

Esophageal cancer: staging system and guidelines for staging and treatment

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Abstract: Survival of esophageal cancer is improving but remains poor. Esophageal cancer stage is based on depth of tumor invasion, involvement of regional lymph nodes, and the presence or absence of metastatic disease. Appropriate work-up is critical to identify accurate pre-treatment staging so that both under-treatment and unnecessary treatment is avoided. Treatment strategy should follow guideline recommendations, and generally should be developed after multidisciplinary evaluation.

Keywords: Esophageal neoplasms; neoplasm staging; esophagectomy

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Introduction

The incidence of esophageal cancer is increasing, with an estimated 17,460 new cases in the United States in 2012 (1-5). More than 90% of esophageal cancers in the United States are either adenocarcinomas (57%) or squamous cell carcinomas (37%) (1-3,6). The distribution of tumor types varies according to race: 64% of cases in whites are adenocarcinomas, while 82% are of squamous cell origin among the black population (6). Interestingly, the incidence among white males has almost doubled while the incidence among blacks has decreased by almost 50% (6). Tobacco use and a history of mediastinal radiation are risk factors for both tumor types (2). Other risk factors for adenocarcinoma include gastroesophageal reflux disease (GERD), obesity, and Barrett's esophagus (2). Barrett's esophagus with high-grade dysplasia is considered a premalignant condition as 50% are found to harbor occult malignant disease at time of biopsy (7). Additional risk factors for squamous cell carcinoma are conditions that cause chronic esophageal irritation and inflammation such as alcohol abuse, achalasia, esophageal diverticuli, and frequent consumption of extremely hot beverages (2). Approximately three quarters of all adenocarcinomas are found in the distal esophagus whereas squamous-cell carcinomas are more evenly

distributed throughout the distal two thirds (2).

Obtaining accurate pre-treatment staging and then subsequently providing stage-appropriate treatment is crucial in optimizing esophageal cancer outcomes. Overall 5-year survival for patients with esophageal cancer remains poor, although some improvement has been achieved with an increase from 5% to 17-19% over the past four decades (4-6). These survival improvements have likely resulted from earlier detection in the setting of Barrett's esophagus, improvements in perioperative care, and the use of adjuvant and induction chemotherapy and radiation. However esophageal cancer treatment and particularly esophagectomy is also associated with significant morbidity. Accurate staging and appropriate treatment can avoid both inadequate and unnecessary treatment to balance the potential benefits of improving prognosis with risks of treatment-related morbidity.

Staging system and guidelines

Staging definitions

Esophageal cancer staging is defined by the American Joint Committee on Cancer (AJCC) Staging System that establishes tumor-node-metastasis (TNM)

Table 1 T, N, and M status and histologic grade definitions for esophagus and esophagogastric junction cancer in the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual

T status	
T _{is}	High-grade dysplasia
T1	Invasion into the lamina propria, muscularis mucosae, or submucosa
T2	Invasion into muscularis propria
T3	Invasion into adventitia
T4a	Invades resectable adjacent structures (pleura, pericardium, diaphragm)
T4b	Invades unresectable adjacent structures (aorta, vertebral body, trachea)
N status	
N0	No regional lymph node metastases
N1	1 to 2 positive regional lymph nodes
N2	3 to 6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes
M status	
M0	No distant metastases
M1	Distant metastases
Histologic grade	
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

sub-classifications based on the depth of invasion of the primary tumor (T), lymph node involvement (N), and extent of metastatic disease (M). The most recent, 7th edition of the AJCC Cancer Staging Manual for esophagus and esophagogastric junction cancers was developed based on a database of 4,627 esophagectomy patients who were not treated with induction or adjuvant therapy (8). This data from 13 institutions in five countries and three continents was collected by the Worldwide Esophageal Cancer Collaboration (WECC) (9). *Table 1* shows the specific 7th edition TNM definitions. The 7th edition differed from the 6th edition in several respects (10,11). The T status classification was changed to define T_{is} as high-grade dysplasia and all non-invasive neoplastic epithelium. Tumors with T4 status due to invasion of local structures

were subdivided into tumors that involved resectable local structures such as pleura and diaphragm (T4a) and unresectable local structures such as aorta and vertebral bodies (T4b).

Regional lymph nodes were also redefined as any paraesophageal lymph node, including cervical or celiac nodes. The N status had been categorized simply as node-negative or node-positive in the 6th edition and was redefined in the 7th edition to N0-N3 based on the number of lymph nodes. The M1a and M1b subclassifications from the 6th edition were redefined to M1. The 7th edition stage groupings were also defined to consider the importance of histopathologic cell type, tumor grade, and tumor location. *Table 2* shows stage grouping for adenocarcinoma and squamous cell carcinoma, which are no longer equivalent in the 7th edition.

Diagnostic and staging work-up

The Society of Thoracic Surgeons has published guidelines on the diagnosis and staging of patients with esophageal cancer (12). The work-up for esophageal cancer often starts when patients present with symptoms such as dysphagia and weight loss in the setting of an unremarkable physical exam (2,13). Therefore, the most common tests used to initially identify and diagnosis esophageal cancer are upper gastrointestinal (GI) tract contrast studies and upper endoscopy with biopsy. An upper GI contrast study typically shows a stricture or ulceration when malignancy is present. Upper GI endoscopy identifies tumor location and length and allows biopsy for pathologic examination. After a histologic cancer diagnosis has been obtained, subsequent studies are performed to determine clinical stage as accurately as possible before treatment is initiated.

Obtaining a computed tomographic (CT) scan of the chest and abdomen with both oral and intravenous contrast should be the first staging study when esophageal cancer is diagnosed histologically. The CT scan is somewhat limited in defining the local extent and nodal involvement of esophageal cancer but is most useful in identifying the presence of distant disease such as liver or lung metastases. Further studies that evaluate T and N status would not typically impact treatment and therefore are generally unnecessary if distant disease is identified and subsequently confirmed by biopsy. Positron-emission tomography (PET) scans improve staging by detecting previously unsuspected metastatic disease in up to 15-20% of patients and should be considered in place of CT scans or as an additional study

Table 2 AJCC 7th edition stage groupings

Stage	Adenocarcinoma				Squamous cell carcinoma				
	T	N	M	Grade	T	N	M	G	Location
0	is	0	0	1	is	0	0	1	Any
IA	1	0	0	1-2	1	0	0	1	Any
IB	1	0	0	3	1	0	0	2-3	Any
	2	0	0	1-2	2-3	0	0	1	Lower
IIA	2	0	0	3	2-3	0	0	1	Upper, middle
					2-3	0	0	2-3	Lower
IIB	3	0	0	Any	2-3	0	0	2-3	Upper, middle
	1-2	1	0	Any	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	1-2	2	0	Any	Any
	3	1	0	Any	3	1	0	Any	Any
	4a	0	0	Any	4a	0	0	Any	Any
IIIB	3	2	0	Any	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	4a	1-2	0	Any	Any
	4b	Any	0	Any	4b	Any	0	Any	Any
	Any	3	0	Any	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any	Any	1	Any	Any

Cancer location definitions: upper thoracic, 20-25 cm from incisors; middle thoracic, 25-30 cm from incisors; lower thoracic, 30-40 cm from incisors.

when the CT scan does not show metastatic disease (14,15).

If CT and PET do not demonstrate distant disease, endoscopic ultrasound (EUS) should be performed to establish the extent of locoregional disease (2). EUS provides more accurate evaluation of the depth of tumor invasion (T status) and the extent of lymph-node involvement (N status) than both PET and CT (16,17). However, EUS is less accurate for early-stage lesions such as T1 or T2 compared to more advanced tumors (18-21). Most incidences of understaging are due to missing nodal disease. The specificity and the sensitivity for identifying lymph node disease are better when EUS is combined with fine-needle aspiration (FNA) compared to EUS alone (22).

Performance of the above staging modalities establishes the pre-treatment clinical stage which can be used to guide subsequent treatment, as will be discussed in the following sections. However, occasionally additional studies may be worthwhile before initiation of treatment. First, bronchoscopy should be considered for tumors in the upper and middle esophagus to rule out airway invasion. CT scan and EUS can be suggestive of airway involvement but are not as accurate as direct visualization of the airway. In addition, distant metastases are unfortunately missed even with completion of the staging evaluation described above.

Small liver or lung metastases can be missed by both PET and CT scans, and patients can also have undetected pleural or peritoneal disease (23). Staging via minimally invasive surgical techniques of thoracoscopy and laparoscopy improves the accuracy of the above non-invasive testing (23-25). Use of these invasive techniques is relatively uncommon but should be considered in select patients, such as those who may be considered to have a high risk of treatment-related complications. Staging laparoscopy in particular may have a role for patients with adenocarcinoma of the esophagus or esophagogastric junction (26).

Treatment guidelines

The National Comprehensive Cancer Network (NCCN) provides guidelines for the treatment of esophageal cancer (27). Treatment options include local mucosal resection or ablation therapies, esophagectomy, chemotherapy, and radiation therapy. Recommended treatment is primarily dictated by stage, tumor location, and patients' medical fitness for receiving a particular therapeutic modality. However, definitive data from randomized trials to guide the treatment of esophageal cancer is lacking for many clinical situations. Outcomes also generally are relatively poor with

many treatment strategies, so establishing optimal treatment for different clinical situations remains an area of active research (28). The NCCN guidelines reflect the lack of definitive evidence and often allow a spectrum of potential treatments for many clinical situations. Given both the generally poor overall prognosis and the potential morbidity associated with therapy, multidisciplinary evaluation by surgery, medical oncology, and radiation oncology should be considered for all patients before a treatment strategy is initiated. Treatment that does not follow guidelines should probably only be used in the context of clinical trials.

The stage groupings described above are very useful for both providing prognosis and guiding treatment. However, patients can be categorized even more simply when considering treatment. When considering treatment for esophageal cancer patients, the approach is initially dictated by whether the patients have been determined to have early stage superficial cancers, cancers that are locally advanced with locoregional disease but no distant metastases, and cancers with distant disease. The general treatment guidelines for each of these categories will be discussed in the following sections.

Superficial cancers

Patients with T1-2N0 esophageal cancer typically are recommended to undergo surgery without induction treatment (27). The prognosis for patients treated for intra- and submucosal (T1) esophageal cancers is significantly better than the prognosis for all other patients found to have esophageal cancer, even those also found in other relatively early-stage disease (8). Esophagectomy is effective oncologically for these cancers, but is associated with considerable morbidity and mortality despite improvements over time and the development of minimally invasive techniques (29-35). Although recent data from high-volume centers have shown low mortality rates of 1% to 3.5%, studies involving population-based databases or multicenter trials show that esophageal resection continues to have relatively high perioperative mortality rates of 8.8% to 14% (30,32,35-37). Local treatments with modalities such as endoscopic mucosal resection, radiofrequency ablation, cryotherapy, and photodynamic therapy can provide effective cancer treatment for superficial cancers with much less treatment-related morbidity (38-50). These local treatments are good treatment options for patients with superficial tumors that involve only the mucosa (T1a), but close endoscopic surveillance should be planned post-

treatment. However, local mucosal therapies at the present time are generally not considered appropriate for superficial tumors that involve the submucosa (T1b), as these lesions have occulted lymph node involvement in as many as 50% of patients (51,52). Therefore esophagectomy without induction therapy is recommended for superficial tumors that involve the submucosa (T1b).

The optimal management of esophageal cancer clinically staged as T2N0M0 is somewhat more controversial (53). Clinical staging modalities for this subset are somewhat unreliable, with significant percentages of patients being both under and over staged (18,54-57). Perhaps because clinical staging inaccuracies lead to a relatively high incidence of patients actually having nodal disease present at the time of surgical resection, induction therapy use in this setting has been increasing and was shown recently to exceed 50% for cases that were reported to the Society of Thoracic Surgeons General Thoracic Database in 2011 (54). However, data that proves a survival benefit to induction therapy over surgery alone is still lacking (58). Consistent with the uncertainty of optimal treatment, the NCCN guidelines for medically fit patients allow a wide spectrum of treatment possibilities that include definitive chemoradiation and esophagectomy with or without induction or adjuvant therapy (27).

Locoregional or locally advanced disease

Approximately 32% of esophageal cancer patients have regional disease at the time of diagnosis, with a 5-year survival of only 10-30% (1,2,8). The treatment for locally advanced esophageal cancer that does not have distant metastases and is potentially resectable (T3-4aN0, T1-4aN1M0) is highly variable in practice (59). The NCCN guidelines reflect a lack of available definitive data on the optimal treatment and essentially consider any combination of esophagectomy and chemoradiation or even definitive chemoradiation as acceptable therapy (27).

Many studies involving various combinations of surgery, chemotherapy, and radiation to treat locally advanced esophageal cancer have been conducted and showed conflicting results (28,37,60-66). However, recent evidence suggests that induction chemoradiation followed by surgical resection is the optimal treatment for patients with T3-4a tumors or nodal disease. Several recent trials, retrospective studies, and meta-analyses all showed a survival benefit to both combined and induction therapy (67-72). Most importantly, a recently published randomized trial

demonstrated a survival benefit to induction chemoradiation followed by surgery compared to surgery alone for esophageal or esophagogastric junction cancer (73).

Radiation alone followed by surgery does not improve survival compared with surgery alone and therefore induction radiation alone is not recommended (27,65). Induction chemotherapy without radiation has variably shown to be beneficial but is used by some high-volume centers, and is recommended as a potential treatment by the NCCN for patients with adenocarcinoma (27,37,64). Definitive chemoradiation is the preferred treatment for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in selected cases.

Metastatic or unresectable disease

Approximately 50% of patients have evidence of distant metastatic disease at the time of diagnosis (2,6). Palliative therapy is recommended for these patients, and can include chemotherapy, clinical trial enrollment if available, or best supportive care. Best supportive care is often the most appropriate treatment option. Patients' performance status should determine whether chemotherapy is added to best supportive care. Specific symptoms that often need palliation include dysphagia, pain, and nausea. Oncologists often are hesitant to pursue feeding tubes in patients with stage IV cancer, but feeding tubes may be reasonable options in some select patients. Radiation or endoscopic management techniques such as dilation and stenting can be used to palliate dysphagia or cases of bleeding from esophageal tumors. Palliative esophagectomy for patients with metastatic disease may have a role in very few cases, but should be considered only in very select cases given the morbidity of surgery and the poor prognosis with or without surgery.

Other considerations

Role of esophagectomy for esophageal cancer

Concurrent chemoradiation is an effective treatment option for patients with squamous cell carcinoma of the cervical esophageal cancer (74-77). The NCCN guidelines recommend definitive chemoradiation for these patients (27). Surgery is recommended as possible treatment for most other cases of esophageal cancer that do not have invasion of unresectable structures or distant metastatic disease. Esophageal resection can be performed via several different

techniques, with the most appropriate technique for any specific individual patient being dependent on both patient and surgeon factors. Several studies have suggested that complete surgical resection provides the best chance for cure in patients who do not have distant disease (64,78,79). For patients with stage I-III disease who receive surgical treatment, 5-year survival is 28%, compared to 10% for those treated medically (78). However, surgery for locoregional esophageal cancer is utilized in only 30-40% of resectable cases, perhaps because esophagectomy is historically associated with significant morbidity and mortality and disappointing long-term results (78,80). Minimizing perioperative morbidity in any manner possible is critical to increase the use of surgical resection so that primary nonsurgical treatment is reserved for those who refuse surgery, have unresectable cancers, or are not thought to be surgical candidates for other reasons.

Squamous cell carcinoma versus adenocarcinoma

Squamous cell carcinoma was previously the most common histology but now accounts for 37% of esophageal cancers (1,3). Adenocarcinoma is now the most common esophageal cancer. Patients with adenocarcinoma and squamous cell carcinoma have been observed to have similar long-term survival across major treatment modalities, suggesting that both histologies respond similarly to treatment and may share significant physiologic and cellular features (81). Accordingly, staging and treatment guidelines for adenocarcinoma and squamous cell carcinoma were previously essentially equivalent. However, recognition of prognosis and response to treatment between the two subtypes led to separate stage groupings and treatment algorithms in the latest, revised staging system and in the NCCN guidelines (8,27).

Esophageal cancer treatment guidelines are still generally similar to both adenocarcinoma and squamous cell carcinoma (27). However, the benefit of surgical resection in improving survival compared to definitive chemoradiation for esophageal squamous cell carcinoma has been questioned (82). In particular, several randomized trials have suggested that definitive chemoradiation could offer equivalent survival to treatment that involves surgery for locally advanced, non-metastatic esophageal SCC (83-85). Currently for medically fit patients with resectable disease, the NCCN treatment guidelines only recommend definitive chemoradiation for patients who decline surgery (27). However, some centers advocate treatment with chemoradiation for esophageal squamous cell carcinoma, with surgery subsequently used

only when there is persistent or recurrent local disease (86).

Adjuvant therapy

Adjuvant therapy after resection may have a role for some esophageal cancer patients. Postoperative radiation may reduce the incidence of local recurrence in those patients who have residual tumor after resection but is not beneficial in the absence of residual disease (2,87,88). Postoperative chemotherapy has not been definitively shown to have an additive effect on survival compared with surgery alone although additional therapy may be warranted in patients who have a high likelihood of metastatic disease based on a large number of tumor positive nodes (89). The NCCN does not recommend adjuvant therapy if patients have had a complete R0 resection for squamous cell carcinoma, but does recommend consideration of adjuvant chemoradiation, or only adjuvant chemotherapy if induction radiation was administered, for patients who have had resection of adenocarcinoma with either node-positive disease or T2-T4a tumors (27). The guidelines also recommend consideration of adjuvant therapy in the setting of microscopic or macroscopic residual disease after resection.

Conclusions

Survival of esophageal cancer is improving but remains poor. Esophageal cancer stage is based on depth of tumor invasion, involvement of regional lymph nodes, and the presence of metastatic disease. Most patients present with either locally advanced or metastatic disease. Appropriate work-up is critical to identify accurate pre-treatment staging so that both under-treatment and unnecessary treatment is avoided. Staging evaluation should start with CT or PET scan, and patients who do not have metastatic disease should have EUS to determine the locoregional extent of disease. Treatment strategy should follow guideline recommendations, and generally should be developed after multidisciplinary evaluation. Surgery or local mucosal treatments should be considered for superficial cancers. Multimodality therapy that includes surgery is generally considered the best treatment for locally advanced cancers, while patients that have metastatic disease should be considered for chemotherapy along with best supportive care.

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