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Staging esophageal cancer[1]

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Abstract

Accurate staging of disease is necessary in patients with newly diagnosed esophageal cancer in order to prompt appropriate curative or palliative therapy. Computed tomography (CT) may be used to evaluate for local spread into adjacent structures (T4 disease) and to diagnose distant metastases (M1). Endoscopic ultrasonography (EUS) is the modality of choice for distinguishing T1 tumors from higher stage lesions and for detecting and sampling regional lymph nodes (N1 disease). Positron emission tomography (PET) scanning is most helpful for detecting previously occult distant metastases. Optimal staging generally requires a multimodality approach.

Keywords: *Esophageal cancer; neoplasm staging; computed tomography; FDG-PET scanning.*

Introduction

Accurate staging of disease in patients with esophageal carcinoma is necessary in order to prompt appropriate curative or palliative therapy. Different imaging modalities have different strengths and weaknesses in evaluating the various features of the disease, and a combined imaging approach is usually necessary for optimal assessment.

Anatomy and epidemiology

The esophagus is divided into four anatomic regions for reporting and staging purposes. The cervical portion extends from the cricoid cartilage to the thoracic inlet. The thoracic esophagus extends from the thoracic inlet to the gastroesophageal junction and is divided into three regions: upper, mid and lower. The upper thoracic esophagus extends from the thoracic inlet to the carina; the mid-thoracic esophagus from the carina to the diaphragm; and the lower thoracic and abdominal esophagus (which measures approximately 3 cm in length) from the diaphragm down to and including the gastroesophageal junction[2,3]. The cervical esophagus ends approximately 18 cm from the incisors; the upper, mid and lower thoracic esophagus end at approximately 24, 32, and 40 cm from the incisors, respectively.

The esophageal wall consists of four layers: mucosa, submucosa, muscularis propria, and adventitia. There is no serosa to serve as a barrier between the esophagus and the surrounding structures; lack of a serosa facilitates tumor spread through the esophageal wall into adjacent structures. A rich plexus of lymphatics encircles the entire length of the esophagus, enabling lymphatic spread of tumor to cervical, mediastinal and upper abdominal lymph nodes. An experimental study showed that dye injected into the esophageal wall at one level may drain to lymph nodes at all other levels of the esophagus in some patients, and also frequently drains directly into the thoracic duct, potentially leading to hematogenous metastases[4]. Because of these features, 'skip metastases' are not uncommon, meaning that distant sites may

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be involved without involvement of lymph nodes close to the primary tumor.

Advanced disease is frequently seen at initial clinical presentation. Only about 24% of esophageal cancer cases are diagnosed while the cancer is still confined to the primary site (localized stage); 30% are diagnosed after the cancer has spread to regional lymph nodes or directly beyond the primary site; 30% are diagnosed after the cancer has already metastasized (distant stage); for the remaining 16% the staging information is unknown[5].

Staging classification

The International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) have staged esophageal cancer using the TNM system whereby T categorizes the depth of invasion into or through the esophageal wall, N the status of regional lymph nodes, and M metastases to distant sites (Table 1)[2]. Stage groupings of the TNM system, based on prognosis, are shown in Table 2[2,3].

Regional lymph nodes are determined according to the level of the primary esophageal tumor[2]. For example, regional sites for cervical esophageal primaries include the cervical, internal jugular, scalene, supraclavicular, and periesophageal lymph nodes. The regional sites for upper, middle, and lower intrathoracic esophageal tumors are periesophageal and subcarinal nodes, and for gastroesophageal junction tumors are lower periesophageal, diaphragmatic, pericardial, left gastric, and celiac nodes. Lymph node metastases to any other sites constitute distant metastatic (M1) disease.

For upper thoracic and for lower thoracic primary tumors only, M1 is broken down into M1a and M1b categories (cervical and mid-thoracic primary tumors have no such breakdown) (Table 3). Tumor spread to cervical lymph nodes from an upper thoracic primary neoplasm falls into the M1a category; spread to any other non-regional lymph nodes represents M1b disease. Similarly, celiac axis lymph node metastases confer M1a status upon primary tumors located in the lower thoracic esophagus, whereas spread to any other non-regional lymph nodes represents M1b disease. Patients with M1a disease have a better prognosis than those with M1b disease and are generally felt to represent surgical candidates.

Patients with newly diagnosed esophageal cancer often present with distant metastases. In a series by Quint *et al.*, 18% of patients presented with M1 disease. Distant metastases were most commonly diagnosed in upper abdominal lymph nodes (45%), followed by liver (35%) and lung (20%). Less commonly, distant metastases were seen in cervical/supraclavicular lymph nodes, bone, adrenal glands, peritoneum, brain, pericardium, pleura, stomach, pancreas, spleen, soft tissues and kidney[6].

Primary tumor (T) staging

Endoscopic ultrasound (EUS) is the major modality used to stage the primary tumor and is particularly helpful in distinguishing T1 lesions from T2–4 lesions[7]. This distinction may be crucial for treatment planning: at some centers, T1 lesions are treated with endoscopic therapy or with esophagectomy alone, whereas higher stage lesions may be treated with neoadjuvant chemoradiation, followed by esophagectomy.

Unlike EUS, computed tomography (CT) is incapable of distinguishing the layers of the esophageal wall in order to determine the depth of tumor invasion, i.e. T1 vs. T2 disease. Gross tumor invasion into mediastinal fat may be diagnosed at CT (T3 disease), manifesting as abnormal soft tissue in the mediastinal fat, with or without obliteration of fat planes between the esophagus and adjacent mediastinal structures[8]. However, most

Table 1   The TNM system

Primary tumor (T)

T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to mucosa or invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures

Regional lymph nodes (N)

N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Table 2   Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVa	Any T	Any N	M1a
Stage IVb	Any T	Any N	M1b

Table 3   M categories

Tumors of the upper thoracic esophagus

M1a	Metastasis in cervical nodes
M1b	Other distant metastasis

Tumors of the mid-thoracic esophagus

M1a	Not applicable
M1b	Non-regional lymph nodes and/or other distant metastasis

Tumors of the lower thoracic esophagus

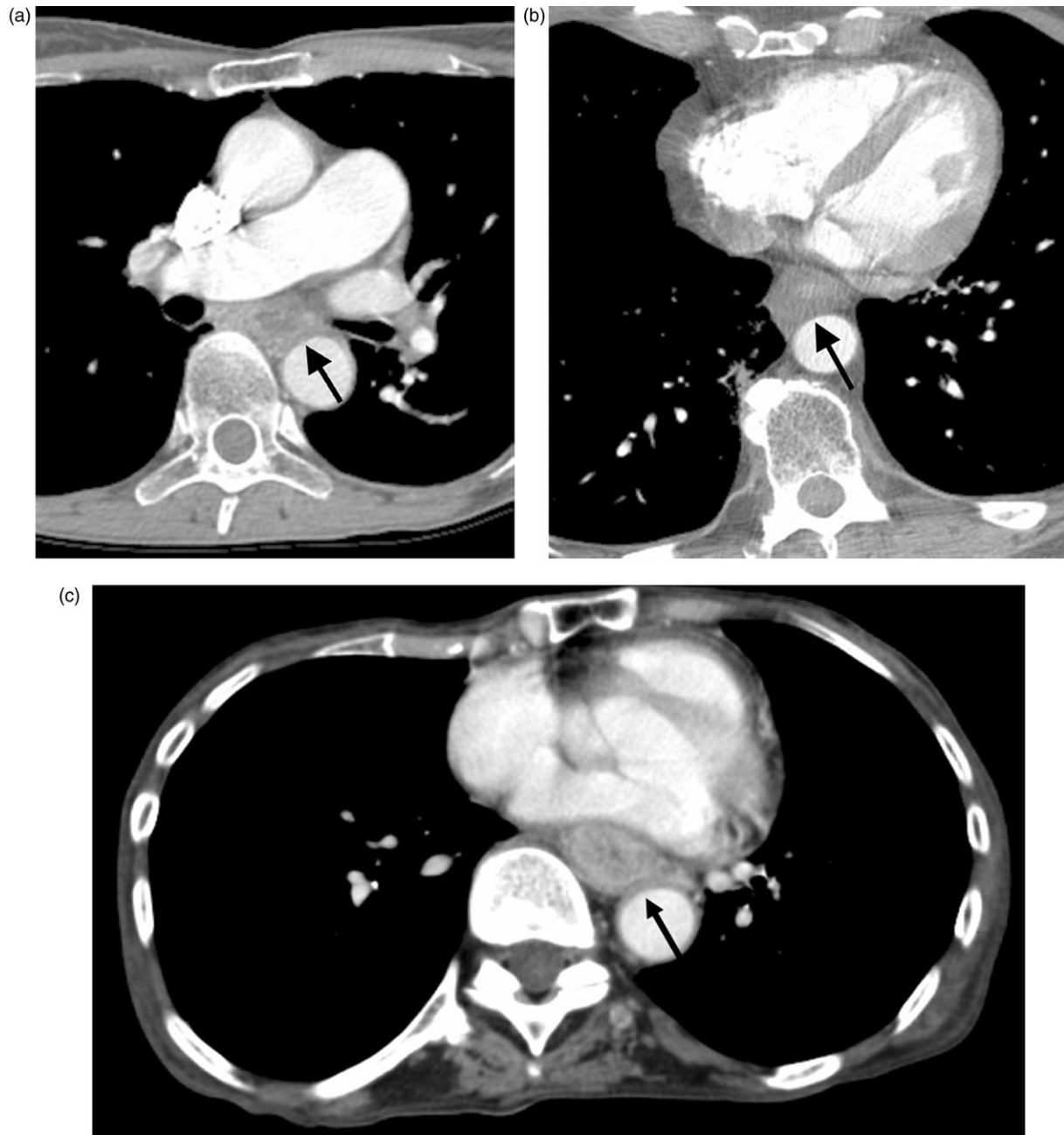|	
M1a	Metastasis in celiac lymph nodes
M1b	Other distant metastasis

Figure 1   **Three patients with broad loss of the fat plane between the esophagus and the aorta (arrows). At surgery, there was no aortic invasion in (A) (squamous cell carcinoma) or (B) (adenocarcinoma), however aortic invasion was present in (C) (squamous cell carcinoma).**

investigators believe that CT is unreliable in detecting or excluding minimal fat invasion. On the other hand, one recent study found that distention of the esophagus with effervescent granules and post-processing the data with multiplanar reconstructions did lead to accurate assessment of extraesophageal tumor spread[9]. In general, the major role of CT in evaluating the T stage is to detect local tumor invasion into adjacent structures (T4 disease), suggesting inoperability. The presence of a fat plane between an esophageal tumor and an adjacent mediastinal structure (e.g. central airway, aorta,

pericardium) is an accurate indicator of lack of invasion of the structure. However, the converse is not necessarily true: lack of a fat plane is not diagnostic for invasion (T4 disease), in either cachectic patients or in those with normal body weight. Moreover, adjacent fat planes are sometimes obscured in patients who have undergone radiation therapy.

Deep invasion of the aortic wall is unresectable, whereas invasion limited to the adventitia is generally resectable[10]. Various CT techniques and criteria have been suggested to help diagnose or exclude unresectable

aortic invasion. An older study reported that contact between the mass and the aorta over more than 90 degrees of the aortic circumference was 80% accurate for diagnosing aortic invasion[11]. Another study found

Figure 2 Esophageal adenocarcinoma causing narrowing of the left mainstem bronchus at CT (arrow). Airway invasion was confirmed bronchoscopically.

that obliteration of the normal fatty triangle located between the spine, esophagus and aorta showed a sensitivity of 100% and specificity of 82% in this setting[12]. Unfortunately, however, these criteria do not appear to be reliable in clinical practice, and other studies have reported lower accuracies; for example, Lehr *et al.* found sensitivity, specificity and accuracy figures of 6%, 85% and 58%, respectively[13]. Thus, suspected aortic invasion is difficult to prove preoperatively, and in most cases, this determination is a surgical one (Fig. 1). Fortunately, however, unresectable aortic invasion is a very rare finding.

Unlike aortic invasion, tumor spread into the central airways is not rare, and should always be considered in a patient with an upper or mid-thoracic primary tumor. Flattening or indentation of the wall of the trachea or left main stem bronchus by an adjacent esophageal mass (particularly on inspiratory images) is suggestive of invasion, although this finding may be caused by simple mass effect upon the membranous portion of the airway, without invasion (Fig. 2). Frank abnormal soft tissue in the lumen of the airway or a fistula between the esophagus and the airway are specific, if extremely uncommon, findings of airway invasion. Overall the reported sensitivity for tracheobronchial involvement ranges from 31 to 100%, specificity from 68 to 98% and accuracies range from 74 to 97%[14]. Imaging features suggesting invasion should be further evaluated with bronchoscopy and confirmed with biopsy.

Pericardial invasion is suggested by pericardial thickening and/or effusion, obliteration of the fat plane between
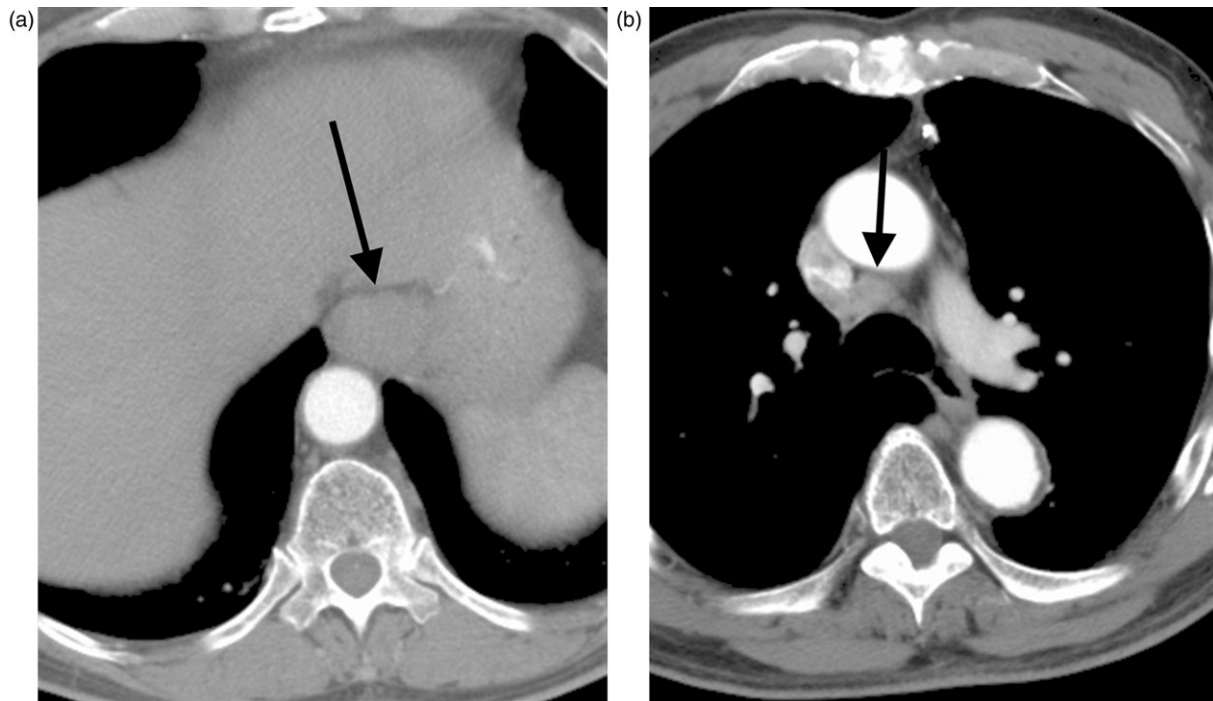

Figure 3 Distal esophageal adenocarcinoma (arrow, A) and right paratracheal lymph node enlargement (arrow, B), suggesting regional nodal metastatic disease. Lymph node biopsy, however, revealed no malignancy.

the tumor and the pericardium, or mass effect upon the pericardium[8,15]. Extensive invasion is unresectable and minimal invasion may be resectable. Similarly, extensive invasion of the diaphragm may also be unresectable.

Although positron emission tomography (PET) is incapable of primary tumor staging, due to its poor spatial resolution, it has been reported that the maximum SUV of the primary tumor correlates well with overall tumor stage and survival; 4-year survival of patients with maximum SUV of ≤ 6.6 was 89%, compared to 31% for maximum SUV > 6.6[16].

Regional lymph node (N) staging

Regional lymph nodes are best evaluated using EUS. Although sensitivity is high (approximating 80%), specificity is somewhat lower (approximating 70%)[17]. Therefore, patient management should not be determined based solely upon an EUS diagnosis of abnormal appearing regional lymph nodes. Rather, EUS-guided lymph node biopsy should be performed for confirmation of lymph node involvement.

Diagnosing metastatic disease to regional lymph nodes with CT is limited for two major reasons. First, a bulky primary esophageal mass may obscure adjacent, involved lymph nodes[15]. Second, the diagnosis of lymph node disease is based solely on size criteria. However, enlarged nodes may be benign and reactive in nature, whereas small nodes may harbor microscopic metastases. Several size criteria for lymph node enlargement have been suggested. Traditionally 10 mm has been considered the upper normal limit for paraesophageal lymph nodes. For subdiaphragmatic nodes, an upper normal threshold of 8 mm has been used, with nodes between 6 and 8 mm considered as indeterminate[18]. However, more recently, Schroder and colleagues have found these figures to be overestimations[19]. In a histopathological study of specimens from 40 patients with esophageal squamous cell carcinoma, 1196 lymph nodes were analyzed; 129 lymph nodes were found to have metastatic infiltration. Average maximum lymph node diameters were 5.1 mm (± 3.8 mm) for tumor-free lymph nodes and 6.7 mm (± 4.2 mm) for tumor-containing lymph nodes. Furthermore, only 9.3% of all resected lymph nodes measured 10 mm or more in maximal diameter. In addition, there was no significant correlation between lymph node size and the frequency of nodal metastases[19].

Using varied size thresholds, recently published helical CT studies have demonstrated diverse results in the detection of regional lymph node metastases, with sensitivities of 11–69%, specificities of 71–95%, and accuracies of 66–83%[20–22] (Fig. 3).

There are conflicting results in the imaging literature regarding the accuracy of PET in staging the regional lymph nodes; a recent meta-analysis revealed a sensitivity of 51% and a specificity of 84% in this setting[23]. The major problem is obscuration of adjacent lymph nodes by
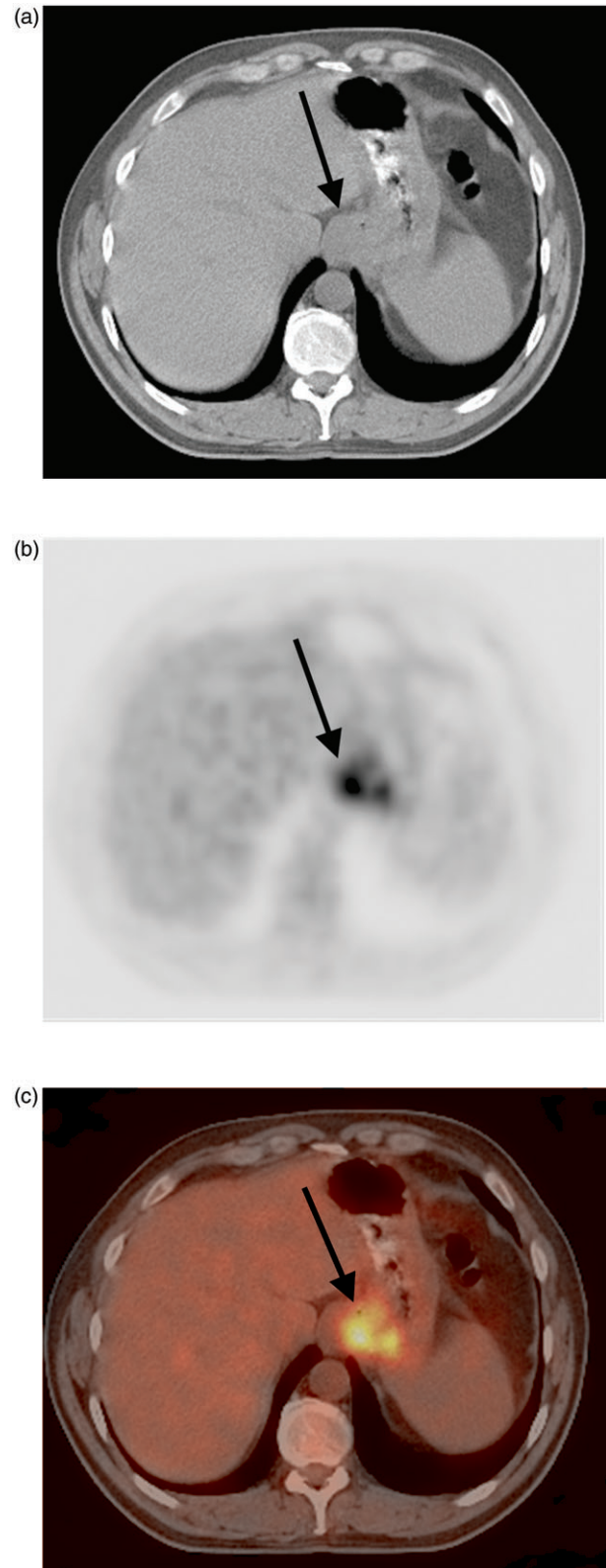
Figure 4 **FDG avid distal esophageal adenocarcinoma (arrow) on PET-CT scanning (A–C). Regional nodal (N1) disease (found at surgery) was not diagnosed preoperatively at PET, probably because uptake in the primary tumor obscured the abnormal, adjacent lymph nodes.**
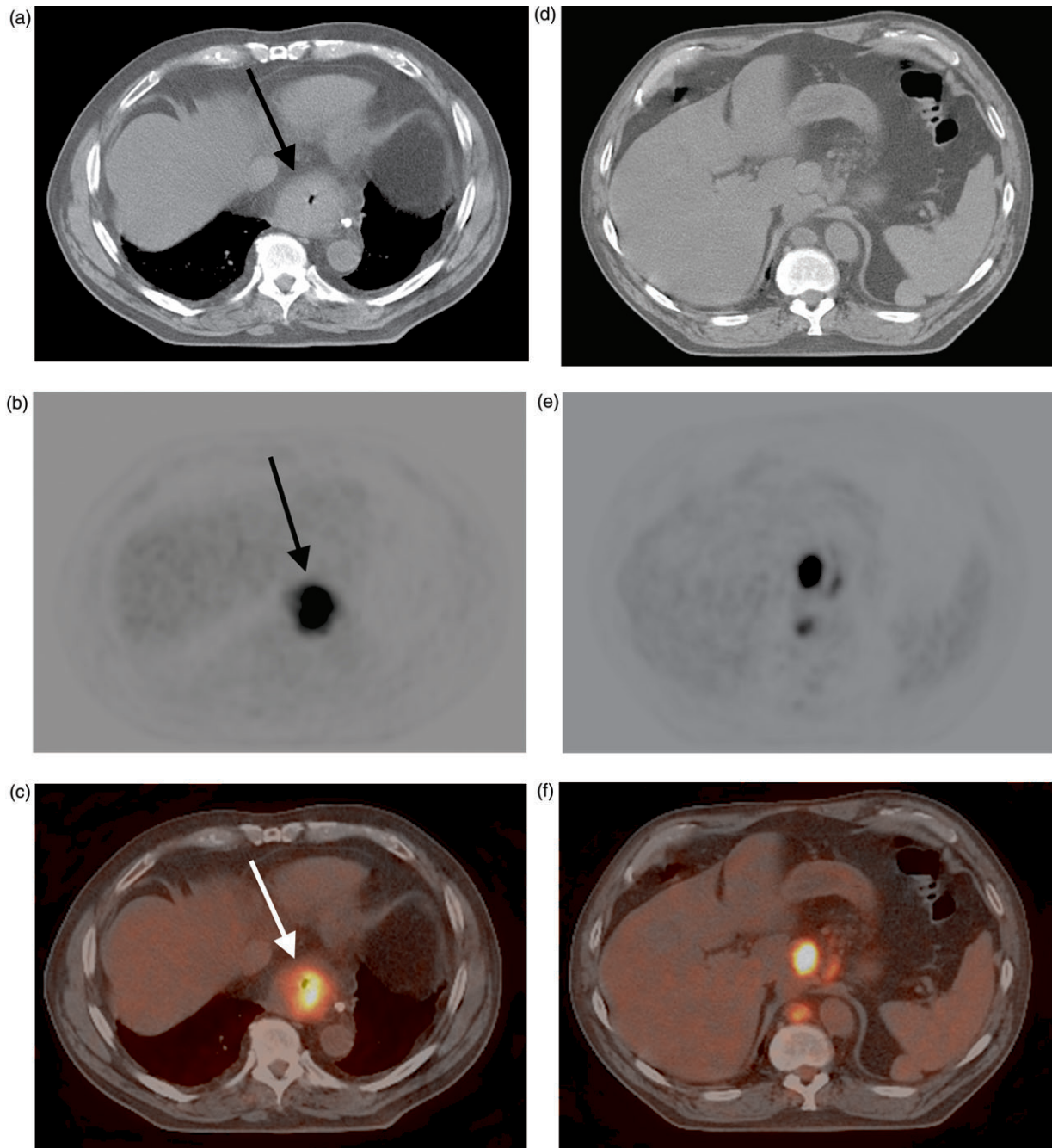
Figure 5 **FDG avid distal esophageal adenocarcinoma (arrow, A–C) on PET-CT scanning. The CT image helps to localize nearby foci of FDG avidity to abnormal lymph nodes in the gastrohepatic ligament and retrocrural region (D–F).**

uptake in the primary tumor, leading to low sensitivity (Fig. 4). However, PET is useful in detecting regional nodal disease that is not immediately near the esophageal primary. Published studies have found that the use of PET-CT helps in more precisely defining the location of FDG avidity in the region of the primary tumor, thereby improving regional lymph node staging accuracy[24,25] (Fig. 5). In one study, the sensitivity, specificity and accuracy of PET-CT were 94%, 92% and 92%, respectively, on a nodal group by group basis[25].

Distant metastatic disease (M) staging

CT scanning is often useful for detection of distant metastatic disease in lymph nodes and non-nodal sites (Figs. 6 and 7). CT scanning of patients with esophageal carcinoma should include an intravenous contrast-enhanced CT of the chest and abdomen with dedicated liver technique to optimize visualization of hepatic metastases. Among 201 CT exams performed for staging purposes, Gollub and colleagues found that none of the pelvic CT scans affected patient management; these
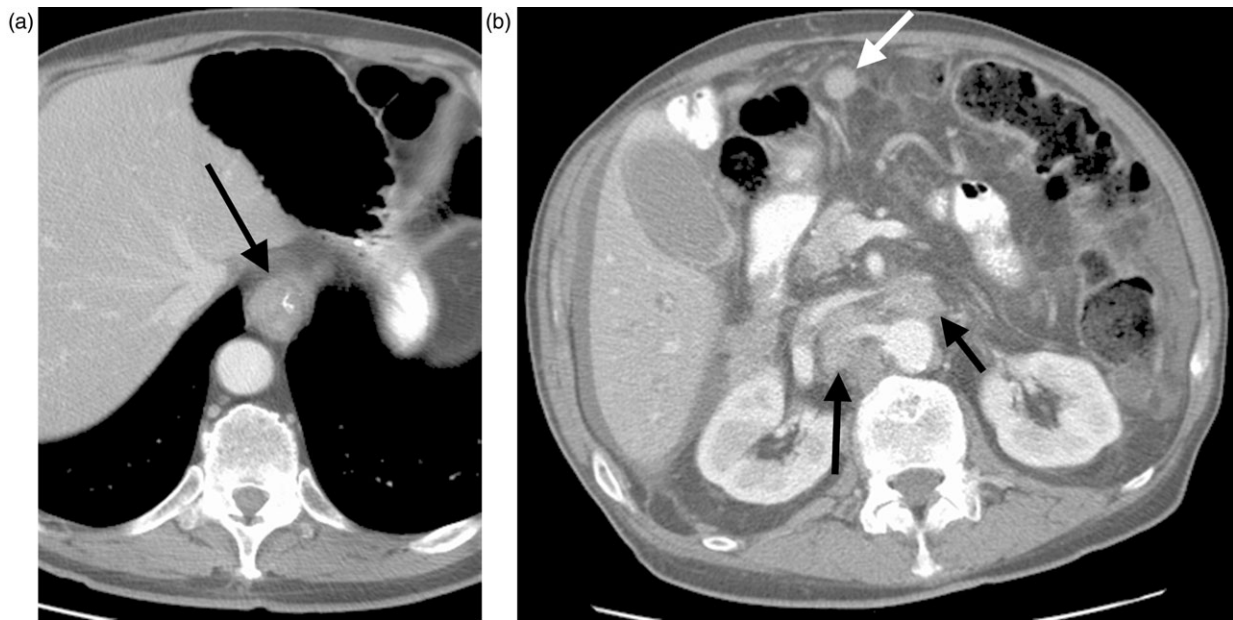
Figure 6 **Primary distal esophageal adenocarcinoma (arrow, A) with extensive distant metastatic disease to sites including retroperitoneal lymph nodes (black arrows, B) and peritoneum (white arrow, B). The findings represent M1b disease.**
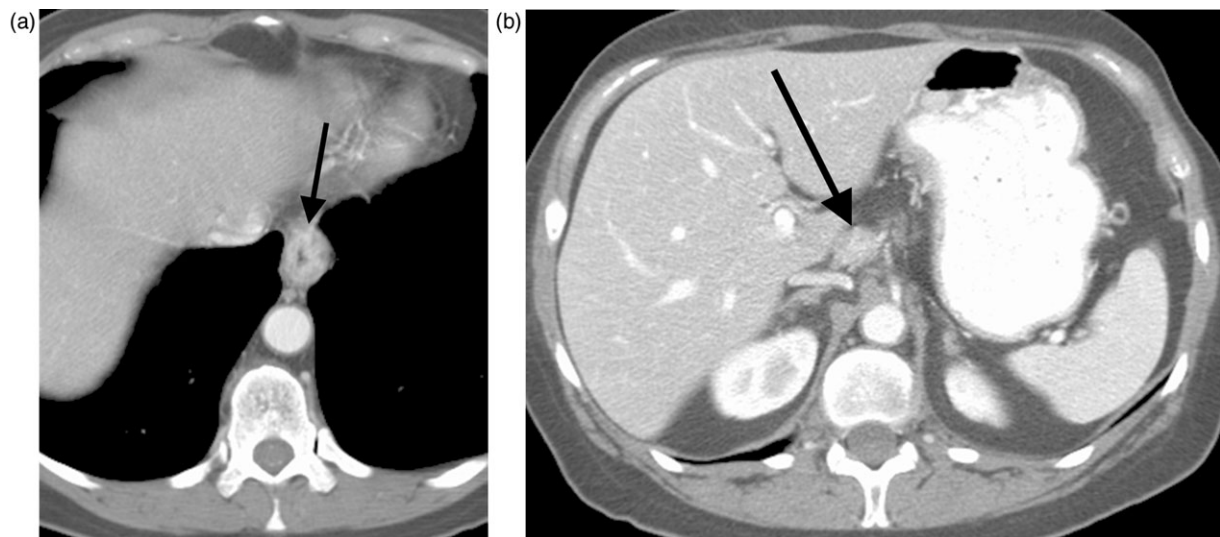

Figure 7 **Distal esophageal adenocarcinoma (arrow, A) with metastasis in a celiac axis lymph node (arrow, B), constituting M1a disease.**

authors concluded that it is therefore unnecessary to perform pelvic CT as part of the staging workup[26].

Although the major role for EUS is in staging the primary tumor and regional lymph nodes, occasionally this modality reveals abnormal appearing distant lymph nodes in the celiac axis region; in this situation, EUS-guided biopsy should be performed for confirmation of metastatic disease.

Perhaps the most important modality in the diagnostic armamentarium for distant metastatic disease detection in esophageal cancer is PET scanning. In 5–40% of patients, PET may reveal previously occult distant metastases in nodal and non-nodal sites[27–29], with moderate sensitivity (~67%) and high specificity (~97%)[23] (Figs. 8 and 9). It may also reveal osseous metastases that are not detected using conventional bone scintigraphy[30]. Using a logistic regression model in patients examined preoperatively with CT, EUS and/or PET, one investigation found that PET was the only modality that predicted intended curative resection, due to the
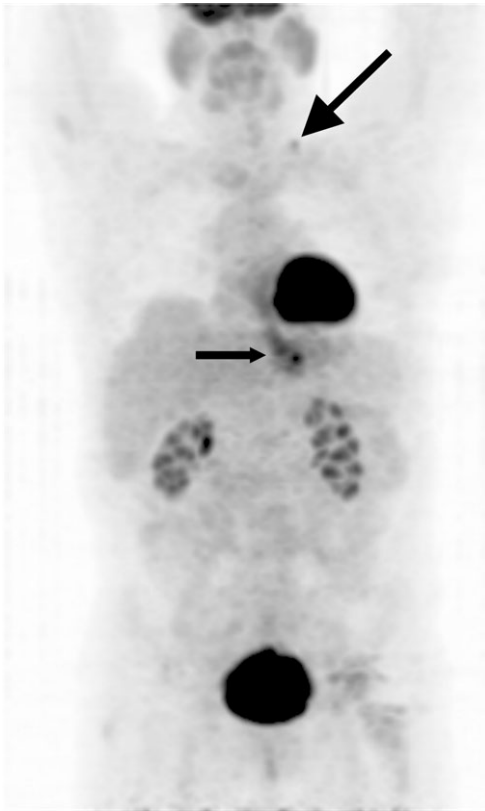
exclusion of distant metastases; furthermore, these authors concluded that PET may be used to prevent unnecessary surgical explorations in patients who did have M1 disease[31]. In another study, the use of FDG-PET changed the clinical management of 27/68 patients (40%): in 12 therapy was changed from curative to palliative (due to detection of previously unsuspected distant metastases), in three from palliative to curative, while in 12 other patients there was a change in the treatment modality or delivery but not in the treatment intent[32].

Magnetic resonance imaging (MRI)

Several authors have reported that there is no real difference in staging accuracy between MRI and CT for esophageal cancer[13,20]. MRI is more costly than CT and less widely available; in addition, it is more difficult to perform, as respiratory and cardiac gating and control of swallowing are needed, in order to optimize images and avoid motion artifacts. Therefore, MRI is rarely used at most institutions for routine staging[15,33]. Experimental work using external surface coils has shown that T2-weighted high resolution MRI is capable of producing detailed images of the esophageal wall; such techniques may be useful for staging in the future[34].

Figure 8 Projection PET image shows an FDG-avid distal esophageal adenocarcinoma (small arrow) and a previously occult distant metastasis within a left supraclavicular lymph node (large arrow), constituting M1b disease.

Workup guidelines

Multiple staging modalities are available for evaluating patients with newly diagnosed esophageal cancer.
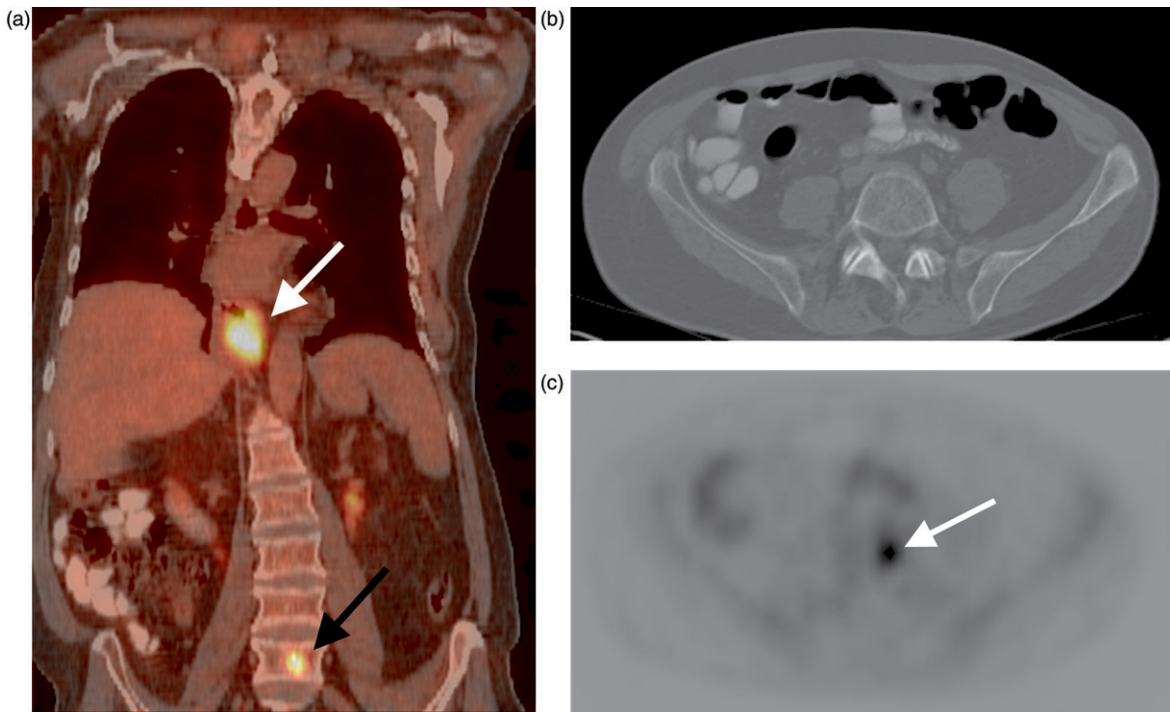

Figure 9 Fused PET-CT image reveals an FDG-avid distal esophageal carcinoma (white arrow, A) and a previously occult distant vertebral body metastasis (black arrow, A). The spine appears normal on an axial CT image at the level of the metastasis (B); axial PET image at the same level shows the lesion (arrow, C).

The following guidelines are followed by multiple authors, yet may be varied according to local preferences and availability of imaging technology. Patients should initially undergo a history and physical exam, in order to detect gross evidence of metastatic disease. In addition, complete upper gastrointestinal (GI) endoscopy or barium upper GI series is indicated to assess for mucosal extent of disease. A CT of the chest and abdomen with bolus administration of intravenous contrast should then be performed to evaluate the primary tumor for T4 disease and to look for lymph node, visceral, and other distant metastatic disease. If the CT shows no distant metastases, and if the tumor is in the cervical, upper thoracic or mid-thoracic esophagus, bronchoscopy is generally performed to assess for airway invasion. PET has been shown to be more accurate than CT in diagnosing distant metastases[35]. Therefore, if the disease appears to be resectable at CT, patients may then undergo PET scanning for detection of occult distant metastases; suspicious lesions should be biopsied for confirmation of disease. Assuming the PET study shows no evidence of distant metastatic disease, EUS will then be performed for better T and N stage evaluation; suspicious lymph nodes detected by EUS (regional or celiac axis) should undergo EUS-guided fine needle aspiration biopsy.

At some institutions, patients with T1N0 disease on EUS and M0 disease on CT and PET will undergo endoscopic therapy or surgery, whereas those with deeper extent of tumor and/or tumor involved regional lymph nodes will undergo neoadjuvant chemoradiation therapy followed by surgery. M1 disease is usually treated non-surgically, with chemoradiotherapy. Some centers perform laparoscopy to look for occult abdominal metastases, particularly for tumors arising at the gastroesophageal junction[36–38].

A cost effectiveness study comparing CT, EUS with fine needle aspiration biopsy (EUS-FNA), PET and thoracoscopy/laparoscopy found that CT plus EUS-FNA was the most inexpensive strategy and offered more quality adjusted life-years, on average, than all other strategies except for PET plus EUS-FNA[39]. The latter strategy, although slightly more effective, was also more expensive. The authors recommended use of PET plus EUS-FNA unless resources are scarce or PET is unavailable. At many institutions, PET is now being replaced by PET-CT, thereby potentially eliminating the need to choose between CT and PET in an individual patient.

Conclusion

Most patients with esophageal carcinoma already have tumor spread beyond the esophageal wall at the time of diagnosis, resulting in a dismal prognosis. Only those few patients with limited disease are suitable for potentially curative therapy. Staging information gleaned from imaging is helpful in triaging patients to the appropriate method of therapy; in particular, imaging detection of distant metastases prevents unnecessary surgery.

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