The Society of Thoracic Surgeons Guidelines on the Diagnosis and Staging of Patients With Esophageal Cancer

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Executive Summary

Diagnosis of Esophageal Cancer

Flexible endoscopy with biopsy is the primary method for the diagnosis of esophageal carcinoma (Class I recommendation: level of evidence B)

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Staging of Esophageal Cancer

1. For early stage esophageal cancer, computed tomography of the chest and abdomen is an optional test for staging. (Class I recommendation: level of evidence B)
2. For locoregionalized esophageal cancer, computed tomography of the chest and abdomen is a recommended test for staging. (Class I recommendation: level of evidence B)
3. For early stage esophageal cancer, positron emission tomography is an optional test for staging. (Class IIB recommendation: level of evidence B)
4. For locoregionalized esophageal cancer, positron emission tomography is a recommended test for staging. (Class I recommendation: level of evidence B)
5. In the absence of metastatic disease, endoscopic ultrasonography is recommended to improve the accuracy of clinical staging. (Class IIA recommendation: level of evidence B)
6. Endoscopic mucosal resection should be considered as a diagnostic/staging tool for small, discrete nodules or areas of dysplasia when the disease appears limited to the mucosa or submucosa as assessed by endoscopic ultrasonography. (Class IIA recommendation: level of evidence B)
7. For locally advanced (T3/T4) adenocarcinoma of the esophagogastric junction infiltrating the anatomic cardia, or Siewart type III esophagogastric tumors, laparoscopy is recommended to improve the accuracy of staging. (Class IIB recommendation: level of evidence C)

Introduction

Esophageal cancer is among the 10 most frequent cancers in the world, and is the seventh leading cause of cancer death. In 2010, the American Cancer Society estimated 16,640 adults (13,130 men and 3,510 women) in the United States would be diagnosed with esophageal cancer, and there would be 14,500 deaths (11,650 men and 2,850 women) [1]. For the past 4 decades, the incidence of esophageal cancer in the United States has increased at the fastest rate of any solid tumor [2–4].

Despite advances in treatment regimens, esophageal cancer remains one of the most lethal of all cancers with a dismal overall 5-year survival rate of less than 15%. The optimal treatment for localized esophageal cancer remains one of the most widely debated topics in oncology. Esophagectomy is considered the gold standard for localized disease. Although patients with early

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Abbreviations and Acronyms

AJCC = American Joint Commission on Cancer
CT = computed tomography
EGD = esophagogastroduodenoscopy
EMR = endoscopic mucosal resection
EUS = endoscopic ultrasonography
FDG = (18)F-fluoro-2-deoxy-D-glucose
FNA = fine-needle aspiration
GEJ = gastroesophageal junction
PET = positron emission tomography
STS = The Society of Thoracic Surgeons

localized disease benefit from surgery, there is increasing evidence that multimodality therapy (neoadjuvant chemotherapy or radiation therapy, or both, followed by esophagectomy) has increased survival benefits when compared with surgery alone for more advanced stages [5]. Accurate staging information is thus critical for the determination of appropriate therapeutic intervention.

The focus of this project was to systematically review the literature with regard to the diagnostic workup and staging of esophageal cancer (Table 1). Evidence-based guidelines must be viewed as recommendations, not as absolutes, and are intended to assist health-care providers in clinical decision-making by providing a range of acceptable approaches for the management of specific conditions. The ultimate judgment regarding care of a particular patient under specific circumstances must be made by the provider, and there are certainly circumstances in which management that falls outside of these guidelines is appropriate.

Methods

A taskforce was assembled through the Workforce on Evidence Based Surgery and the General Thoracic Surgery Workforce of The Society of Thoracic Surgeons (STS) with the goal of addressing the factors affecting the treatment of localized esophageal cancer. For this systematic review on the diagnosis and staging of esophageal cancer, specific search terms were identified and targeted searches were run in PubMed/MEDLINE, Embase, and the Cochrane databases in June 2011. The results were limited to publications since 1990, and human subjects. We augmented our computerized literature search by manually reviewing the reference lists of identified studies and relevant reviews. In addition, the writing group identified articles from personal files. The following three medical subject heading (MeSH) terms were used: "esophageal neoplasms," "early detection of cancer," and "neoplasm staging." Additional search strategies incorporated the MeSH subheadings of "analysis," "anatomy and histology," "classification," "diagnosis," "diagnostic use," "histology," "methods," "pathology," "standards," "trends," "ultrasonography," "positron emission tomography," and "trends."

In all, 4,064 articles and abstracts were identified through the initial Embase search, and 2,874 articles were identified through PubMed/MEDLINE. The Cochrane database identified 2 additional reviews and 191 clinical trials. Abstracts were reviewed by at least two authors and excluded if data were duplicative, not specifying esophageal cancer, purely descriptive, or incomplete. The resulting 80 articles served as the source for the review; 46 are cited and the remaining are listed in the Appendix. Guideline recommendations were formulated and reviewed by all members of the writing group before approval by the Workforce on Evidence Based Surgery and the STS Executive Committee.

Table 1. Classification of Recommendation and Level of Evidence

Classification of recommendation

- Class I (benefit $>>>$ risk): Procedure/treatment SHOULD be performed/administered
- Class IIA (benefit $>>$ risk): Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/administer treatment.
- Class IIB (benefit $>$ risk): Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/treatment MAY BE CONSIDERED.
- Class III (no benefit): Procedure/test, not helpful. Treatment, no proven benefit.
- Class IV (harm): Procedure, without benefit or harmful. Treatment, harmful to patients.

Level of evidence that best fits the recommendation

- Level A: Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.
- Level B: Limited populations evaluated. Data derived from a single randomized trial or non-randomized studies.
- Level C: Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care are available.

Diagnosis of Esophageal Cancer

Class I Recommendation: Flexible endoscopy with biopsy is the primary method for the diagnosis of esophageal carcinoma. (Level of evidence B)

Early cancers of the esophagus generally are asymptomatic, although ulcerated lesions may sometimes present with evidence of gastrointestinal bleeding. Most patients thus present at an advanced stage when the diagnosis is made, with dysphagia being the most common symptom [6]. Dysphagia associated with esophageal cancer has classically been described as persistent dysphagia that progresses from solids to liquids. However, any dysphagia in a patient above the age of 40 years should increase the suspicion for esophageal cancer and prompt endoscopic examination. Odynophagia, regurgitation, and weight loss can also be seen in advanced cases.

Table 2. Template for Upper Gastrointestinal Endoscopy for Esophageal Cancer to Initially Stage Esophageal or Gastroesophageal Junction Carcinoma

Patient name:
MR#:
Date of procedure:

Esophagogastroduodenoscopy findings

Initial measurements defining presence of metaplasia, hiatal hernia and upper/lower esophageal boundaries (distance from incisors)

Squamocolumnar junction	_____ cm
Gastroesophageal junction	_____ cm
Diaphragmatic pinch	_____ cm
EUS (for upper esophageal cancers)	_____ cm

Presence of Barrett's esophagus
- Measurements from incisors
- Prague classification [44]: C_____ M_____

Presence of other mucosal abnormalities (ulcer, stricture, nodules or mass)
- Measurements from incisors
- Length of lesion
- Percent of circumferential involvement
- Position in relation to the GEJ (length of extension into cardia if present)
- Describe any skip lesions
- Tumor morphology (Paris or Kudo classification) [45, 46]

Tumor description	
Proximal border	_____ cm
Distal border	_____ cm
Tumor circumference	_____ %
Extension into cardia	_____ cm

Describe anatomy of foregut, such as previous fundoplication or resections.

Photograph/image of abnormalities.
- If there is extension into stomach, retroflex photo as well.

Biopsy of all suspicious lesions with documentation of location of biopsy.
- Multiple biopsies increase diagnostic accuracy.

EUS = endoscopic ultrasonography; GEJ = gastroesophageal junction.

REPORT

The diagnosis of esophageal cancer is established with flexible endoscopy with biopsy [7]. Traditionally barium swallow was used as a diagnostic tool in esophageal cancer care, a so-called "road map" before endoscopy. Polypoid tumors, strictures with mucosal irregularity, and "apple core" constrictions are characteristic findings on barium studies for malignancy. The barium swallow examination may also provide information that can help with surgical planning, including the location of the tumor, the axis of the esophagus at the level of the tumor (angulation can add to difficulty in resection), the presence of other pathology (such as a hiatal hernia or diverticulum). At experienced centers, however, features such as location and size of the tumor can be more accurately assessed by endoscopy than by barium studies [8]. There has thus been debate of the value of barium studies as an initial diagnostic test [9, 10]. One situation where a barium study is essential is when there is suspicion of a tracheoesophageal fistula [11]. Barium studies may provide supportive data in the differentiation of gastroesophageal junction (GEJ) tumors from gastric tumors [12] in situations where large tumors are seen on retroflexion.

The modern work-up of esophageal disorders is therefore focused on upper gastrointestinal endoscopy, which is an essential component for any patient suspected of having an esophageal neoplasm. Endoscopy can provide a complete visual description of gross tumor characteristics including length, location relative to the GEJ, and description and length of any extension into the gastric cardia. Presence, length, and location of any areas of

Table 3. Endoscopic Ultrasonography Findings

EUS examination

Scope: radial, linear miniprobe, frequency: 20 mHz, 12 mHz

T stage _____

Wall thickness (maximal) _____ mm
(Specify T1a versus T1b if applicable)

N stage _____ (N0, N1, etc; avoid Nx if possible)

Describe LN findings (size, location from incisors and anatomic location, echogenicity, shape)

EUS = endoscopic ultrasonography; LN = lymph node.

metaplasia within the esophagus should be noted as well. Biopsy must be obtained at the time of endoscopy; several biopsies will increase the diagnostic accuracy of the study. The diagnostic yield approaches 100% when six or more samples are obtained using a standard endoscopic biopsy protocol [13, 14]. Biopsy of necrotic or fibrotic areas should be avoided. Brush cytology can be helpful in cases of tight malignant strictures where conventional biopsies may be difficult to obtain [15]. In these cases, to maximize the yield, brushings should be obtained before biopsy [16]. In situations where standard biopsy or brushings do not yield a diagnosis in cases with high suspicion, endoscopic ultrasonography (EUS) should be considered [17]. However, as endoscopic ultrasound probes are typically larger in size, care should be used when attempting biopsies in the setting of stricture, in particular when dilating the tumor stricture.

Suspicious lesions other than the index lesions should also be biopsied as submucosal spread or skip lesions within the esophagus are not uncommon. Knowledge of all of these characteristics affects prognosis and treatment and surgical decisions. Elements that are considered critical to an endoscopy report for esophageal cancer are included in Tables 2 through 5.

Table 4. Endoscopic Mucosal Resection Findings

Indication for EMR
Therapeutic versus diagnostic
Location of all suspicious lesions and index lesions resected

Lesion description		
	Proximal border	_____ cm
	Distal border	_____ cm
	Lesion circumference	_____ %
	Position	_____ o'clock

Classify lesion (flat, nodular, ulcerated, polypoid, exophytic mass)

Type of apparatus (EMR-multiband kit, cap, ESD knife)

En bloc or piecemeal resection
Complete resection or partial

EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection.

Table 5. Biopsy Protocols

Gastroesophageal junction lesions
Specify estimated distance tumor extends below rugal folds at gastroesophageal junction.
Biopsy and label separately area of extension into cardia at 1 cm, 2 cm, 3 cm.

Endoscopic ultrasonography–fine-needle aspiration
Of interest is any lymph node that appears involved that can be safely biopsied without traversing primary tumor.
Of particular interest are nonregional nodes such as porta hepatis, celiac, and paraaortic stations.

Staging of Esophageal Cancer

For patients with resectable esophageal cancer, optimal outcomes and treatment decisions are dependent on accurate pretreatment disease evaluation. According to the American Joint Commission on Cancer (AJCC), stage is divided into descriptive components: tumor (T), nodal (N), and metastasis (M).

Esophageal Cancer AJCC Staging System

The seventh edition of the esophageal AJCC staging system [18] includes significant modifications to the sixth edition (Fig 1). The basis for these changes from the World Esophageal Cancer Consortium includes observations that (1) nodal burden was a significant contributor to outcome [19–21]; (2) nodal location (N1 versus M1a) was arbitrary and not consistently correlated with prognosis [22]; and (3) the prognosis of squamous cell carcinoma and adenocarcinoma differed [23]. The most prominent changes in the new staging system [24] include the following:

(1) Accounting for nodal burden by classifying the number of involved lymph nodes into categories: N1, 1 to 2; N2, 3 to 6; N3, 7 or more
(2) Eliminating the distinction between local (N) and regional (M1a) nodal disease, and categorizing all nodal disease between the thoracic inlet and celiac axis as local-regional nodal disease (N), and any nodes beyond this region as M1
(3) Using a different staging system for adenocarcinoma and squamous cell carcinoma
(4) Precisely defining the three types of GEJ tumors based on location, and including all three exclusively in the esophageal staging system
(5) Including tumor grade as part of the system

Because the dataset used in creating this new staging system excluded patients who received preoperative therapy, the staging system will tend to overestimate the prognosis of locally advanced tumors, as many of the institutions that contributed data for the creation of the new staging system also treated locoregionally advanced cancers with neoadjuvant therapy.

Fig 1. (A) Summary of changes in American Joint Committee on Cancer (AJCC) esophageal cancer TNM staging, seventh edition. (B) Definitions of TNM. (C) Stage groupings by histology. (Reprinted with permission from AJCC: Esophageal and esophagogastric junction. In: Edge SB, Byrd DR, Compton CC, et al, eds: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 103-15 [18].)

A

Summary of Changes

- Tumor location is simplified, and Esophagogastric junction and proximal 5cm of stomach are included
- Tumors arising at the esophagogastric (EG) junction, or arising in the stomach less than or equal to 5 centimeters from the EG junction and crossing the EG junction are staged using the TNM system for Esophageal Adenocarcinoma*
- Tis is redefined and T4 is subclassified
- Regional lymph nodes are redefined. N is subclassified according to the number of regional lymph nodes containing metastasis
- M is redefined
- Separate stage groupings for squamous cell carcinoma and adenocarcinoma
- Stage groupings are reassigned using T, N, M and G classifications

**Further clarification available in Chapter 11 Stomach, AJCC Staging Manual*

B

Primary Tumor (T)[a]

Tx	**Primary tumor cannot be assessed**
T0	**No evidence of primary tumor**
Tis	**High-grade dysplasia[b]**
T1	**Tumor invades lamina propria, muscularis mucosae, or submucosa**
T1a	**Tumor invades lamina propria or muscularis mucosae**
T1b	**Tumor invades submucosa**
T2	**Tumor invades muscularis propria**
T3	**Tumor invades adventitia**
T4	**Tumor invades adjacent structures**
T4a	**Resectable tumor invading pleura, pericardium or diaphragm**
T4b	**Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.**

[a] (1) At least maximal dimension of the tumor must be recorded, and (2) multiple tumors require the T(m) suffix.

[b] High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Regional Lymph Nodes (N)

Nx	**Regional Lymph Nodes cannot be assessed**
N0	**No regional lymph node metastasis**
N1	**Metastases in 1-2 regional lymph nodes**
N2	**Metastases in 3-6 regional lymph nodes**
N3	**Metastases in ≥ 7 regional lymph nodes**

Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.

Distant Metastasis (M)

M0	**No distant metastasis**
M1	**Distant metastasis**

(Continued)

REPORT

Fig 1. Continued.

C

Adenocarcinoma

Stage	Tumor (T)	Node (N)	Metastases (M)	Grade (G)
0	is (HGD)	0	0	1, X
IA	1	0	0	1-2, X
IB	1	0	0	3
	2	0	0	1-2, X
IIA	2	0	0	3
IIB	3	0	0	Any
	1-2	1	0	Any
IIIA	1-2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
IIIB	3	2	0	Any
IIIC	4a	1-2	0	Any
	4b	Any	0	Any
	Any	N3	0	Any
IV	Any	Any	1	Any

Squamous Cell Carcinoma [a]

Stage	Tumor (T)	Node (N)	Metastases (M)	Grade (G)	Location [b]
0	is (HGD)	0	0	1, X	Any
IA	1	0	0	1, X	Any
IB	1	0	0	2-3	Any
	2-3	0	0	1, X	Lower, X
IIA	2-3	0	0	1, X	Upper, Middle
	2-3	0	0	2-3	Lower, X
IIB	2-3	0	0	2-3	Upper, Middle
	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	Any
	4b	Any	0	Any	Any
	Any	N3	0	Any	Any
IV	Any	Any	1	Any	Any

[a] Or mixed histology, including a squamous component or not otherwise specified.

[b] Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.

Definitions

For the remaining recommendations, the following definitions will be used: early stage cancer refers to nodular high-grade dysplasia or T1a as defined by EUS; locoregionalized esophageal cancer refers to esophageal cancers from T1b to T4, any N, and M0; and distant metastatic disease refers to M1 disease.

Class I Recommendation: For early stage esophageal cancer, computed tomography (CT) of the chest and abdomen is an optional test for staging. (Level of evidence B)

Class I Recommendation: For locoregionalized esophageal cancer, CT of the chest and abdomen is a recommended test for staging. (Level of evidence B)

Class IIB Recommendation: For early stage esophageal cancer, positron emission tomography (PET) is an optional test for staging. (Level of evidence B)

Class I Recommendation: For locoregionalized esophageal cancer, PET is a recommended test for staging. (Level of evidence B)

Class IIA Recommendation: In the absence of metastatic disease, EUS is recommended to improve the accuracy of clinical staging. (Level of evidence B)

Class IIA Recommendation: Endoscopic mucosal resection (EMR) should be considered as a diagnostic/staging tool for small, discrete nodules or areas of dysplasia when the disease appears limited to the mucosa or submucosa as assessed by EUS. (Level of evidence B)

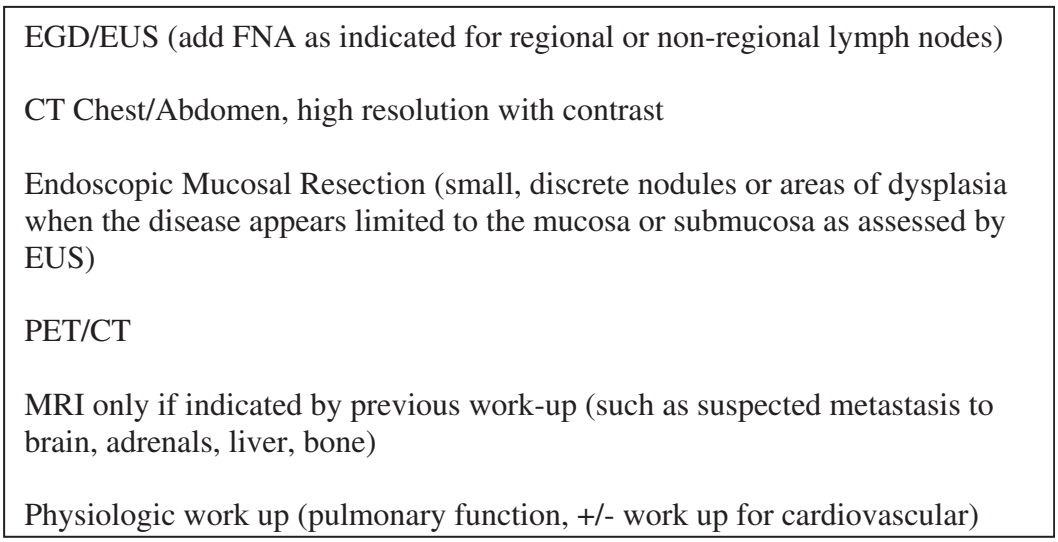

Fig 2. Diagnostic work-up for newly diagnosed esophageal cancer. (CT = computed tomography; EGD = esophagogastroduodenoscopy; EUS = endoscopic ultrasonography; FNA = fine-needle aspiration; MRI = magnetic resonance imaging; PET = positron emission tomography.)

Assessment of disease stage typically includes a combination of endoscopy and imaging, notably esophagogastroduodenoscopy (EGD)/EUS, CT, and integrated PET/CT. Magnetic resonance imaging is reserved for secondary evaluation of the liver or adrenals.

The most common method of pretreatment work-up is outlined in Figure 2. Because there are complex interrelations between the different diagnostic studies, we will discuss the ability of each study to predict individual staging components.

Tumor

An accurate determination of tumor depth is important to treatment planning. There is good statistical association of depth of invasion to lymphadenopathy and overall outcome [25]. For determining depth of invasion, EUS is fairly accurate with sensitivities ranging from 81% to 92% depending on the depth of tumor penetration. More advanced tumors seem to have a better chance at an accurate EUS depth determination; the deeper the tumor, the more sensitive the EUS [26]. Moreover, treatment decisions are directly correlated to depth of tumor involvement. Transmural tumors are more likely to receive multimodality therapy given the possibility of advanced locoregional (with positive LN) or systemic involvement, and very early lesions may be amenable to surgery alone or even potentially curative endoscopic therapy. When a PET scan is to be performed, it is usually done before EUS to exclude metastatic spread to avoid unnecessary procedures.

Contrast-enhanced CT imaging of the chest and abdomen with both oral and intravenous contrast is one of the initial evaluations of patients with esophageal cancer. Axial CT images of an esophageal tumor may visualize an abnormal area of wall thickening, usually defined as being greater than 5 mm [27]. However, it is difficult to accurately measure the esophageal wall thickness, so compared with EGD/EUS, CT is relatively insensitive for T description (0.83 compared with 0.67) [28] as it cannot resolve invasion through the different histologic layers of the esophageal wall. The sensitivity is particularly poor in early esophageal neoplasms, where an abnormality is often not detected.

Although no test other than surgery very accurately predicts invasion into adjacent structures (T4 disease), this may be suggested on CT by contiguity between the esophagus and adjacent organs and the loss of normal periesophageal fat planes. This finding of contiguity is not synonymous with invasion, however, and hence does not preclude an attempt at resection. Aortic invasion may be suggested by encasement greater than 90 degrees, and diaphragmatic invasion by loss of the retrocrural fat planes. Intravascular ultrasonography may be considered as a modality to confirm preservation of the periaortic fat plane or direct aortic wall invasion in suspicious cases. Tracheal invasion may be suspected where a mid-esophageal tumor bulges into the posterior membranous portion of the airway but this requires bronchoscopy to confirm. Sensitivity of airway involvement assessment can be increased with the use of endobronchial ultrasonography when obvious tumor is not visualized in the lumen of the airway but suspicion remains. In the absence of definitive evidence of obvious invasion into surrounding structures, the assignment of a T4 stage should be considered tentative and thus not considered an absolute contraindication to surgery.

Integrated PET/CT imaging provides both functional and anatomic information for guiding clinical decision making; however, understanding its limitations and interpretative pitfalls is critical to optimizing this examination's usefulness. Most esophageal malignancies are (18)F-fluoro-2-deoxy-D-glucose (FDG) avid. Therefore, tumor location can be visualized which may provide

information that would guide radiation and surgery decisions [29]. However, whereas FDG avidity in the esophagus is most often related to the primary tumor, confounding factors may be responsible for hypermetabolism seen on the scan that may blur the apparent longitudinal extent of the tumor. Esophagitis, previous interventions (biopsy or stent placement), and mucosal ulceration are common causes of false positive FDG uptake, appearing as linear or focal areas of high activity in the esophagus. For all of these reasons, evaluation of the apparent metabolic activity of the primary esophageal tumor should be correlated with the findings at endoscopy. Barring any anatomic reason seen on endoscopy, PET may be complementary in indicating occult submucosal disease.

Finally, a diagnostic endoscopic mucosal resection can accurately determine depth of invasion for patients suspected of having very early disease. Typically, patients who are determined to have nodular areas of Barrett's dysplasia suspicious for invasive cancer or have superficial esophageal tumors are considered for a diagnostic mucosal resection. Compared with EUS, this procedure more accurately defines several prognostic indicators, specifically, T1a versus T1b depth of invasion, and presence of lymphovascular invasion. The resected tissue is evaluated histologically, which results in the most accurate physical determination of depth. Experienced centers have shown exceptional safety and excellent results. Perforation risk and bleeding risk are the most relevant and range from less than 1% to 2%, respectively [30–32].

As we currently lack any accurate molecular modalities for determining prognosis, pathologic analysis should be considered the standard to which all other modalities are compared. Many patients are treated with neoadjuvant therapy before resection, however, and this comparison is only relevant for patients treated with resection alone. Routine use of molecular markers by immunohistochemistry or polymerase chain reaction is not yet recommended for determining prognosis in locoregional disease.

Nodes

Computed tomography has a relatively poor diagnostic performance (sensitivity 0.5, specificity 0.83) for regional nodal metastases, depending entirely on size criteria [33]. As a general rule, lymph nodes that are greater than 1 cm in short axis are considered suspicious for malignancy; however, smaller lymph nodes are also frequently involved, and larger lymph nodes may simply be reactive. FDG-PET also has limitations in determining regional disease (sensitivity 0.57, specificity 0.85) largely because "spillover" signal from an avid adjacent primary tumor may render detection of regional nodes difficult. The lymph node status is best explored by EGD/EUS with or without fine needle aspiration (FNA [sensitivity 85% and 97%, respectively]) [34]. Given this high specificity and a low level of false negative results, EUS is particularly good for its negative predictive value. Moreover, EUS-guided FNA allows for cytologic diagnosis. In the context of staging, the main potential advantage of EUS-FNA over EUS alone is that it increases the specificity of lymph node staging. In the past many advocated for EUS-FNA of all visualized celiac nodes as this was considered metastatic disease in the old staging system. In the new staging system, all lymph nodes between the thoracic inlet and celiac axis are considered regional. Thus EUS-FNA sampling is typically restricted to those situations where nodal status influences therapeutic approach. Care should be taken to avoid biopsy of lymph nodes through the tumor itself.

Detection of any lymphadenopathy may alter treatment decisions for more superficial tumors that are being considered for an EMR or more limited anatomic resection. However, it is important to remember that the presence of locoregional nodal metastases is not a contraindication to surgery as they will normally be resected with the primary tumor. Knowledge of suspected positive lymph nodes may also direct approach and extent of surgical resection. One objective for the complementary pairing of CT and PET is to identify suspicious lymph nodes that would escape detection by EUS because they are not immediately adjacent to the esophagus. A combination of EGD/EUS and PET/CT is the optimal method for prospectively evaluating the N status of esophageal cancer. Thoracoscopy/laparoscopy LN staging has been used with high accuracy but has not met with wide acceptance with the advent of EUS-FNA.

Metastasis

For patients with deeper tumors (T2 to 4), decisions based on regional nodes are diminished and focus therefore on nonregional lymph nodes and distant metastatic disease seems more relevant. Distant organ metastases from esophageal cancer most commonly occur in the liver, lungs, and bones [35]. Many metastases are readily detectable by CT (sensitivity 81%) [36], and notably the evaluation for pulmonary metastases is best performed by high-resolution contrast-enhanced CT scan. However, CT has a relatively poor specificity (82%) [37] and cannot readily differentiate between indeterminate pulmonary nodules and metastatic disease. Furthermore, 7% to 20% of esophageal cancer metastases are occult or are difficult to prospectively diagnose by CT alone [38]. A combination of CT and PET-CT is the optimal method for detection of metastatic disease from esophageal cancer.

Of the three individual tests, PET/CT has the highest sensitivity and specificity for the detection of distant metastases. One meta-analysis indicates that a pooled sensitivity and specificity was 0.71 and 0.93, respectively [36]. It has also been reported that as many as 20% of patients were diagnosed with distant metastases by FDG-PET that were not demonstrable by other means. The increased sensitivity and specificity of PET-CT over other imaging modalities for the detection of distant metastases makes it an indispensable tool in the evaluation of patients with newly diagnosed esophageal cancer.

However, geographical areas that are endemic for granulomatous disease may have a higher false positive rate, leading to a lower positive predictive value. Overall, because the detection of metastatic disease by PET/CT will have such a profound influence on treatment options, consideration should be given to obtain histologic confirmation of metastatic disease. PET/CT is very useful for its negative predictive value, especially for areas of suspected adrenal metastasis or bone lesions.

Class IIB Recommendation: For locally advanced (T3/T4) adenocarcinoma of the esophagogastric junction infiltrating the anatomic cardia or Siewart type III esophagogastric tumors, laparoscopy is recommended to improve the accuracy of staging. (Level of evidence C)

Staging laparoscopy may aid in increasing the accuracy of staging to help guide the most appropriate therapy, as well as place a feeding tube in those patients where neoadjuvant therapy is planned. Combined thoracoscopic and laparoscopic staging has been described to improve staging for esophageal cancer by increasing the number of positive lymph nodes as compared with conventional staging [39]. Compared with final pathologic staging, thoracoscopic and laparoscopic staging has a sensitivity ranging from 64% to 90%, a specificity of 60% to 96%, and an accuracy of 60% to 92% [40]. However, the drawback to this increased accuracy is increased cost and need for an invasive procedure. A small number of reports have been published by highly specialized centers, which may make the reproducibility of their results difficult [39–42]. The impact of the surgeon's expertise on the diagnostic accuracy of the procedure is unknown. As data are limited, staging thoracoscopy and laparoscopy should thus be used only by surgeons with adequate clinical experience with these techniques. Further research is needed to establish the true value of this staging modality. Recent use of laparoscopy with assessment of peritoneal fluid cytology raises the possibility for additional value of this technique in gastroesophageal cancers [43].

Conclusion

In summary, endoscopy with biopsy is the diagnostic test of choice for esophageal cancer. Goals of endoscopy are to determine the presence and location of esophageal cancer and to biopsy any suspicious lesions. Location of the tumor relative to the teeth and GEJ, the length of the tumor, the extent of circumferential involvement, and degree of obstruction should be noted. If present, the location and extent of Barrett's esophagus should be documented. Several biopsies should be performed to provide sufficient material for histology analysis.

Staging of esophageal cancer should first be done with CT and PET/CT. If the patient is a surgical candidate, then EUS should be used to determine the locoregional extent of disease. As EUS can be unreliable in the diagnosis of superficial esophageal cancer, diagnostic EMR should be considered in these situations for accurate diagnosis. There are limited data on the use of staging thoracoscopy and laparoscopy and hence these techniques should only be used by those who have experience with them.

References

1. Cancer facts and figures 2010. American Cancer Society. Available at: http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-and-figures-2010. Accessed December 19, 2010.
2. Vlot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:12879.
3. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin North Am 2002;11:235–56.
4. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–6.
5. van Hagen P, Hulshof MCCM, van Laschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–84.
6. Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons patient care evaluation study. J Am Coll Surg 2000;190:562–72.
7. Glaws WR, Etzkom KP, Wenig BL, et al. Comparison of rigid and flexible esophagoscopy in the diagnosis of esophageal disease: diagnostic accuracy, complications and cost. Ann Otol Rhinol Laryngol 1996;105:262–6.
8. Dooley CP, Larson AW, Stace NH, et al. Double-contrast barium meal and upper gastrointestinal endoscopy. A comparative study. Ann Intern Med 1984;101:538–45.
9. Esfandyari T, Potter JW, Vaezi MF. Dysphagia: a cost analysis of the diagnostic approach. Am J Gastroenterol 2002;97:2733–7.
10. Spechler SJ. AGA technical review on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. Gastroenterology 1999;117:233–54.
11. Burt M. Management of malignant esophagorespiratory fistula. Chest Surg Clin North Am 1996;6:765–76.
12. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998;85:1457–9.
13. Graham DY, Schwartz JT, Cain GD, et al. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982;82:228–31.
14. Lal N, Bhasin DK, Malik AK, et al. Optimal number of biopsy specimens in the diagnosis of carcinoma of the oesophagus. Gut 1992;33:724–6.
15. Jacobson BC, Hirota W, Baron TH, et al. The role of endoscopy in the assessment and treatment of esophageal cancer. Gastrointest Endosc 2003;57:817–22.
16. Zargar SA, Khurro MS, Jan GM, et al. Prospective comparison of the value of brushings before and after biopsy in the endoscopic diagnosis of gastroesophageal malignancy. Acta Cytol 1991;35:549–52.
17. Faigel DO, Deveney C, Phillips D, Fennerty MB. Biopsy-negative malignant esophageal stricture: diagnosis by endoscopic ultrasound. Am J Gastroenterol 1998;93:2257–60.
18. Edge SB, Byrd DR, Compton CC, et al, eds. AJCC cancer staging manual. 7th ed. New York: Springer, 2010:103–15.
19. Roder JD, Busch R, Stein HJ, Fink U, Siewert JR. Ratio of invaded to removed lymph nodes as a predictor of survival in squamous cell carcinoma of the oesophagus. Br J Surg 1994;81:410–3.
20. Kunisaki C, Akiyama H, Nomura M, et al. Developing an appropriate staging system for esophageal carcinoma. J Am Coll Surg 2005;201:884–90.
21. Rizk N, Venkatraman E, Park B, Flores R, Bains MS, Rusch V. The prognostic importance of the number of involved lymph

nodes in esophageal cancer: implications for revisions of the American Joint Committee on Cancer staging system. J Thorac Cardiovasc Surg 2006;132:1374–81.
22. Korst RJ, Rusch VW, Venkatraman E, et al. Proposed revision of the staging classification for esophageal cancer. J Thorac Cardiovasc Surg 1998;115:660–70.
23. Siewert JR, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001;234:360–9.
24. Rice TW, Blackstone EH, Rusch VW. A cancer staging primer: esophagus and esophagogastric junction. J Thorac Cardiovasc Surg 2010;139:527–9.
25. Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcomes of resected esophageal cancer. Ann Surg 2002;236: 376–85.
26. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol 2008;14:1479–90.
27. Rasanen JV, Sihvo EI, Knuuti MJ, et al. Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. Ann Surg Oncol 2003;10:954–60.
28. Kato H, Nakajima M, Sohda M, et al. The clinical application of (18)F-fluorodeoxyglucose positron emission tomography to predict survival in patients with operable esophageal cancer. Cancer 2009;115:3196–203.
29. Muijs CT, Beukema JC, Pruim J, et al. A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. Radiother Oncol 2010;97:165–71.
30. Thosani N, Singh H, Kapadia A, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc 2012;75:242–53.
31. Seerden TC, Larghi A. Staging of early adenocarcinoma in Barrett's esophagus. Gastrointest Endosc Clin North Am 2011;21:53–66.
32. Zehetner J, DeMeester SR, Hagen JA, et al. Endoscopic resection and ablation versus esophagectomy for high-grade dysplasia and intramucosal adenocarcinoma. J Thorac Cardiovasc Surg 2011;141:39–47.
33. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer 2008;98:547–57.
34. Puli SR, Reddy JB, Bechtold ML, et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol 2008;14:1479–90.
35. Quint LE, Hepburn LM, Francis IR, Whyte RI, Orringer MB. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. Cancer 1995;76:1120–5.
36. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol 2004;22:3805–12.
37. Bruzzi JF, Truong MT, Macapinlac H, Munden RF, Erasmus JJ. Integrated CT-PET imaging of esophageal cancer: unexpected and unusual distribution of distant organ metastases. Curr Probl Diagn Radiol 2007;36:21–9.
38. Weber WA, Ott K. Imaging of esophageal and gastric cancer. Semin Oncol 2004;31:530–41.
39. Krasna MJ, Reed CE, Nedziecki D, et al. CALGB 9380: a prospective trial of feasibility of thoracoscopy/ laparoscopy in staging esophageal cancer. Ann Thorac Surg 2001;71:1073–9.
40. Krasna MJ, Jiao X, Mao YS, et al. Thoracoscopy/laparoscopy in the staging of esophageal cancer. Surg Laparosc Endosc Percutan Tech 2002;12:213–8.
41. Romijn MG, van Overhagen H, Spillenaar Bilgen EJ, et al. Laparoscopy and laparoscopic ultrasonography in the staging of oesophageal and cardinal carcinoma. Br J Surg 1998;85:1010–2.
42. Bonavina L, Incarvone R, Lattuada E, et al. Preoperative laparoscopy in management of patients with carcinoma of the esophagus and of the esophagogastric junction. J Surg Oncol 1997;65:171–4.
43. Mezhir JJ, Shah MA, Jacks LM, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. Ann Surg Oncol 2010;17:3173–80.
44. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C&M criteria. Gastroenterology 2006;131:1392–6.
45. Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach and colon. November 30 to December 1, 2002. Gastrointest Endosc 2003;58(Suppl):3–43.
46. Inoue H, Sasajima K, Kaga M, et al. Endoscopic in vivo evaluation of tissue atypa in the esophagus using a newly designed integrated endocytoscope: a pilot trial. Endoscopy 2006;38:891–5.

Appendix. Additional References

1. Lightdale CJ. Practice guidelines: esophageal cancer. Am J Gastroenterol 1999;94:20–9.
2. Stein HJ, Brucher BLDM, Sendler A, Siewert JR. Esophageal cancer: patient evaluation and pre-treatment staging. Surg Oncol 2001;10:103–11.
3. Wang KK, Wongkeesong M, Buttar NS. AGA technical review on the role of the gastroenterologist in the management of esophageal carcinoma. Gastroenterol 2005;128:1471–505.
4. NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers, version 2.2011. Available at: www.nccn.org.
5. Ibrahim NBN. Best practice no. 155: guidelines for handling esophageal biopsies and resection specimens and their reporting. J Clin Pathol 2000;53:89–94.
6. Gaur P, Sepesi B, Hofstetter WL, et al. Endoscopic esophageal tumor length: a prognostic factor for patients with esophageal cancer. Cancer 2011;117:63–9.

Endoscopic Ultrasonography

7. Dittler HJ, Siewar JR. Role of endoscopic ultrasonography in esophageal carcinoma. Endoscopy 1993;25:156–61.
8. Grimm H, Binmoeller KF, Hamper K, et al. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. Endoscopy 1993;25:224–30.
9. Heintz A, Hohne U, Schweden F, et al. Preoperative detection of intrathoracic tumour spread of esophageal cancer: endosonography versus computed tomography. Surg Endosc 1991;5:75–8.
10. Manzoni G. Endosonography and CT in the evaluation of tumour invasion. Recent Adv Dis Esophagus 1993;532–9.
11. Peters JH, Hoeft SF, Heimbucher J, et al. Selection of patients for curative or palliative resection of esophageal cancer based on preoperative endoscopic ultrasonography. Arch Surg 1994;129:534–9.
12. Takemoto T, Ito T, Aibe T, et al. Endoscopic ultrasonography in the diagnosis of esophageal carcinoma, with particular regard to staging it for operability. Endoscopy 1986;18(Suppl 3):22–5.
13. Ziegler K, Sanft C, Friedrich M, et al. Evaluation of endosonography in TN staging of oesophageal cancer. Gut 1991;32:16–20.
14. Francois E, Peroux J, Mourox J, et al. Preoperative endosonographic staging of cancer of the cardia. Adbom Imaging 1996;21:483–7.
15. Greenberg J, Durkin M, Van Drunen M, et al. Computed tomography or endoscopic ultrasonography in preoperative staging of gastric and esophageal tumors. Surgery 1994;116: 696–702.

16. Hordijk ML, Zander H, van Blankenstein M, et al. Influence of tumor stenosis on the accuracy of endosonography in preoperative T staging of esophageal cancer. Endoscopy 1993;25:171–5.
17. Kelly S, Harri KM, Berry E, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-esophageal carcinoma. Gut 2001;49:534–9.
18. Lightdale CJ, Kulkarni KG. Role of endoscopic ultrasonography in the staging and follow-up of esophageal cancer. J Clin Oncol 2005;23:4483–9.
19. Sakano A, Yanai H, Sakaguchi E, et al. Clinical impact of tumor invasion depth staging of esophageal squamous cell carcinoma using endoscopic ultrasonography. Hepato-Gastroenterol 2010;57:1423–9.
20. Crabtree TD, Yacoub WN, Puri V, et al. Endoscopic ultrasound for early stage esophageal adenocarcinoma: implications for staging and survival. Ann Thorac Surg 2011;91:1509–16.

Positron Emission Tomography

21. Rankin SC, Taylor H, Cook GJ, et al. Computed tomography and positron emission tomography in the pre-operative staging of oesophageal carcinoma. Clin Radiol 1998;53:659–65.
22. Choi JY, Lee KH, Shim YM, et al. Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. J Nucl Med 2000;41:808–15.
23. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000;18:3202–10.
24. Meltzer CC, Luketich JD, Friedman D, et al. Whole-body FDG positron emission tomographic imaging for staging esophageal cancer comparison with computed tomography. Clin Nucl Med 2000;25:882–7.
25. Kato H, Kuwano H, Nakijima M, et al. Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. Cancer 2002;94:921–8.
26. Wren SM, Stijns P, Srinivas S. Positron emission tomography in the initial staging of esophageal cancer. Arch Surg 2002;137:1001–6.
27. Yoon YC, Lee KS, Shim YM, et al. Metastasis to regional lymph nodes in patients with esophageal squamous cell carcinoma: CT versus FDG PET for presurgical detection—prospective study. Radiology 2003;227:764–70.
28. Van Westreenen HL, Westerterp M, Bossuyt PMM, et al. Systematic review of the staging performance of 18 F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol 2004;22:3805–12.
29. Walker AJ, Spier BJ, Perlman SB, et al. Integrated PET/CT fusion imaging and endoscopic ultrasound in the pre-operative staging and evaluation of esophageal cancer. Molec Imaging Biol 2011;13:166–71.
30. Choi J, Kim SG, Kim JS, et al. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET) and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc 2010;24:1380–6.
31. Shan W, Kollmannsberger CK, Wilson D, et al. The utility of PET/CT in the treatment management of gastroesophageal cancer (GEC): impact on staging and treatment decisions. J Clin Oncol 2010;28(Suppl 1).

Staging Laparoscopy

32. Chang L, Stefanidis D, Richardson WS, et al. The role of staging laparoscopy for intra-abdominal cancers: an evidence-based review. Surg Endosc 2009;23:231–41.