The clinical presentation of esophageal cancer in the United States and Europe has been changing, but unfortunately, esophageal cancer remains a dreadful disease. Patients with esophageal cancer commonly present (after a prolonged asymptomatic preclinical period) with advanced inoperable disease and a very poor prognosis. As described in Chapter 1, the majority of cases of esophageal cancer are of the squamous cell or adenocarcinoma types. Squamous cell carcinomas typically arise in the proximal to midesophagus, whereas adenocarcinomas are most commonly found in the distal esophagus.

Whereas historically, esophageal squamous cell carcinoma was the most common histologic type of esophageal cancer, more recent reports have shown that over the past few decades, there has been a marked increase in the incidence of adenocarcinomas of the distal esophagus, esophagogastric junction, and gastric cardia. This has had an important impact on the development of new approaches to screening, diagnosis, and prevention for this disease. As the predominant cell type of esophageal cancer is changing, so is the location of the tumor, from the upper and midesophagus more distally toward the esophagogastric junction. This may also play an important role in patterns of growth and spread and in the choice of the most appropriate and accurate staging modalities.

Patients with esophageal cancer most often present with symptoms of dysphagia, weight loss, and chest pain with or without swallowing. The diagnostic assessment usually begins with an upper-gastrointestinal barium radiographic study (barium swallow) or endoscopy. Once a diagnosis of esophageal cancer has been made, the patient should then undergo a complete staging assessment to evaluate the initial stage and extent of disease. Reliable and precise pretreatment clinical staging information is crucial to providing the patient with an accurate prediction of survival and to determining appropriate management options. Determination of extent of disease at initial presentation can identify those unfortunate patients who present with advanced unresectable stage IV disease and thus spare them potential additional morbidity and the cost of unnecessary surgery.

Given the recent significant increase in the incidence of adenocarcinomas of the esophagogastric junction, precise localization of tumors detected in or around this area may be helpful in better characterizing this entity and may be useful in developing better approaches to managing these tumors. These lesions may be more accurately defined as distal esophageal tumors, “true” esophagogastric-junction tumors, or proximal gastric tumors.

Precise pretreatment staging of esophageal cancer is very important in the initial evaluation and assessment of these patients. Since prognosis and management options are highly dependent on accurate staging, optimal pretreatment assessment and stratification by stage will allow these patients to be offered the most appropriate stage-specific treatment options. In addition, precise determination of extent of disease is essential for those patients who are being considered for an investigational treatment protocol.
This chapter will discuss approaches to the diagnosis and staging of esophageal cancer as practiced in the United States and specifically at a comprehensive cancer center. The various staging modalities that have been evaluated will be discussed, and we will present what we feel represents the state-of-the-art approach to the pretreatment staging of esophageal cancer. Both diagnosis and staging will be addressed together under each modality heading. Some of the methods presented have been shown to be highly sensitive and specific but are not yet widely available and thus cannot be considered the standard of care.

STAGING

Over the past century, esophageal cancer staging has evolved with the development of the international classification system of cancer staging. This system permits the accurate description of tumors to facilitate communication between clinicians caring for patients, to guide therapy, to predict prognosis, and to help standardize subject enrollment and evaluate results in investigative research.

The Tumor-Node-Metastasis System

The American Joint Committee on Cancer (AJCC) Staging and End Result Reporting was originally organized in 1959 with the support of medical, surgical, radiologic, and pathologic societies, the American Cancer Society, and the National Cancer Institute. Through the creation of task forces appointed to consider malignant neoplasms at different locations, the AJCC published the first comprehensive manual on cancer staging in 1977. Based on published data, the manual’s emphasis was on simplicity, practicality, and credibility.

These guidelines were originally created in parallel to those published by the International Union Against Cancer (Union Internationale Contre le Cancer [UICC]), which is a consortium of multiple national committees on tumor-node-metastasis (TNM) staging, including American, British, Canadian, French, German, Italian, and Japanese groups. The AJCC manual and the UICC guidelines have since been revised several times and have together become an internationally recognized system of cancer staging. The most recent edition of the AJCC cancer staging manual was published in 1997.3

According to the AJCC, esophageal cancer is classified according to the extent of the primary tumor (T) and the presence and extent of lymph node metastases (N) and distant organ metastases (M) (Table 2–1).

The primary tumor (T) stage is based on the depth of tumor invasion into and through the wall of the esophagus. Histologically, the esophageal wall consists of four distinct layers including the mucosa, submucosa, muscularis propria, and adventitia. In contrast to other segments of the luminal digestive tract, the esophagus does not have a serosal layer. The earliest pathologic (p) T stage of an esophageal cancer is classified as either pTis (ie, carcinoma in situ, for a squamous cell carcinoma) or high-grade dysplasia (for an adenocarcinoma). A pTis or high-grade dysplasia lesion is limited to the

<table>
<thead>
<tr>
<th>Table 2–1. TUMOR-NODE-METASTASIS STAGING SYSTEM FOR ESOPHAGEAL CANCER*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T)</td>
</tr>
<tr>
<td>TX  Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0  No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
</tr>
<tr>
<td>T1  Tumor invades lamina propria or submucosa</td>
</tr>
<tr>
<td>T2  Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3  Tumor invades adventitia</td>
</tr>
<tr>
<td>T4  Tumor invades adjacent structures</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
</tr>
<tr>
<td>NX  Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0  No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1  Regional lymph node metastasis</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
</tr>
<tr>
<td>MX  Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0  No distant metastasis</td>
</tr>
<tr>
<td>M1  Distant metastasis</td>
</tr>
<tr>
<td>Tumors of the lower thoracic esophagus</td>
</tr>
<tr>
<td>M1a Metastasis in celiac lymph nodes</td>
</tr>
<tr>
<td>M1b Other distant metastasis</td>
</tr>
<tr>
<td>Tumors of the midthoracic esophagus</td>
</tr>
<tr>
<td>M1a Not applicable</td>
</tr>
<tr>
<td>M1b Nonregional lymph nodes and/or other distant metastasis</td>
</tr>
<tr>
<td>Tumors of the upper thoracic esophagus</td>
</tr>
<tr>
<td>M1a Metastasis in cervical lymph nodes</td>
</tr>
<tr>
<td>M1b Other distant metastasis</td>
</tr>
</tbody>
</table>

*American Joint Committee on Cancer (AJCC) classification.
epithelial layer of the mucosa and represents noninvasive disease. A pT1 tumor represents the earliest stage of invasive disease and is a tumor that penetrates into the lamina propria (as can be seen in glandular epithelium associated with adenocarcinoma) or submucosa. A pT2 tumor invades deeper into the muscularis propria layer. A pT3 tumor penetrates through all esophageal wall layers and out into the adventitia. A locally advanced pT4 tumor invades adjacent mediastinal structures, such as the tracheobronchial tree, the pericardium, or the aorta.

Nodal staging for esophageal cancer is based on the presence or absence of lymph node metastases. Documentation of metastatic disease is based on spread to distant metastatic foci and (in certain cases) may be dependent on the primary tumor location within the esophagus.

The AJCC divides the esophagus into four regions to assist localization and staging. Localization affects tumor classification, lymphatic drainage, and appropriate management options. The very superior portion of the esophagus, the cervical esophagus, extends from the lower edge of the cricoid cartilage to the thoracic inlet, located approximately 18 cm from the incisor teeth. The remainder of the esophagus is divided into upper, middle, and lower thoracic portions. The upper thoracic esophagus extends from the thoracic inlet to the level of the tracheal bifurcation, approximately 24 cm from the incisors. The middle thoracic esophagus extends from the tracheal bifurcation to the level of the distal esophagus, approximately 32 cm from the incisors. The lower thoracic esophagus is the approximate 8 cm of distal esophagus and includes the intra-abdominal portion and the esophagogastric junction, approximately 40 cm from the incisors.

As preoperative staging has evolved over the past two decades, the system has been modified to represent the clinical (cTNM) and pathologic (pTNM) staging of tumors separately because histopathologic confirmation of stage may not always be available when treatment decisions are being made. According to the AJCC, the determination of the pathologic nodal staging for an esophageal tumor is generally based on the evaluation of six or more lymph nodes removed from the mediastinal lymphadenectomy specimen. Nearby lymph node groups are classified by the AJCC as either regional or distant nodes, depending on their relationship to the location of the primary esophageal tumor (Table 2–2). Lymph node involvement beyond the regional lymph nodes constitutes distant metastases. For example, when staging a tumor of the intrathoracic esophagus, involvement of the lymph nodes of the cervical or celiac axis would be considered to be metastatic (M1) disease.

The determination of M1 disease for an esophageal tumor may be based on the documentation of metastatic spread either to distant lymph nodes or to other solid organs. The most common sites for metastatic spread of esophageal cancer include the liver, lungs, bones, and the peritoneal cavity. Clearly, early determination of metastatic disease prior to the initiation of therapy is very important for determining operability, planning appropriate treatment, and determining potential eligibility for investigational treatment protocols.

The disease stage is determined according to the actual information for each of these T, N, and M factors (Table 2–3). For example, a tumor limited to the esophageal mucosa or submucosa and without lymph node or distant metastases (T1 N0 M0) represents stage I (early) disease whereas a tumor penetrating through the esophageal wall, invading an adjacent neighboring organ, and having regional

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**Table 2–2. CLASSIFICATION OF REGIONAL LYMPH NODES, BASED ON ESOPHAGEAL TUMOR LOCATION**

<table>
<thead>
<tr>
<th>Regional lymph nodes</th>
<th>Cervical esophagus</th>
<th>Scalene</th>
<th>Internal jugular</th>
<th>Upper cervical</th>
<th>Periesophageal</th>
<th>Supraclavicular</th>
<th>Cervical, NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathoracic esophagus (upper, middle, and lower)</td>
<td>Tracheobronchial</td>
<td>Superior mediastinal</td>
<td>Peritracheal</td>
<td>Carinal</td>
<td>Hilar (pulmonary roots)</td>
<td>Periesophageal</td>
<td>Perigastric</td>
</tr>
</tbody>
</table>

*American Joint Committee on Cancer (AJCC) classification. Adapted from Fleming ID, Cooper JS, Henson DE, et al., editors. AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven; 1997.*
lymph node involvement and distant metastases (T4 N1 M1) reflects stage IV (advanced) disease.

**Staging of Cancer of the Esophagogastric Junction**

The recent increase in the incidence of esophageal cancer has been associated with a rapid increase in the rate of adenocarcinomas of the distal esophagus and esophagogastric junction. However, physicians at different institutions (and even at the same institution) may not classify and approach tumors located in this region in the same way. Some physicians consider and treat these lesions as esophageal tumors whereas other physicians consider them to be proximal gastric cancers or even separate and distinct entities. To help to clarify this confusion, a recent consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) agreed that these tumors should be more clearly defined and classified so as to develop a more consistent approach to managing them. These groups have defined adenocarcinomas of the esophagogastric junction as tumors that “have their center within 5 centimeters proximal and distal of the anatomical cardia.” Furthermore, they have developed a classification system for three distinct types of tumors of the esophagogastric junction, based on the tumor’s apparent point of origin (Table 2–4).

The classification of adenocarcinomas located within the region of the esophagogastric junction into more distinct tumor types may significantly help in the ongoing study and understanding of this potentially heterogenous group of tumors. Whereas type I adenocarcinomas are believed to arise predominantly from specialized intestinal Barrett’s epithelium in the distal esophagus, there appears to be a low prevalence of intestinal metaplasia at or below the level of the gastric cardia in type II and III tumors (32% and 9%, respectively). In addition, the development of dysplastic changes in segments of intestinal metaplasia at or below the gastric cardia appears to be much less frequent an occurrence as compared to such changes seen in distal esophageal intestinal metaplasia. Furthermore, the differing behaviors of tumors of the esophagogastric junction may also be somewhat accounted for by different patterns of lymphatic spread. For tumors of the distal esophagus, main lymphatic pathways extend both cephalically into the mediastinum and caudally toward the region of the celiac axis, whereas tumors at or below the gastric cardia spread predominantly toward the regions of the celiac axis, the splenic hilum, and the para-aortic lymph nodes.

The more precise classification and staging of distal esophageal tumors at or close to the esophagogastric junction may help physicians gain a better understanding of these tumors’ natural history, patterns of spread, and expected response to therapy. This knowledge will be invaluable for the design of future clinical research protocols and treatment plans for managing patients with these tumors.

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**Table 2–3. CLASSIFICATION OF STAGE GROUPINGS FOR ESOPHAGEAL CANCER***

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T N0 M0</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T N1 M0a</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T N0 M1b</td>
</tr>
</tbody>
</table>

TNM = tumor-node-metastasis.

**Table 2–4. CLASSIFICATION* OF CANCERS ARISING IN THE REGION OF THE ESOPHAGOGASTRIC JUNCTION**

<table>
<thead>
<tr>
<th>Type I tumor</th>
<th>Adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus (ie, Barrett’s esophagus); may infiltrate the esophagogastric junction from above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II tumor</td>
<td>True carcinoma of the cardia; arises from the cardiac epithelium or short segments with intestinal metaplasia at the esophagogastric junction; often referred to as a “junctional carcinoma”</td>
</tr>
<tr>
<td>Type III tumor</td>
<td>Subcardial gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below</td>
</tr>
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</table>

METHODS FOR STAGING ESOPHAGEAL CANCER

Barium Radiography and Upper-Gastrointestinal Endoscopy

In a patient presenting with signs and symptoms suggestive of a possible esophageal malignancy, the diagnostic evaluation typically begins with either a single- or double-contrast barium swallow or an upper-gastrointestinal (UGI) endoscopy. Both modalities provide a good structural assessment of the esophageal lumen and the overlying mucosa. On barium study, abnormal radiographic findings that suggest possible esophageal malignancy include an intraluminal mass–like filling defect, asymmetric stricturing, and mucosal irregularities (Figure 2–1). On occasion, however, an esophageal cancer may even present radiographically as an apparent smooth circumferential stricture.

Figure 2–1.  A, Barium swallow demonstrates an “apple core” filling defect with associated luminal narrowing (arrow) resulting from a proximal esophageal cancer. B, Barium swallow demonstrates a distal esophageal tumor above a hiatal hernia (arrows). C, Barium swallow demonstrates circumferential narrowing (arrow) due to a distal esophageal tumor extending to the level of the esophagogastric junction. D, Barium swallow demonstrates distal esophageal wall infiltration (arrow) with minimal proximal dilatation caused by an esophageal carcinoma.
In one study of barium radiography in esophageal disease, four radiologists, blinded to the clinical history, reviewed the barium esophagrams from 35 patients (6 normal, 16 with benign esophageal disease, and 13 with small malignant tumors < 3.5 cm in diameter) and accurately diagnosed the small cancers in 73 percent of tumor cases. Of the false-negative evaluations, 21 percent were interpreted as cases of benign esophageal disease and 6 percent as normal. Thus, although barium radiography may be a relatively good initial study in the assessment of symptomatic patients, small malignancies may be missed. In addition, all patients with abnormal barium studies need further investigation by UGI endoscopy (with biopsies and cytologic brushings) to rule out a potential malignancy (Figure 2–2).

In the United States, UGI endoscopy is currently the procedure of choice for the initial diagnostic evaluation of symptomatic patients. When combined with endoscopic biopsy, UGI endoscopy serves as the primary screening tool for patients with the pre-
malignant condition of Barrett’s esophagus. Endoscopy not only permits the careful inspection and precise localization of any esophageal lesion but (most important) also allows targeted biopsies of abnormal areas, for a prompt and definitive histologic diagnosis.

Although barium radiography is a very good technique for diagnosing esophageal strictures in patients with dysphagia and although UGI endoscopy with biopsy and cytologic brushing is highly accurate in providing both a gross morphologic description and a histologic confirmation of malignancy, neither of these modalities alone is adequate to provide a complete preoperative staging assessment for esophageal malignancies. Although both techniques do provide an excellent structural examination of the esophageal lumen, neither modality can assess extraluminal disease. Thus, additional staging procedures are necessary (1) to provide accurate information regarding the depth of tumor invasion and the status of locoregional lymph nodes and (2) to assess for potential distant metastases.
Computed Tomography

Over recent years, computed tomography (CT) has become the method most used in the initial staging of newly diagnosed esophageal malignancies. Once an esophageal cancer has been confirmed by UGI endoscopy and biopsy, the patient’s extent of disease evaluation often begins with a CT of the chest and abdomen. Current high-resolution helical CT is helpful in identifying metastatic disease to such sites as the liver, lungs, mediastinal and retroperitoneal lymph node areas, and intraperitoneal areas.

Imaging with CT can usually identify medium to large esophageal masses by the evident thickening of the esophageal wall and by the proximal luminal dilation caused by the obstruction (Figure 2–3, A to D). However, CT cannot accurately determine the depth of tumor invasion within the esophageal wall because of its inability to define individual layers of wall tissue and often cannot even identify the presence of small T1 and T2 masses. The resolution of current CT can only help to confirm the presence of an esophageal mass and the suspicion of invasion of adjacent mediastinal organs (T4), but it does not permit the accurate classification of T stage.

Lymph node metastases are identified on CT scans by the finding of enlarged and rounded hypodense structures in the mediastinum, adjacent to the stomach, and in the retroperitoneum or porta hepatis (see Figure 2–3, E to G). Mediastinal lymph nodes >1.0 cm in maximum short-axis diameter in the transverse plane are considered to represent nodal metastases and can sometimes be seen by CT.

On a CT scan, distant metastatic disease to the liver or lung usually appears as one or more hypodense round areas within the liver or lung parenchyma that enhance after the administration of intravenous contrast material (see Figure 2–3, H and I). Peritoneal disease can be strongly suggested by the finding of a thickening of the omentum or peritoneal surfaces, irregular contours on the bowel surface, or the presence of ascites.

When reviewing the many studies in the literature that report on the sensitivity, specificity, and accuracy of CT in the preoperative staging of esophageal cancer, one must take into account that many of these studies were not prospective, used early-generation CT technology, were limited by small sample sizes, and may have used varying definitions of metastatic disease (ie, celiac lymph node involvement) in their assessments.

One study from Duke University evaluated CT in the staging of 76 esophageal cancer and esophagogastric cancer patients. The study compared the findings in these patients with the findings in 26 control patients without esophageal cancer and who had a normal mediastinum at surgery. A group of four radiologists were blinded to the patients’ underlying diagnoses; they identified the CT scans of all 26 controls as normal. In the 61 cancer patients who were explored, there was an 88 percent accuracy rate for the detection of both local mediastinal invasion (depth of tumor penetration) and distant abdominal metastases. In a separate cohort of 12 patients, CT was less accurate in staging tumors of the esophagogastric junction and yielded accuracy rates of 50 percent for the prediction of both mediastinal invasion and distant metastases. In this study, CT correctly staged 94 percent of patients with esophageal cancer and 42 percent of those with cancers of the esophagogastric junction. Some of the difficulty with CT in assessing the T stage of distal tumors in the region of the esophagogastric junction may be related to poor gastric distention and/or the presence of a hiatal hernia in this region.

In a study from Vanderbilt University, CT findings in 18 esophageal cancer patients were compared with their operative findings and surgical pathology. The accuracy of CT for localized tumor involvement was 77 percent whereas its accuracy was 94 percent for detecting direct aortic invasion and 88 percent for detecting tracheobronchial invasion. Computed tomography demonstrated a 72 percent accuracy for local lymph node involvement in mediastinal nodes; however, it was inaccurate for assessing distant lymph node metastases to intra-abdominal nodes in 11 of 18 patients. In 9 of these 11 cases (6 middle-thoracic and 3 lower-thoracic cases), positive celiac or left gastric nodes were found that were not detected by CT (false-negatives). In the other 2 cases, CT predicted abdominal lymph node involvement due to radiographically enlarged nodes (these were confirmed as being increased in size at surgery, but pathology failed to
Figure 2–3. Computed tomography of esophageal masses and metastatic spread. A, An early-stage cancer of the esophagogastric junction (same patient as in Figure 2–2A) (arrow indicates tumor). B, A small distal esophageal tumor (arrow). C, An obstructing tumor (arrow) of the distal esophagus. D, A polypoid mass (arrow) filling the esophageal lumen. E, Metastatic spread of esophageal cancer to a subcarinal lymph node (arrow). This was confirmed by endoscopic ultrasonography (EUS)–guided fine-needle aspiration (FNA). F, Metastatic spread of esophageal cancer to perigastric and celiac lymph nodes (arrow indicates lymph node). This was confirmed by EUS-guided FNA. G, A suspicious-appearing necrotic celiac lymph node (n) in a patient with an esophagogastric-junction cancer (T). H, A distal esophageal tumor (t) and two hypodense liver metastases (arrows). I, Two small peripheral left lung metastases (arrows) in a patient with an esophageal cancer (confirmed by thoracoscopy).
demonstrate metastatic disease [false-positives]). Finally, accuracy for distant metastatic disease (not including the celiac or left gastric nodes) was 94 percent. Overall, surgical findings altered the TNM staging in 8 (73%) of 11 patients.

Another study of CT from Washington University (St. Louis, MO) reviewed CT findings in 30 esophageal cancer patients and correlated those findings with surgical findings, in 28 of 30 of the patients, or autopsy findings.13 They reported findings similar to that of the Vanderbilt study, in that CT was demonstrated to be accurate for assessing tumor size, local invasion of the tracheobronchial tree, and metastatic disease to distant intra-abdominal lymph nodes (celiac and left gastric nodes) and solid organs (liver and adrenals), but to be inaccurate for assessing spread to regional periesophageal lymph nodes. Interestingly, most of the periesophageal nodes that were positive for metastatic tumor were not enlarged whereas the positive distant intra-abdominal nodes (M1 disease) were enlarged.

An important limitation of CT in staging esophageal tumors is its lack of sensitivity for accurately determining lymph node metastases (N stage). Also, an important factor, illustrated by both the Vanderbilt and Washington University studies, is that even normal-sized lymph nodes might contain microscopic foci of metastatic disease that is beyond the level of detection offered by CT.

In another retrospective study that assessed the accuracy of preoperative staging by CT in 33 patients with esophageal cancer, a comparison was made with surgical and pathologic findings.14 Of note, this cohort of patients was preselected for having no evidence of liver metastases, based on preoperative staging assessment. This study used the AJCC TNM classification for tumor staging. Enlarged lymph nodes seen by CT were defined as being > 1 cm in diameter. The study reported excellent rates for sensitivity (100%), specificity (97%), and accuracy (97%) for the detection of tracheobronchial invasion but found that CT was not as accurate for determining aortic involvement (with rates of 100% for sensitivity, 52% for specificity, and 55% for accuracy). Once again, CT fared poorly in determining regional lymph node metastases (celiac nodes were defined as regional nodes for distal esophageal tumors whereas they were defined as distant nodes for proximal and midesophageal tumors), demonstrating rates of only 61 percent for sensitivity, 60 percent for specificity, and 61 percent for accuracy. The authors perceived this to be related to the difficulty of CT in distinguishing periesophageal nodes from adjacent tumor. Computed tomography did somewhat better with distant lymph node involvement, showing sensitivity, specificity, and accuracy rates of 67 percent, 87 percent, and 85 percent, respectively. The sensitivity of CT for the detection of distant liver metastases could not be assessed in this study because the patients were preselected for not having liver metastases, but excellent specificity and accuracy rates (100% for both) were demonstrated for this modality. Overall, however, CT was able to correctly stage only 39 percent (13 of the 33 patients). The authors attributed the understaging by CT to its inability to accurately define depth of tumor invasion and to determine direct periesophageal mediastinal invasion.

An additional study that compared preoperative CT with surgical and pathologic findings in a cohort of 50 patients with esophageal cancer (University of Bern, Bern, Switzerland) found a very high accuracy rate for the detection of direct tumor invasion into the tracheobronchial tree (100%) for proximal thoracic tumors and for aortic involvement (95 to 100%) for proximal, middle, and distal tumors.15 However, CT assessment of intra-abdominal lymph node metastases demonstrated sensitivity, specificity, and accuracy rates of 57 percent, 100 percent, and 80 percent, respectively. The low sensitivity for the detection of distal intra-abdominal nodes thus limited the overall accuracy rates for CT staging to only 80 percent, 68 percent, and 65 percent for upper, middle, and lower thoracic esophageal tumors, respectively.

Despite the limitations of CT for assessing T stage and N stage, our institution continues to rely on chest and abdominal spiral CT with oral and intravenous contrast early in the evaluation to detect those patients with apparent metastatic disease. The identification of metastatic disease at presentation permits immediate triage of these patients to systemic therapy or investigational treatment protocols, with the avoidance of surgery. Patients in whom initial CT does not reveal metastatic disease then
undergo more advanced staging evaluations and are more appropriately offered curative surgical treatment or multimodality treatment protocols with curative intent.

**Endoscopic Ultrasonography**

Endoscopic ultrasonography (EUS) is a new and powerful imaging modality that has been developed over the past 15 years. It provides detailed imaging of the esophageal wall, nearby lymph nodes, and other adjacent structures. This modality makes use of the ability to introduce an ultrasound transducer directly into the gastrointestinal tract, thus bringing it into close proximity to the tumor. This eliminates the artifacts, created by intraluminal air and food, found in standard transcutaneous ultrasonography and CT.

Coupled with the development of new high-frequency ultrasound transducers, EUS permits the detailed evaluation of most areas of the gastrointestinal tract that are within the reach of standard endoscopes (Figure 2–4). While it does require sedation for most evaluations of the upper-gastrointestinal tract, EUS examinations are performed with the ease and comfort of most routine upper-gastrointestinal endoscopies. There is minimal risk, and EUS has proved to be well tolerated by most patients.

Many studies have shown that the resolution power of currently available EUS instruments provides superior assessment of almost all neoplasms of the esophagus, in addition to those involving the stomach, pancreas, and rectum. The 5-, 7.5-, and 12-MHz probes fitted on these scopes permit the assessment of microscopic tissue planes in the gastrointestinal tract, including the distinction of the normal multilayered histologic architecture of the mucosa, submucosa, muscularis propria, and serosa. The first wall layer is bright and corresponds to a border echo and the superficial mucosa; the second is dark and corresponds to the deep mucosa (including the muscularis mucosae); the third is bright and corresponds to the submucosa and the acoustical interface between the submucosa and muscularis propria; the fourth is dark and corresponds to the muscularis propria; and the fifth is bright and corresponds to the adventitial interface (Figure 2–5). In contrast to CT, the ability of EUS to distinguish wall layers allows it to provide a more accurate determination of depth of invasion by tumors; EUS thus has the potential to identify early-stage intramural disease.

On EUS, normal esophageal wall thickness is about 0.3 cm. On EUS, an esophageal malignancy appears as a hypoechoic abnormality within the wall, disrupting the normal wall echolayers. The lower-frequency transducers permit the evaluation of extramural disease (including local and regional lymphadenopathy and disease in adjacent organs such as the liver, spleen, and pancreas), in addition to the identification of ascites. Thus, EUS provides accurate assessment of depth of tumor invasion into and through the wall of the esophagus (Figure 2–6, A to C), detection of direct invasion into adjacent structures (see Figure 2–6, D and E), and identification of local lymph node metastases (see Figure 2–6, F and G), making it an ideal modality for determining clinical tumor stage according to the TNM method of cancer staging.

Computed tomography characterizes lymph nodes that are abnormally large (> 1 cm in diameter) as sus-
precocious for tumor involvement. In addition to size, EUS also uses additional criteria (such as rounded shape, homogeneous hypoechoic pattern, and sharply demarcated borders) to assess for metastatic lymph nodes.\textsuperscript{20,21} Nodes that appear to be benign on EUS may be > 1 cm in diameter but are typically elongated in shape, demonstrate a hyperechoic pattern with distinct cortical and medullary areas, and have less sharply demarcated borders.\textsuperscript{22}

In locoregional staging for esophageal cancer, EUS is superior to CT.\textsuperscript{23} This is due to its more precise imaging of distinct esophageal wall layers and its better ability to assess malignant nodal disease.

In numerous studies of preoperative endosonographic assessment of esophageal cancer by EUS as compared with surgical pathology in resected specimens, the accuracy of EUS for determining depth of tumor invasion (T stage) has been reported to range from 75 to 90 percent.\textsuperscript{24-34} In studies comparing EUS to CT for preoperative T staging, the accuracy of EUS ranges from 76 to 89 percent, and that of CT ranges from 49 to 59 percent.\textsuperscript{21,26,27} At our institution, a prospective comparative study of preoperative EUS versus dynamic CT for esophageal cancer in 50 patients demonstrated an accuracy of 92 percent for T staging with EUS and 60 percent for T staging with CT ($p < .0003$).\textsuperscript{19} A reasonable estimation of the overall accuracy of EUS for T staging, based on the now extensive published literature, is approximately 85 percent.\textsuperscript{23}

Although EUS is highly accurate for determining T stage, it may have some difficulty distinguishing between T1 (mucosal invasion) and T2 (submucosal invasion) tumors.\textsuperscript{35} Since T2 tumors are associated with a high risk (30 to 70%) of lymph node metastases, this differentiation between early-stage T1 and T2 disease is extremely important if one is to consider the option of minimally invasive endoscopic resection to treat T1 lesions.\textsuperscript{23} The accuracy of EUS for T staging superficial esophageal tumors has been reported to be 72 percent.\textsuperscript{34} The use of small catheters (which can be passed through the instrument channel of a standard endoscope) containing higher-frequency 20-MHz transducers that offer higher resolution of esophageal wall layers may help overcome this issue in the future.\textsuperscript{36}

For staging regional lymph node metastases (N stage), EUS has also been found to be more accurate than CT. The distinction between benign and malignant nodes is still a problem. Unlike CT, however, EUS not only can assess lymph node size but can also evaluate for additional criteria, such as well-circumscribed, rounded, and hypoechoic nodal characteristics, to predict metastatic nodal involvement. With CT, normal-sized lymph nodes containing occult microscopic metastases lead to understag-
Figure 2–6. Endoscopic ultrasonography (EUS) of esophageal tumors and lymph node metastases. A, A T1 esophageal tumor (T) extending into the submucosa. (arrow) in the same patient shown in Figure 2–2A. B, A T2 esophageal tumor extending into the muscularis propria (arrow) (T = tumor, Ao = aorta.) C, A T3 esophageal tumor infiltrating through all wall layers and out into the adventitia (arrows) (T = tumor, Ao = aorta.) D, A T4 esophageal tumor (T) invading the aorta (Ao) arrow indicates point of invasion. E, A T4 esophageal tumor (T) invading the trachea (Tr). Arrow indicates point of invasion. (Ao = aorta.) F, Locoregional lymph node metastases in a patient with an esophageal tumor. (n = periesophageal lymph node; Ao = aorta; LA = left atrium.) G, Lymph node metastases involving the perigastric (In) and celiac-axis (LN) lymph nodes in a patient with an esophageal tumor (confirmed by EUS-guided fine-needle aspiration).
ing whereas benign enlarged inflammatory nodes lead to overstaging.

In a study from the Cleveland Clinic, EUS features of lymph node metastases were assessed in 100 patients with esophageal cancer. When stringent criteria regarding lymph node size (> 1 cm), shape (round), border demarcation (sharp), and central echo pattern (homogeneous and hypoechoic) were applied, the sensitivity and specificity of EUS in detecting lymph node metastases were 89.1 percent and 91.7 percent, respectively; when all four features were present, accuracy of predicting lymph node metastases was 100 percent.

Multiple reports of preoperative EUS assessment of regional lymph node metastases in esophageal cancer demonstrate accuracy rates ranging from 70 to 90 percent. In comparing preoperative EUS to CT for N staging, the accuracy rates for EUS range from 72 to 80 percent whereas accuracy rates for CT range from 46 to 58 percent. In the study from our institution, CT demonstrated an accuracy of 90 percent in the staging of distant metastases, as compared to the 70 percent accuracy of EUS (p < .02). One potential advantage of EUS, as compared to CT, may be in the more accurate detection of M1 disease related to celiac node involvement.

Another limitation of EUS in the preoperative assessment of esophageal cancer is its inability to completely evaluate severely strictured esophageal tumors. As it is common for patients to present with advanced disease, there have been reports of high-grade malignant strictures in 20 to 44 percent of patients at initial presentation. These strictures may prevent passage of the echoendoscope and thus not allow a complete EUS staging examination.

For the detection of advanced (T4) disease, EUS has been demonstrated to be more accurate than CT in determining vascular invasion of the aorta or pericardium. In another series (a recent multicenter retrospective cohort study of 79 patients with stage T4 esophageal cancer as determined by preoperative EUS staging), EUS was more accurate than CT in determining T4 tumor invasion, with rates of 87.5 percent and 43.8 percent, respectively (p = .0002). The accurate preoperative determination of locally advanced T4 disease would clearly have an impact on the treatment options offered to the patients as the patients would no longer be initial surgical candidates but would perhaps (in some centers) be eligible for investigational protocols evaluating the usefulness of preoperative neoadjuvant chemoradiotherapy.

In esophageal cancer patients, EUS is not as accurate as CT in the detection of distant metastatic disease to such common sites as the liver, lungs, and peritoneal cavity. In the series from our institution, CT demonstrated an accuracy of 90 percent in the staging of distant metastases, as compared to the 70 percent accuracy of EUS (p < .02). One potential advantage of EUS, as compared to CT, may be in the more accurate detection of M1 disease related to celiac node involvement.

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An increased risk of perforation has been reported in patients with high-grade malignant strictures who undergo esophageal dilatation followed by EUS staging. In a study of 79 patients with esophageal cancer from the Cleveland Clinic, 26.6 percent presented with a high-grade malignant stricture; of these 21 patients, 24 percent developed an esophageal perforation as a result of the wire-guided dilatation or as a direct result of the EUS procedure. However, some other ultrasonographers have reported that such high-grade malignant strictures
can be safely dilated to allow passage of the echoendoscope just prior to the EUS staging procedure.\textsuperscript{33}

As a result of the experience of several esophageal perforations at our institution, we do not typically dilate high-grade malignant esophageal strictures during EUS staging. Instead, our approach in these cases is to perform a limited ultrasonographic staging examination at the upper extent of the tumor or to use the new wire-guided thin-caliber EUS scope (MH 908, Olympus), which easily passes even obstructing tumors to permit full staging without the increased risk.

**Endoscopic Ultrasonography–Guided Fine-Needle Aspiration**

Although both CT and EUS can detect enlarged and suspicious-appearing lymph nodes, both techniques are limited to morphologic characterization. The presence of enlarged and inflammatory lymph nodes in esophageal cancer can reduce the specificity of both imaging modalities for detecting lymph node metastases. An important recent advance in the field of endoscopic ultrasonography was the use of EUS-guided fine-needle aspiration (FNA) to sample submucosal lesions, nearby lymph nodes, and other adjacent structures throughout the gastrointestinal tract.

The linear-array ultrasonographic endoscope provides scanning that is oriented parallel to the long axis of the endoscope and is capable of tracking the passage of a biopsy needle (Figure 2–8). Ultrasonography-guided tissue sampling can thus be obtained by the passage of a cytology needle through the instrument channel of the scope and directly into the plane of the ultrasonographic image (Figure 2–9), permitting very precise positioning of the needle in lesions and nodes as small as 1 cm and as far as 5 cm from the wall of the gastrointestinal tract.

In a series from the University of California at Irvine, EUS-guided FNA was used to assess submucosal gastrointestinal tract lesions and extraluminal lymph nodes and masses in 38 patients.\textsuperscript{43} Of the 46 lesions that were sampled, 34 were extraluminal (8 peri-esophageal nodes, 1 mediastinal mass, 6 celiac nodes, 12 pancreatic masses, 1 perigastric mass, 1 liver mass, 1 periduodenal node, 2 pericolonic masses, 1 perirectal mass, and 1 perirectal node) and 12 were submucosal (8 gastric, 3 duodenal, and 1 esophageal). The overall diagnostic accuracy of FNA was 87 percent. In patients with known malignant lesions, the sensitivity and specificity of FNA was 91 percent and 100 percent, respectively. Celiac nodes were successfully sampled and diagnostic in 5 (83%) of 6 patients. In this study, EUS-guided FNA provided an initial tissue diagnosis of malignancy in 66 percent of cancer patients without a previous diagnosis, and the preoperative stage was changed for 44 percent of cancer patients. No complications were reported in this series.

Another group, from Indiana University, recently reported their experience with EUS-guided FNA in 288 patients with suspected gastrointestinal or mediastinal masses.\textsuperscript{44} They reported an 87 percent overall diagnostic accuracy, an 89 percent sensitivity, and a 100 percent specificity. Within their cohort, subgroup analysis demonstrated that FNA had an accuracy of 95 percent for the diagnosis of mediastinal lymph nodes (n = 43) and an accuracy of 85 percent for intra-abdominal lymph nodes (n = 13). Their immediate complication rate was 2 percent, all

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**Figure 2–8.** Pentax linear array endoscopic ultrasound scope with fine-needle aspiration (FNA) biopsy needle (arrow).
related to FNA of pancreatic lesions (2 with bleeding and 2 with pancreatitis).

Endoscopic ultrasonography–guided FNA is rapidly becoming an important tool in the staging of patients with gastrointestinal cancers and other malignancies (including primary lung cancer) and has both diagnostic and therapeutic implications.

**Bronchoscopy**

Bronchoscopy has been performed by some physicians as part of the initial preoperative staging assessment in patients presenting with esophageal tumors involving the cervical and upper thoracic esophagus to assess for direct tracheobronchial invasion indicative of locally advanced stage T4 disease. Bronchoscopy allows direct visualization and biopsy of any suspicious areas in the trachea or bronchi. If the bronchoscopic examination is positive for direct invasion, the patient is no longer a candidate for surgical resection and may be offered treatment with combined chemotherapy and radiation therapy or may be offered available investigational treatment protocols.

A recent prospective study from Munich, Germany, evaluated the diagnostic usefulness of bronchoscopy in the preoperative assessment of 116 patients with esophageal cancer, to determine direct airway invasion and resectability. The investigators compared the findings of 150 bronchoscopy examinations in this cohort with their intraoperative findings and surgical pathology. The overall accuracy of bronchoscopy (with brush cytology and biopsy) for determining direct tracheobronchial invasion in patients who were otherwise surgical candidates was 95.8 percent. In addition, the results of bronchoscopy and CT were discordant in 40 percent of the patients, with higher specificity and positive predictive value for bronchoscopy than for CT.

To date, we are not familiar with any comparative studies between bronchoscopy and EUS. At our institution, bronchoscopy is selectively used to assist in the staging of patients with cervical and upper thoracic esophageal malignancies.

**Magnetic Resonance Imaging**

The role of magnetic resonance imaging (MRI) in the preoperative staging of esophageal cancer is currently under investigation; however, results to date do not appear to demonstrate that MRI adds anything to CT imaging in this group of patients.

In a recent prospective study from Osaka, Japan, MRI and CT results were compared with surgical or autopsy findings in 31 patients with esophageal cancer. The accuracy rates of MRI and CT for detecting regional lymph nodes were 68 percent and 65 percent, respectively; for distant nodes, it was 77 percent for both modalities. As with CT, MRI has a decreased accuracy for detecting regional lymph node metastases because it misses normal-size lymph nodes with metastases. Overall, the accuracy rates for predicting resectability were similar, being 87 percent for MRI and 84 percent for CT.

In a study from Milan, Italy, investigators evaluated preoperative MRI in assessing direct locoregional and mediastinal lymph node spread in 32 esophageal cancer patients and compared the results with surgical pathology. They reported accuracy rates of 84 percent for the detection of mediastinal invasion, 87 percent for detecting tracheobronchial invasion, 91 percent for detecting aortic invasion, and 72 percent for detecting mediastinal lymph node metastases. Despite such good results, the overall accuracy rate for predicting resectability was only 75 percent for MRI in this study.
In an earlier study from the University of Michigan of the use of MRI for staging esophageal cancers, MRI and CT findings in 10 esophageal cancer patients were compared with their operative findings and surgical pathology, and with the MRI and CT assessments of 20 control patients with normal esophagi. 48 Both MRI and CT had low overall accuracy in staging (40% and 70%, respectively). The investigators attributed this poor accuracy primarily to the inability of MRI and CT to detect precise depth of tumor invasion (T stage).

Minimally Invasive Surgical Staging: Laparoscopy, Laparoscopic Ultrasonography, and Thoracoscopy

Over the past decade, improvements in anesthesia and laparoscopic techniques and instrumentation have fueled the development of minimally invasive surgery for the management of benign diseases as well as the diagnosis, staging, and treatment of many types of cancers. Adding to successful experiences with laparoscopic cholecystectomy, surgeons have worked to develop minimally invasive surgery for cancer management.

Initial studies of laparoscopy in the staging of upper-gastrointestinal malignancies indicate that laparoscopy is highly sensitive for detecting metastatic disease, particularly the identification of small tumor implants on the peritoneal surfaces and liver that are not detected by conventional imaging modalities (Figure 2–10, A to C). Laparoscopy also permits the evaluation of lymph nodes for metastatic disease (see Figure 2–10, D). In a study from our institution, laparoscopic exploration in 110 patients with gastric cancer accurately staged 94 percent of patients for metastatic disease, with a sensitivity of 84 percent and a specificity of 100 percent. 49 The prevalence rate of metastatic disease is 37 percent in all patients who had been preselected by an abnormal CT scan.

A large study of laparoscopic staging in 280 patients with cancer of the esophagus and 89 patients with gastric cardia cancer demonstrated metastatic disease to the liver, peritoneum, omentum, stomach, and lymph nodes in 52 patients (14%) and to the gastric wall or regional lymph nodes in 36 patients (9.7%). 50 The rate of false-negative findings by laparoscopy in this series was 4.4 percent (2.8% for liver metastases, 1.2% for peritoneal seeding, and 0.4% for omental implants).

A recent advance in minimally invasive surgical staging is the addition of laparoscopic ultrasonography (LUS) in the evaluation of patients with upper-gastrointestinal malignancies (Figure 2–11). One study from Denmark evaluated EUS, laparoscopy, LUS, CT, and transcutaneous ultrasonography in patients with upper-gastrointestinal malignancies. 51 Forty-four patients with esophageal, gastric, and pancreatic cancer were studied preoperatively, and the results of these examinations (which were used to determine the resectability and curability of the tumors, based on TNM staging) were compared to findings at laparotomy. The reported accuracy for predicting resectability and curability was 91 percent for EUS, 64 percent for CT and ultrasonography combined, 68 percent for laparoscopy alone, 95 percent for LUS alone, and 95 percent for EUS and LUS combined.

In a study from the University of Amsterdam, the Netherlands, laparoscopy and LUS was performed in 233 patients with upper-gastrointestinal tumors (tumors of the esophagus, gastric cardia, liver, bile duct, and pancreas) believed to be surgically resectable after conventional preoperative staging. 52 Of the 64 patients with esophageal or gastric cardia cancers (preoperative evaluation included EUS), findings at laparoscopy prevented laparotomy in 4 patients (6%) because of the detection of unsuspected metastatic disease.

The application of laparoscopic techniques and instruments in the chest has resulted in advances in video-assisted thoracoscopy and in the application of thoracoscopy to the surgical staging of esophageal cancer. Thoracoscopy allows the direct visualization of the entire thoracic esophagus, the accurate assessment of tumor invasion into the adventitia and adjacent mediastinal structures, and the evaluation and sampling of regional lymph nodes for histology. 53 It can also detect occult pleural and pulmonary metastases. However, to assess for intra-abdominal disease (including liver metastases and peritoneal implants) and to sample perigastric and celiac lymph nodes, thoracoscopy must be combined with diagnostic laparoscopy. Furthermore, tumors of the esopha-
gastrogastric junction also require a combined laparoscopic approach to completely evaluate the inferior aspect of the primary tumor and to assess for intrabdominal disease.

A study from the University of Pittsburgh compared the accuracy of EUS with thoracoscopic and laparoscopic staging in evaluating lymph node metastases in 26 patients with surgically resectable esophageal cancer (24 patients with adenocarcinoma of the esophagogastric junction and 2 with squamous cell carcinoma of the midthoracic esophagus). In 5 patients (19%), complete assessment by EUS was not possible due to high-grade malignant stricture that did not allow passage of the scope; in 3 of these 5 patients, laparoscopy and thoracoscopy revealed N1 disease. Endoscopic ultrasonography detected N1 disease in 13 patients, and laparoscopy and thoracoscopy confirmed N1 disease in 12 (92%) of these 13 patients. The sensitivity and specificity of EUS for nodal evaluation were 65 percent and 66 percent, respectively. The sensitivity of EUS decreased to 44 percent when EUS was used for detecting occult metastatic disease in lymph nodes less than 1 cm in diameter. No disease staged as T3 by EUS was up-

Figure 2-10. A, Solitary liver metastasis, shown at laparoscopy. (M = liver metastasis; L = liver; G = grasper [instrument diameter = 0.3 cm]; D = diaphragm, TL = triangular ligament.) (×15 original magnification.) (Courtesy of Dr. Tracey Weigel.) B, Multiple small metastases involving the right lobe of the liver, shown at laparoscopy. Arrow indicates falciform ligament. (M = liver metastasis; L = liver.) (×15 original magnification.) (Courtesy of Dr. Tracey Weigel.) C, Multiple small (<0.1 cm in diameter) metastatic nodules studding the peritoneal surface in the region of the gastrohepatic ligament, shown at laparoscopy. Arrows indicate instrument port (port diameter = 0.5 cm). (M = metastatic peritoneal nodule; S = stomach; D = diaphragm.) (×15 original magnification.) (Courtesy of Dr. Tracey Weigel.) D, Metastatic disease to a left gastric artery lymph node, shown at laparoscopy. Black arrows indicate lymph node, white arrows indicate left gastric artery. (RP = retroperitoneum; RC = right crus of diaphragm; D = diaphragm.) (×15 original magnification.) (Courtesy of Dr. Tracey Weigel.)
staged to T4 by laparoscopy or thoracoscopy. However, whereas EUS did not detect distant metastases in any patient, laparoscopy identified M1 disease due to liver metastases in 4 (15%) of 26 patients.

In a more recent study from the Pittsburgh group, staging with laparoscopy and thoracoscopy was compared to conventional staging with CT and EUS in 53 patients with esophageal cancer. In this cohort, after CT and EUS staging (1 case as carcinoma in situ, 1 case as stage I, 23 as stage II, 20 as stage III, and 8 as stage IV disease), laparoscopy and thoracoscopy changed the stage in 17 patients (32%), down-staging disease in 10 patients and up-staging disease in 7 patients.

In a study from the University of Rotterdam ‘Dijkigt’ in the Netherlands, conventional preoperative imaging (including EUS) was compared with laparoscopy and LUS in staging 40 patients with esophageal cancer and 20 patients with gastric cardia cancer. In 1 (2.5%) of 40 patients with esophageal cancer, laparoscopy detected M1 disease due to a liver metastasis. Of the 20 patients with gastric cardia cancer, laparoscopy detected 4 (20%) with M1 disease (peritoneal seeding in 3 and omental metastases in 1) whereas LUS detected an additional 4 (20%) (liver metastasis in 2 and celiac lymph node metastasis in 2), demonstrating the detection of otherwise unsuspected M1 disease in 8 (40%) of the 20 patients by laparoscopy and LUS combined.

Minimally invasive surgical staging with thoracoscopy and laparoscopy for patients with cancers of the esophagus and the esophagogastric junction offers the ability to detect a small but significant number of patients with distant M1 disease that would not be detected by conventional preoperative imaging studies. In addition, direct tissue sampling of lymph node and peritoneal lesions increases the specificity for finding such abnormalities. The improved accuracy of preoperative staging offered by these procedures may improve the selection of patients for surgery and increase the curative resection rates at some hospitals while reducing the number of unnecessary laparotomies.

There are, however, limitations and risks related to thoracoscopy and laparoscopy staging procedures. Both procedures are invasive and are performed in an operating room under general anesthe-

Figure 2–11. Laparoscopic ultrasonography (LUS) of a liver metastasis in a patient with an esophagogastric-junction tumor (M = metastasis; L = liver.) (Courtesy of Dr. Tracey Weigel.)
also reported its operating-room times and the length of hospital stays. The average operating-room time was 4.2 hours (a range of 1 to 6 hours), and the average length of hospital stay was 3.4 days (a range of 1 to 11 days). The authors did note, however, that both of these times decreased during the course of their study; for the last 10 patients, the average operating-room time was 3.6 hours and the average hospital stay was 1.8 days.

A potential role for minimally invasive preoperative staging is to complement the use of EUS or CT for properly stratifying (on the basis of optimal staging) those patients who are candidates for therapy in the context of a clinical trial.

**Positron Emission Tomography**

Positron emission tomography (PET) is a relatively new imaging modality that makes use of the ability to visualize tumors by virtue of differences in metabolic activity between tumor and normal tissue. Tumor tissues are generally more metabolically active than normal non-neoplastic tissues and have increased glycolytic activity. The administration of \(^{18}\)F-fluoro-2-deoxy-D-glucose (FDG) to an individual with cancer therefore results in a greater uptake of FDG by the tumor tissue than by most normal tissues. Once FDG enters cancer cells, it is phosphorylated and trapped within the cells, thereby rendering the cells radioactive. This enables cancerous tumors to be detected by the radioactivity emitted from the trapped radiolabeled FDG. Tumors of sufficient size and with a sufficient uptake of FDG are therefore readily detected by using a gamma camera. Through the technique of tomographic imaging, whole-body PET can provide detailed images that can be superimposed on conventional CT scans, correlating the areas of increased radioisotope activity with anatomic sites of disease (Figure 2–12).

Imaging by PET is currently under investigation to determine its potential role in preoperative staging for esophageal cancer. In a study from the University of Pittsburgh, PET was performed in 35 patients with esophageal cancer, and results were compared with surgical findings and pathology.\(^57\) For the detection of locoregional lymph node metastases, PET demonstrated a sensitivity of 45 percent, a specificity of 100 percent, and an overall accuracy of 48 percent. There were 11 false-negative PET study results for small (mean diameter of 0.52 cm), intracapsular locoregional nodal metastases. For detecting distant metastases, PET showed a sensitivity of 88 percent, a specificity of 93 percent, and an accuracy of 91 percent. It detected nine sites of distant metastases not identified by conventional scanning. One false-negative PET study result occurred in a patient with a small (0.2 cm) liver lesion. The investigators concluded that current PET technology was not accurate enough to detect small locoregional nodes. Its potential benefit in staging patients with esophageal cancer may be its ability to identify unsuspected distant metastases, which it accomplished in up to 20 percent of study patients who were found to be falsely negative for M1 disease by conventional preoperative staging modalities.

In a prospective study from Amsterdam, PET was evaluated in 26 patients with esophageal and esophagogastric cancers and was compared with CT and surgical findings, primarily to determine its ability to stage metastatic disease.\(^58\) The rate of visualization of the primary tumor was 81 percent with CT and 96 percent with PET. Neither CT nor PET was good at determining the depth of wall penetration (T stage). For N staging, the sensitivity of CT was 38 percent, its specificity was 100 percent, and its overall accuracy was 62 percent whereas PET showed a sensitivity of 92 percent, a specificity of 88 percent, and an accuracy of 90 percent. In regard to determining M stage, CT detected distant metastases in 5 patients, with one false-positive liver hemangioma, and PET detected distant metastases in 8 patients, with one false-positive in the supraclavicular area (that was not confirmed on subsequent cytology assessment). The overall diagnostic accuracy for determining resectability was 65 percent for CT and 88 percent for PET.

In a more recent report, the investigators at the University of Pittsburgh updated their data to describe their prospective experience with 100 PET scans in 91 patients with esophageal cancer.\(^59\) They compared PET with CT, bone scan, and surgical findings. In this study, a total of 70 distant metastases were confirmed in 39 patients by minimally invasive surgical staging or clinical correlation.
Positron emission tomography identified 51 metastases in 27 of the 39 cases, demonstrating a sensitivity of 69 percent, a specificity of 93.4 percent, and an accuracy of 84 percent, whereas CT detected only 26 metastases in 18 of the 39 cases, indicating a sensitivity of 46.1 percent, a specificity of 73.8 percent, and an accuracy of 63 percent \( (p < .01) \).

Another recent prospective comparison of PET with conventional staging modalities for preoperative assessment of esophageal cancer was reported from Leuven, Belgium.60 The authors evaluated 43 patients with esophageal cancer and 31 with esopha-gogastric cancer and compared their findings with CT and EUS findings. Positron emission tomography detected the primary tumors in 70 (95%) of 74 patients and gave false-negative results in 4 patients with early-stage T1 lesions. In the 34 patients (46%) with advanced (stage IV) disease, PET demonstrated a higher accuracy rate (82%) for diagnosing stage IV disease than did the combination of both CT and EUS, which had an accuracy of 64 percent \( (p = .004) \). Positron emission tomography also demonstrated additional benefit in 16 patients (22%) by up-staging 11 patients (15%) and by down-staging 5 patients (7%). In the 39 patients (53%) who underwent a 2- or 3-field lymphadenectomy, lymph node metastases were detected in 21 local and 35 regional or distant nodes. For the detection of local lymph node metastases, PET demonstrated a lower sensitivity (33% as compared to EUS at 81% \( [p = .027] \)) but a higher, although not statistically significant, specificity (89%, compared to 67% for EUS). For the detection of regional and distant nodal metastases, PET demonstrated a sensitivity of 46 percent, similar to that of the combination of CT and EUS (43%) \( (p = \text{not significant}) \); however, its specificity was 98 percent, compared to 90 percent for the combination of CT and EUS \( (p = .025) \).

Positron emission tomography for staging these cancers remains investigational, but further study may prove it to be a useful adjunct as a preoperative staging tool.

**Computed Tomography of the Head and Radionuclide Bone Scan**

Some clinicians routinely perform CT of the head and radionuclide bone scan imaging in patients...
with newly diagnosed esophageal carcinoma, on the rationale that it is crucial to rule out distant metastases (M1 disease) in these patients.

In a study from the University of Michigan, the records of 838 patients with esophageal cancer were retrospectively reviewed to assess the frequency and location of metastatic disease at initial presentation. In this cohort, 147 patients (18%) had M1 disease. In 110 (75%) of these 147 patients, distant metastatic disease was detected preoperatively by conventional imaging or clinical examination; in 102 (69%) of the 147 patients, this was detected by CT of the chest or abdomen. The most common site of detected distant metastases was in the intra-abdominal lymph nodes (45%), followed by the liver (35%), lungs (20%), cervical/supraclavicular nodes (18%), bone (9%), adrenals (5%), peritoneum (2%), and brain (2%), and by the stomach, pancreas, pleura, skin/body wall, pericardium, and spleen (each 1%). In this study, neither bone scan nor CT of the head detected unsuspected metastatic disease in any case staged as M0 by chest and abdominal CT.

In a prospective study that compared several different imaging modalities for the preoperative staging assessment of 33 patients with esophageal cancer, radionucleotide bone scan detected a metastatic lesion in one case that was missed by CT. Thus, this study recommended the use of bone scan, along with CT and bronchoscopy, in the standard preoperative evaluation of these patients.

**SUMMARY**

To provide a reproducible and practical means of categorizing the extent of disease, the staging of malignancies has become internationally standardized. Accurate preoperative staging of a newly diagnosed esophageal cancer is very important in the planning of treatment but becomes most important in centers where treatment may vary according to stage. In the past, staging was performed surgically, but recent technologic advances in radiographic and minimally invasive imaging now permit accurate nonsurgical staging in most patients with esophageal cancer.

Following a tissue confirmation of malignant disease (most commonly performed by UGI endoscopy with biopsy), we recommend that the initial staging evaluation be performed by CT of the chest and abdomen, primarily to rule out distant metastatic disease. In the absence of radiographic evidence of metastatic disease found by CT, EUS should be performed to determine the depth of tumor invasion into the esophageal wall and to identify any locoregional lymph node metastases. Although still investigational, PET seems to add important information about distant metastatic disease undetected by CT and EUS, and this modality may someday replace CT in the staging of gross distant metastases. Bronchoscopy remains important in the evaluation of upper and midthoracic esophageal tumors, to rule out locally advanced stage T4 disease due to direct tracheobronchial invasion, but this could be obviated by the use of EUS. The role of laparoscopy in staging tumors of the esophagogastric junction is currently being investigated, but its role in the assessment of cervical, upper thoracic, and middle thoracic esophageal cancer is minimal. Currently, there does not seem to be a role for bone scan, CT of the head, or MRI.

At this time, we feel that EUS provides accurate locoregional T and N staging in esophageal and esophagogastric-junction tumors, plays a vital role in the triage of patients to surgery or neoadjuvant chemotherapy protocols, but remains complementary to the use of CT. The recent addition of EUS-guided FNA offers a significant improvement in the ability of EUS to accurately determine metastatic lymph node involvement. Further improvements in PET are likely to result in greater reliance on this modality for preoperative staging.

The approach to the staging of esophageal cancer at different institutions varies because of the limited availability of different imaging modalities such as EUS and PET. However, as more individuals are trained in EUS, and as the approach to treating esophageal cancer becomes more tailored to stage, EUS and PET are likely to become the standards in the staging of patients with esophageal cancer.

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