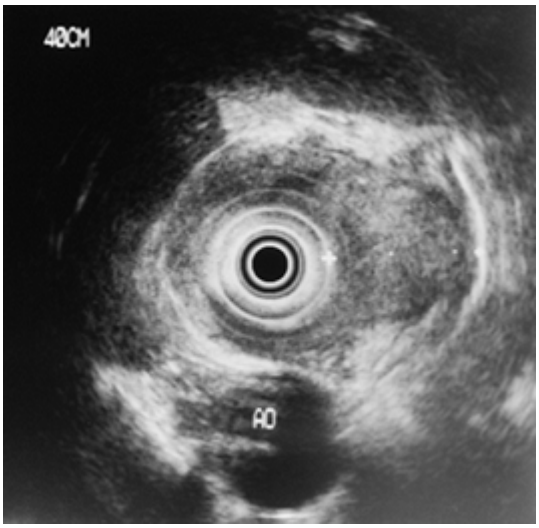


Figure 18-8. This EUS image demonstrates a large esophageal tumor invading the left pleura. AO, aorta.

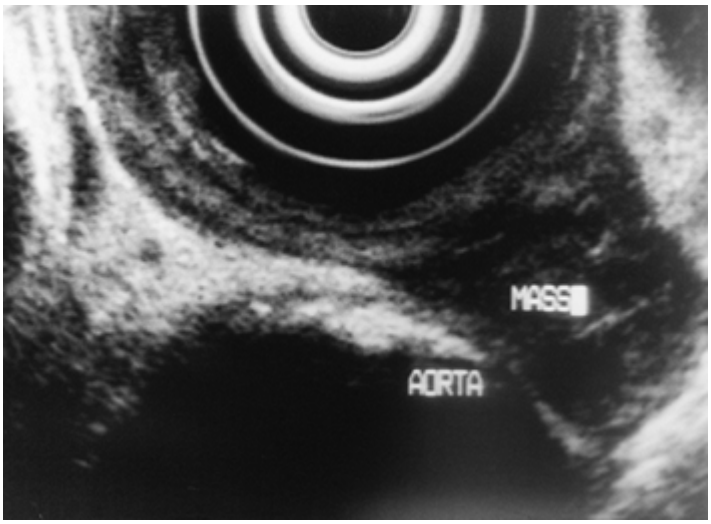


Figure 18-9. This EUS image demonstrates a large esophageal tumor that closely borders the

aorta with focal involvement of the aortic wall.

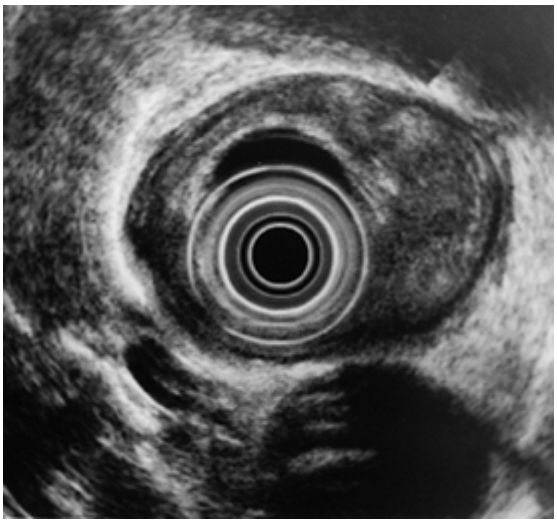


Figure 18-10. A T3 tumor is depicted here. These lesions typically are large and invade into and through the muscularis propria without invasion into adjacent structures.

A large number of studies have looked into the staging accuracy of EUS and CT scan. It has been demonstrated that EUS is more accurate than CT scan for locoregional staging (both T and N classification). EUS appears to be superior in defining abdominal lymph node metastases (especially celiac axis nodes), although CT scan is still the better imaging study to detect distant organ metastases. Nonetheless, CT scan should be considered as complementary to EUS and should be combined with EUS to determine the extent of extraesophageal invasion into the mediastinum and distant metastases. The ideal algorithm for managing these patients should include a CT scan of chest and abdomen, and, if negative for metastasis, an EUS should be done to rule out locally advanced disease.

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A few other diagnostic tools have also been employed to assist in the staging of esophageal cancer. Bronchoscopy is widely used for assessment of bronchial invasion, primarily in mid-esophageal tumors. Although bronchial invasion is common, invasion into the bronchial lumen is rare. Therefore, bronchoscopy generally provides only indirect evidence of bronchial invasion, such as luminal indentation or narrowing. Diagnostic laparoscopy has been utilized in the assessment of peritoneal metastases. It offers the advantage of tissue biopsy under direct vision and an access for laparoscopic ultrasound. Thoracoscopy has also been used to better assess mediastinal and pulmonary metastases.

Differential Diagnosis

The differential diagnosis of patients with dysphagia or odynophagia includes

esophageal mucosal diseases, motility disorders, and benign and malignant obstructing lesions. The insidious onset of progressive dysphagia to solids and then to liquids with associated weight loss in patients over 40–50 years of age almost invariably points to esophageal cancer. Patients with benign obstructing lesions of the esophagus, such as benign peptic strictures, webs and rings, and achalasia, may present with features resembling esophageal cancer. Barium esophagram offers indirect evidence for benign versus malignant processes; however, endoscopy with biopsies should still be employed to distinguish benign from malignant disease.

Achalasia is a motility disorder with impaired relaxation of the lower esophageal sphincter and aperistalsis of the esophageal body. The classic radiographic appearance on the barium esophagram is a smooth, tapered distal esophagus referred to as a “bird's beak” appearance. Tumors at the gastroesophageal junction may at times mimic the signs, symptoms, and manometric findings of achalasia. Hence, endoscopy is required in all patients

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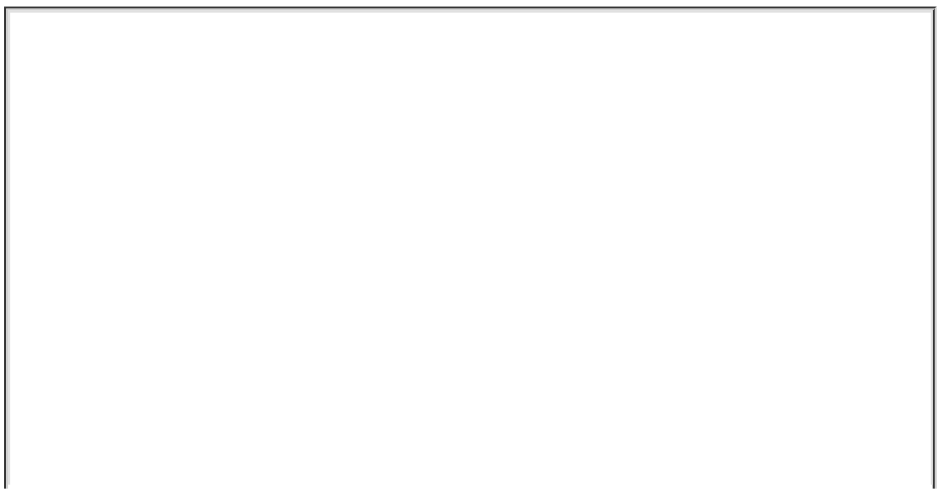
with suspected achalasia to exclude undiagnosed malignancy (“pseudoachalasia”).

Malignant tumors of the esophagus other than squamous cell carcinoma and adenocarcinoma are exceedingly rare. These tumors usually cannot be distinguished based on clinical grounds and require histologic confirmation. Mucoepidermoid carcinoma and cystic adenoid carcinoma of the esophagus are rare yet extremely aggressive and can be missed on endoscopic biopsy due to their primarily submucosal growth pattern.

Treatment

The next step following the diagnosis of esophageal cancer is to determine whether the patient is a candidate for major curative surgery. Unfortunately, over 60% of patients with esophageal cancer are not candidates for surgery at the time of presentation due to the advanced stage of disease or significant comorbidity that would result in high perioperative mortality. The combination of a thin wall, absence of a serosa, and an extensive lymphatic drainage system facilitates early regional and distant metastases in esophageal cancer. Extensive medical problems, most commonly severe cardiopulmonary disease, are contraindications to surgery. These factors demand that treatment of esophageal cancer be based on a systematic evaluation (Table 18-5). Cancer staging is generally not required for patients who are not candidates for surgery.



Surgery
Transhiatal
Thoracoabdominal: right (Ivor Lewis) or left *en bloc*
Radiation
Combined modality chemoradiation
Dilation
Ablation
Chemical sclerosant injection
Electrocautery: monopolar or bipolar
Argon plasma coagulation
Nd:YAG laser
Photodynamic therapy
Endoscopic mucosal resection
Protheses/stents

Table 18-5. Therapeutic interventions for palliation or cure of esophageal cancer.

Surgery

A. GENERAL CONSIDERATIONS

Surgical therapy has long been the preferred approach for both cure and palliation of patients with resectable tumors. Patients in the subgroup with limited local spread (T1–T2) and no regional nodal involvement are potentially curable by surgery. Patients who are deemed surgical candidates based on their good medical condition should undergo thorough staging to determine if they have curable

disease, incurable but resectable disease, or unresectable disease. Resectable tumors are characterized by the absence of extension into mediastinal structures and the absence of nodal or organ metastases. Direct invasion of the aorta, bronchi, pleura, or laryngeal nerve or distant organ metastases are evidence of nonresectable disease. Preoperative radiation with or without chemotherapy may sometimes downstage the cancer to a resectable or potentially curable stage.

Prior to surgery, it is important to confirm that the patient has sufficient cardiopulmonary reserve. Respiratory function is best assessed by the forced expiratory volume (FEV_1), which, ideally, should be 2 L or more. Any patient with an FEV_1 of less than 1.25 L is a poor surgical candidate due to the high risk of respiratory insufficiency postoperatively. Cardiac reserve should be assessed and a resting ejection fraction of less than 40% is an ominous finding.

Perioperatively, nutritional support should be provided to improve postoperative complications and recovery. A poor nutritional status affects the host resistance to infections and impairs anastomotic and wound healing. As oral intake is usually inadequate in patients with advanced disease, a feeding jejunostomy tube is the most reliable and safest method for nutritional support in those with a functional small bowel. A gastrostomy is inadvisable for these patients because it may interfere with the use of the stomach for reconstruction. The jejunostomy also minimizes the danger of regurgitation into the pharynx and possible aspiration. Total parenteral nutrition may

also be indicated for some patients.

B. SURGICAL APPROACH

The surgical options available for esophageal tumor resection include (1) transhiatal, (2) combined right thoracic and abdominal (Ivor Lewis), (3) left thoracoabdominal, and (4) en bloc, either two field or three field. In a simple esophagectomy, whether by the transhiatal or the transthoracic route, there is no specific attempt to remove lymph node tissues in the mediastinum or upper abdomen. Cure is thus uncommon and occurs only by chance. En bloc resection involves a radical esophagectomy to include mediastinal, upper abdominal (two field), and/or cervical (three field) lymphadenectomy.

Transhiatal esophagectomy is currently the preferred surgical approach for palliation of esophageal cancer independent of its location. In patients with distal esophageal cancer, transhiatal esophagectomy may be curative when adequate inspection of the paraesophageal cancer tissue is provided by the abdominal incision. The operation consists of abdominal and cervical incisions and a cervical gastroesophageal anastomosis. This procedure does not allow visual inspection of the mediastinal bed, which theoretically is necessary to ensure removal of the locally invasive tumor, although it offers a slightly better 3-year survival and operative mortality than the transthoracic approach (25% versus 20% and 5% versus 10%, respectively).

En bloc resection remains the definitive surgical cure for esophageal cancer. The operation consists of removal of a tissue block completely surrounded by normal tissue. Two or three fields of lymphatic resection are included depending upon the tumor location: upper abdominal celiac and splenic nodes (field one), infracarinal posterior mediastinal nodes (field two), and upper mediastinal and cervical (field three). Recent studies encouraged inclusion of the surrounding mediastinal pleura, the azygos vein, the thoracic duct, and possibly the pericardium at the time of surgery to improve the overall survival. The overall 5-year survival of en bloc resection approaches 40% although the operative mortality still ranges from 5 to 10%.

Locally advanced tumors (T1N1, T2N1, T3N0, and T3N1) are resectable but incurable. These tumors are associated with a high recurrence rate following surgery. The optimal intervention in these patients remains controversial, and practices vary widely depending on the local surgical expertise and the assessment of the patient's preexisting medical condition.

Palliation Therapy

As the majority of patients present with incurable disease, pallative therapy remains the mainstay of treatment options for esophageal cancer. The options currently available include radiation therapy, chemotherapy, endoscopic dilation and ablation (chemical injection, electrocautery, argon plasma coagulation, and laser), photodynamic therapy, and esophageal prostheses/stents. They are all palliative procedures employed as adjuvant therapy to surgery or for patients who are not considered surgical candidates.

The treatment again varies according to availability and local expertise, patient preference, and cost.

A. RADIATION THERAPY

External beam radiation therapy alone provides reasonable palliation for esophageal cancer, especially for those who are medically unable to undergo surgery or chemotherapy. At the end of treatment, radiotherapy achieves palliation of dysphagia in 70–90% of patients. The 5-year survival curves are similar to those for surgery for patients with a comparable cancer stage (5–10%). It is recommended that for patients treated with curative intent, radiation therapy should be limited to tumors <10 cm with no evidence of distant metastasis. Contraindications to radiotherapy include tracheal or bronchial involvement, cervical esophagus location of the tumor, or stenosis that cannot be bypassed. The major complications of radiation therapy in esophageal cancer are airway fistulas (10–15%) and esophageal strictures (20–40%).

In an attempt to improve its effectiveness, radiotherapy has been given in a hyperfractionated manner. Several recent studies employing continuous hyperfractionated accelerated radiotherapy demonstrate a slightly improved median survival and prolonged relief of dysphagia, although there is no significant improvement in the 5-year survival rates. In addition, many studies have looked into the role of radiation therapy as an adjuvant to surgery to improve local tumor control and survival. Several randomized control studies comparing the benefit of preoperative and/or postoperative radiation in addition to surgery demonstrated disappointing results. There is no additional survival benefit, and there seems to be a higher rate of operative complications following radiation.

By combining external beam radiation with intraluminal irradiation using cobalt-60, cesium-137, or iridium-192, it is possible to increase the dose of radiation to the tumor without significantly increasing the dose of radiation to normal tissue. A major limitation of intraluminal irradiation is the effective treatment distance. Initial studies have demonstrated promising results with improved median survival and 5-year survival, and more clinical trials are underway.

B. CHEMOTHERAPY

1. Single agent

Despite the increasing choice of agents, chemotherapy alone has been of little benefit to patients with esophageal cancer. The most commonly employed classes of agents for treating esophageal cancer include (1) antibiotics—bleomycin and mitomycin C, (2) antimetabolites—5-fluorouracil (5-FU) and methotrexate, (3) alkaloids—vindesine and vinorelbine, (4) platinum analogs—cisplatin, carboplatin, and oxaliplatin, (5) taxanes—paclitaxel and docetaxel, and (6) topoisomerase inhibitors—etoposide and irinotecan. The clinical response rates for most single agents are very poor (5–15%), although cisplatin and the taxanes are exceptions and have been the focus of most combination chemotherapy. The response durations are also very brief, ranging from 2 to 4 months.

2. Combination chemotherapy

Combination chemotherapy has typically demonstrated better clinical response rates than single agent chemotherapy. Most trials of combination chemotherapy are based on cisplatin, as it alone has a response rate of 20–25%. In general, the cisplatin-based combination chemotherapy has yielded a response rate of 25–35%. The results are even more impressive in locoregional disease, yielding 45–75%. Unfortunately, the higher response rates do not translate into improved response duration or improved

survival. In addition, the higher response rate of combination chemotherapy needs to be balanced against a higher systemic toxicity. To date, there is no role for chemotherapy, single agent or combination, as an adjuvant to surgery.

3. Combined-modality therapy

As primary management, combined-modality therapy of chemoradiation has achieved better median survival and 5-year survival when compared with radiation alone. In addition, there is much current interest in the role of chemoradiation as induction therapy prior to surgery. Theoretically, induction chemoradiation therapy has several advantages over primary surgery alone or postoperative chemoradiation. As the local blood circulation is not yet disrupted by surgical dissection, preoperative chemotherapy should result in better drug delivery to the tumor. Preoperative treatment also allows for identification of patients who may in turn benefit from further postoperative therapy if needed. In addition, concurrent chemoradiation can take advantage of the radiation-sensitizing properties of many chemotherapeutic agents (eg, paclitaxel, 5-FU, and cisplatin), resulting in a synergistic antitumor effect. Distant control should be enhanced as remote micrometastases are treated early in the course instead of having to wait for postsurgical recovery. Preliminary results from recent studies are encouraging, and many trials are currently underway to define the role of chemoradiation further.

C. ENDOSCOPIC THERAPY

Whereas endoscopy has mainly been used to diagnose cancers, new technologies such as photodynamic therapy and endoscopic mucosal resection have provided endoscopic treatments with the potential of curing early stage tumors of the esophagus.

1. Dilation

Esophageal dilation is most commonly performed with either expandable through-the-scope balloons or wire-guided polyvinyl bougies under fluoroscopy. A small percentage of patients can be successfully dilated to allow for soft diet consumption. However, the benefit from dilation is usually of short duration, and

other methods are usually required for more prolonged symptom relief. One of the major complications of esophageal dilation is perforation.

2. Ablation

Tumor ablation treatments available for palliation include photodynamic therapy, chemical sclerosant injection, monopolar and bipolar electrocautery, argon plasma coagulation (APC), and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. The simplest and least expensive intervention for esophageal cancer ablation is the injection of a chemical sclerosant during endoscopy. Absolute alcohol is the most widely employed chemical agent. The method has been shown to be capable of results similar to laser therapy. The major problem with chemical injection relates to a lack of control as the sclerosant tracks along the tissue planes, causing damage to normal tissue and, sometimes, perforations. Patients may experience temporary worsening of symptoms until adequate tumor necrosis occurs.

Monopolar and bipolar electrocautery are falling out of favor and are rarely used as it is difficult to control the depth of treatment. A newer method, argon plasma coagulation, uses ionized argon gas to convey electrical energy to achieve thermal desiccation of tumor tissue. Unfortunately, the effect is generally superficial, and it is less efficient in relieving dysphagia in advanced esophageal cancer than the tissue ablation achieved using lasers.

High-power Nd:YAG laser can provide palliation of dysphagia by coagulating and vaporizing malignant tissue under endoscopic control. Tumors amenable to laser therapy are exophytic or polypoid, preferably located in a straight segment of the esophagus such as in the mid-esophagus or lower esophagus, and shorter than 5 cm. Multiple endoscopic laser treatment sessions may be required to reduce the size of the intraluminal tumor to improve swallowing. Periodic follow-up is performed to reduce any recurrent intraluminal tumor growth. Although more expensive, laser treatment is more widely available.

3. Photodynamic therapy (PDT)

PDT has emerged as an attractive palliative treatment for esophageal cancer and its complications. PDT has been successful in reducing tumor bulk and in opening the esophageal lumen in patients with complete obstruction, a situation in which Nd:YAG therapy was considered too risky. PDT has also been utilized as a salvage therapy in patients whose stents have failed because of tumor ingrowth/overgrowth.

The treatment begins with an intravenous injection of a photosensitive chemical, porfimer sodium (Photofrin). It is administered at a dose of 2 mg/kg of body weight and preferentially concentrates in the tumor tissue. After 40–50 hours following the injection, the area of the esophageal cancer is exposed to a red light at a wavelength of 630 nm, delivered from a continuous-wave dye laser via an optical fiber diffuser for a total cumulative light dose of 300 J/cm. The red light has been chosen for greatest depth of penetration (5 mm). The process initiates a photochemical reaction and the effect takes place over the ensuing hours to days, ultimately resulting in necrosis of the tumor. Improvement in the dysphagia is usually noted within 5–7 days, although some patients may experience worsening of dysphagia initially due to local tissue inflammation and edema. The major issue with PDT is retention of the photosensitive dye in the skin (up to 6 weeks), which requires patients to avoid direct sun exposure or risk severe sunburn. Other complications following PDT include fever, leukocytosis, nausea, and pleural effusion. Severe complications, which fortunately are uncommon, include atrial arrhythmias, stricture formation, hemorrhage, and perforation. The advantage of PDT in early esophageal cancer (T1 or T2 disease) is the overall greater than 80% cure rate.

4. Endoscopic mucosal resection (EMR)

The development of EMR, or mucosectomy, was sparked by the need to treat superficial flat and polypoid neoplasms of the mucosa of the gastrointestinal (GI) tract with minimally invasive procedures. Long-term studies have demonstrated that EMR outcomes are similar to those of surgery, which has led to acceptance of EMR as a standard treatment, especially in early stage GI cancers. The availability of endoscopic ultrasound to determine the depth of tumor invasion and lymph node metastases as well as chromoendoscopic techniques to reveal tumor borders otherwise not visible without

staining further facilitate the ease and use of EMR.

Numerous EMR techniques have been described, such as injection and snare cautery, injection with precut, EMR with cap, or EMR with band ligation. Nevertheless, the general principles are the same. EMR involves expansion of the submucosal layer and lifting of the mucosa to allow for a safe longitudinal resection. Injection of an expansion solution (typically normal saline) into the submucosa creates a bleb and increases the distance between the mucosa and muscularis propia. This lifting of the mucosa is essential to prevent transmural burning or perforation. A snare is placed over the base of the “neopolyp” and the mucosa is resected with electrocautery. The cancerous lesion is removed en bloc and allows for a complete detailed histopathologic analysis.

In esophageal cancers, EMR has been applied mainly for squamous cell carcinoma and much less for Barrett's esophagus-related adenocarcinoma. EMR is indicated when the lesion is superficial and without evidence of lymph node metastasis. Although conventional EUS is accurate in determining tumor depth and lymph node metastasis of large or bulky lesions, it is less precise for small, flat, or depressed tumors. Therefore,

in these instances, high-frequency ultrasound probes have been recommended. The application of Lugol's solution further assists in visual distinction between a cancerous lesion and normal mucosa (squamous cell carcinoma or dysplasia does not stain). Once the lesion is identified and staged, approximately 20 mL of saline is injected into the submucosa, causing more than half-circumferential mucosal lifting. EMR can then be safely performed. EMR should be avoided if the lesion cannot be lifted by submucosal saline injection (nonlifting sign), which does occur when a tumor has indeed invaded the muscularis propia or when there has been fibrosis due to prior polypectomy. There is no consensus on the maximal lesion size suitable for EMR in esophageal cancer. However, it is recommended that the lesion should be less than 3 cm in height and should not exceed one-third of the esophageal circumference in width to avoid the late complication of stenosis. For larger lesions, other alternatives, such as photodynamic therapy, should be considered.

The major complications of esophageal EMR are bleeding, perforation, and stenosis. Bleeding during EMR is almost always controllable by injection of a low-concentration epinephrine-saline solution, thermal coagulation, or endoscopic clipping. Large perforations invariably require immediate surgery, although small perforations may be manageable with more conservative measures. Stenosis can occur when circumferential resection has been attempted.

5. Esophageal prostheses

Placement of esophageal prostheses (“stents”) is another appealing method for the palliation of malignant strictures and provides effective relief of dysphagia in most cases. The prostheses are usually inserted surgically or endoscopically with fluoroscopic guidance. A wide variety of stents have been developed and modified over the years that provide good mechanical support for maintaining esophageal lumen patency and reduce complications such as stent migration and tumor ingrowth. At present, the expandable metal stents are the most widely applied form of prostheses. The principal merits of such stents are the ease of insertion and the remarkably low risk of esophageal perforation. Covering the stent with a polymer sheet effectively reduces tumor ingrowth and provides for treatment of tracheoesophageal fistulas, while the

outer flange diameters have been increased, thereby making a funnel-shaped stent that adheres to the esophageal wall to significantly lower the rate of migration. Early complications of expandable metal stents have included incomplete expansion, perforation, bleeding, and pain. Late complications include tumor overgrowth/ingrowth, ulceration, food impaction, and stent migration. Patients who have received prior radiation and chemotherapy are more prone to develop complications. Stents that cross into the gastric cardia may cause significant gastroesophageal reflux that can usually be controlled with proton-pump inhibitors; however, a new stent has been developed that prevents reflux via a valve mechanism. In cases in which patients developed an airway fistula, such as bronchoesophageal or tracheoesophageal fistula, stent placement is the optimum therapy. Furthermore, a second stent may be placed in the airway if there is significant stenosis causing dyspnea.

Prognosis

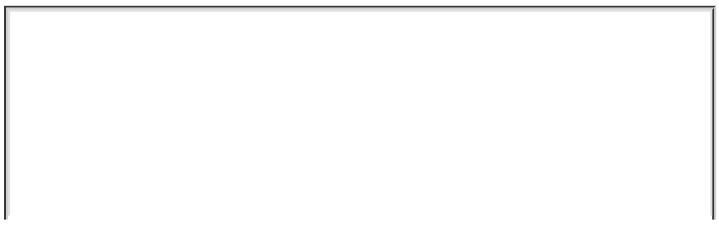
Despite the widespread use of endoscopy, significant advances in surgical techniques and neoadjuvant chemoradiation therapy, and improvements in postoperative care, the prognosis for patients with esophageal cancer remains poor. The reported overall 5-year survival rates are at best 10–15%. Delayed clinical manifestations and rapid intramural invasion and distant metastases account for the poor prognosis of this GI malignancy. Patients with an early stage of disease carry a better prognosis. For patients with T1 or T2 disease and no nodal involvement, the 5-year survival rate is greater than 40%. On the other hand, patients with T3 or T4 lesions have a 5-year survival of less than 25%.

Stage 0, I, and II tumors are considered resectable for cure. The 5-year survival for such patients who are sufficiently fit to undergo surgery ranges from greater than 85% for stage 0, to 50% for stage I, to 40% for stage II. On the other hand, stage III tumors are rarely resectable for cure, and stage IV cancers are considered incurable and nonresectable by most clinicians. The presence or absence of nodal involvement also has a significant prognostic impact. The 5-year survival for N0 disease is over 70%, whereas N1 disease is associated with a survival near 40%, independent of the T classification.

BENIGN ESOPHAGEAL TUMORS

General Considerations

A variety of benign mass lesions can arise from different wall layers in the esophagus (Table 18-6). These tumors are usually asymptomatic and slow growing, noted only as incidental findings during routine radiography or endoscopy. Occasionally, they may be discovered during the evaluation of dysphagia or vague chest discomfort. The most common benign esophageal tumor is the leiomyoma. Because the tumor arises from the muscularis propria, it is covered by an intact submucosa and mucosa, making it difficult to biopsy endoscopically.



Leiomyoma
Hemangioma
Granular cell tumor
Congenital esophageal cyst
Fibrovascular polyp
Bronchogenic cyst
Inflammatory fibroid polyp (eosinophilic granuloma)
Lymphangioma
Squamous cell papilloma
Lipoma
Neurofibroma

Table 18-6. Benign esophageal tumors.

Inflammatory polyps and granulomas can arise in the setting of esophagitis and may be confused with

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malignant lesions from time to time. Endoscopic removal is possible, although usually not indicated. Endoscopic biopsy and regression with therapy for esophagitis clearly distinguish the clinical course of inflammatory polyps and granulomas from cancers.

Clinical Findings

A. SYMPTOMS AND SIGNS

Although the vast majority of benign esophageal tumors are clinically silent and go undetected, large or strategically located tumors may become symptomatic. Similar to their malignant counterparts, dysphagia is the most common presentation for patients with benign esophageal tumors. Less common presenting symptoms include odynophagia, retrosternal pain or thoracic pressure, food regurgitation, anorexia, and weight loss. Respiratory complaints such as cough, dyspnea, or sore throat may also contribute to the presentation. Occasionally, leiomyomas can outgrow their own blood supply, leading to necrosis and ulceration of the overlying mucosa and resulting in overt GI hemorrhage such as hematemesis or melena.

B. IMAGING

Endoscopic appearance and biopsy can identify some benign esophageal tumors. However, EUS provides high-resolution images that define the individual esophageal wall layers and can readily identify lesions in the deeper layers (ie, submucosa and muscularis propria) that elude endoscopic biopsy diagnosis. If necessary, EUS-guided FNA can be performed for diagnostic purposes. Leiomyomas are generally noted as hypoechoic mass lesions within the muscularis propria. Occasionally, the echopattern is more heterogeneous, which may indicate hemorrhage into the tumor. Cystic lesions may appear as anechoic structures within the mucosa and submucosa, whereas inflammatory growths are always superficial and localized to the mucosa.

Treatment

Small, mucosal-based and submucosal esophageal tumors can be removed endoscopically using EMR techniques or possibly obliterated by endoscopic injection of sclerosants or by APC. Larger mass lesions, especially leiomyomas, are generally removed surgically if they are associated with severe symptoms or other complications, eg, bleeding. In many instances, the resection can now be accomplished by minimally invasive techniques.

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