Radiologic Evaluation of Esophageal Cancer

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Abstract

Various methods are currently employed for esophageal cancer staging, including computed tomography (CT), positron emission tomography (PET), endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and histopathologic based staging, which encompasses endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). However, no single modality can accurately stage every patient with esophageal cancer on its own. Given the crucial role of accurate staging in devising an optimal therapeutic approach, the use of a combination of these modalities is often necessary.

Keywords

Esophageal cancer · Radiology · CT · PET-CT · Endoscopic ultrasound

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Introduction

Esophageal cancer staging remains a complementary mix of multiple diagnostic modalities including computed tomography (CT), 18 FDG positron emission tomography (18 FDG PET), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) and esophagogastroduodenoscopy (EGD), being its approach multi-disciplinary and highly complex. As imaging remains the cornerstone of diagnosis, radiologists play an essential role in esophageal cancer staging [1].

Current treatment strategies range from organ preserving modalities to multimodality therapy combining surgery with chemotherapy with or without radiation [2, 3]. Organ sparing techniques, including endoscopic mucosal resection (EMR) and endoscopic submucosal resection (ESR) have shown optimal results in patients with node negative—T1a tumors (tumor confined to the mucosa), proving survival rates of 80–90% in properly selected cases [4].

Patients with deeper tumors such as T1b-T2 without clinical suspicion of nodal involvement are candidates for upfront radical surgical treatment, being esophagectomy with lymphadenectomy the pillar of curative intent therapy [5].

In cases of extended locally advanced disease and/or lymph node compromise (T3-N^+), several randomized studies have reported improved overall and disease-free survival with multimodality therapy, including chemotherapy with or

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without radiation followed by radical surgery. In any case, a proper patient selection and accurate staging will help to determine the optimal therapy in order to achieve the best oncological outcome [2, 3, 6–9].

The globally used TNM classification system maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) includes the depth of local invasion by the primary tumor (T), the extent of regional lymph node involvement (N), and the presence or absence of distant metastasis (M), providing a stage grouping on the basis of T, N, and M [10]. Furthermore, separate stage groupings are described for the two main histologic subtypes, squamous cell carcinoma (SCC) and adenocarcinoma (EAC).

For both EAC and SCC, T0 disease denotes high-grade dysplasia; T1 disease is divided into T1a and b and denotes absence or presence of invasion through the muscularis mucosa into the submucosa, respectively. T2 denotes invasion into the muscularis propria, T3 denotes invasion to the adventitia, and T4 denotes invasion into surrounding structures. This is further subdivided in T4a, defined as resectable disease (including diaphragm, pleura, and pericardium) and T4b, defined as unresectable (including trachea, aorta and, vertebral body).

Nodal disease is classified as N1 if fewer than three nodes are involved, as N2 if 3–6 nodes are involved, and N3 if 7 or more are involved. Any extra nodal metastases are classified as M1 [10] (Table 1).

The available techniques for accurate staging include both imaging and invasive studies. The aforementioned comprises mainly endoscopic ultrasound (EUS), CT and PET-CT. More invasive methods such as EMR, ESD or even laparoscopy can also help staging esophageal cancer [9].

This chapter provides a detailed review of the different imaging methods describing their applications, strengths and weaknesses for esophageal cancer staging. As no radiologic study will obtain the diagnosis and staging by itself, all of them should be considered as complimentary to one another. Consequently, the adequate combination of the studies will help obtaining an accurate staging.

Tumor "T" Staging

CT Scan and T Staging

CT remains the most commonly used study for preoperative T staging of esophageal cancer. CT scanners can provide volumetric data on the primary tumor, demonstrating an overall accuracy of 80% in the determination of T stage. However, as CT is unable to accurately differentiate the layers of the esophageal wall and the depth of tumor invasion, accuracy and specificity of the study decreases in early stages such as T1 and T2. Recently, multi-detector row CT with dynamic enhanced images has shown improved accuracy for T staging [8, 11, 12].

According to the literature, the accuracy of CT with respect to T-stage as compared to final histology is around 60% for T1 lesions and 75% for T3 lesions, acknowledging its lower specificity in earlier tumors [11, 12]. As proper staging of T1 against T2 tumors is required to consider a curative endoscopic treatment, these cases may be aided by EUS. On the other hand, CT scan seems to be more accurate on advanced tumors. For example, T3 stage is detected on multi-detector CT as periesophageal fat infiltration with 75% sensitivity and 78% specificity, and T4 stage is identified with loss of fat planes between the tumor and adjacent mediastinal structure with 75% sensitivity and 86% specificity (Fig. 1) [13].

Local invasion of tracheobronchial tree, aorta and/or heart can be assessed with almost 100% of sensitivity, however its specificity ranges from 52 to 97%. Loss of the fat plane between the esophagus and airway, visualization of a tracheoesophageal fistula and/or tumor contact > 90º with the aorta represent very poor prognostic factors. Similarly, abutment of the tumor against the pericardium with associated pericardial effusion are concerning features (Fig. 2) [8, 12–15].

Table 1 AJCC 8th edition staging of esophageal cancer

	Clinical criteria
T stage	
Tx	Cannot be assessed
T0	High-grade dysplasia—confined by basement membrane
T1a	Invades lamina propria or muscularis mucosa
T1b	Invades into submucosa
T2	Invades muscularis propria
T3	Invades adventitia
T4a	Invades pleura, pericardium, azygous vein, diaphragm, peritoneum
T4b	Invades adjacent structures such as aorta and vertebral body
N stage	
NX	Cannot be assessed
N0	0 involved nodes
N1	1–2 involved regional nodes
N2	3–6 involved regional nodes
N3	7 or more involved regional nodes
M stage	
MX	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
ADC Grade	
GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
SCC Grade	
GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
SCC Location	
LX	Cannot be assessed
Upper	Cervical esophagus to azygous vein
Middle	Lower border of azygous vein to inferior pulmonary vein
Lower	Inferior pulmonary vein to stomach

(continued)

Table 1 (continued)

Clinical (c) stage	T	N	M
ADC			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	0	0
III	T2 T3-4a	N1 N0-1	M0 M0
IVA	T1-4a T4b T1-4	N2 N0-2 N3	M0 M0 M0
IVB	T1-4	N0-3	M1
SCC			
0	Tis	N0	M0
I	T1	N0-1	M0
II	T2 T3	N0-1 N0	M0 M0
III	T3 T1-3	N1 N2	M0 M0
IVA	T4 T1-4	N0-2 N3	M0 M0
IVB	T1-4	N0-3	M1

ADC Adenocarcinoma, *SCC* Squamous cell carcinoma

Despite its high level of accuracy, diagnosis of T4 stage may represent a challenge in some cases, particularly in patients who had received surgery or radiotherapy or with cachexia due to the loss of fat planes [13].

MRI and "T" Staging

Currently, the use of magnetic resonance imaging (MRI) in patients with esophageal cancer is limited. This may be explained by the lack of uniform techniques for image acquisition and differences in image quality observed over time related to diverse MRI technologies. However, the quality of MRI continues to improve and is gaining ground for esophageal cancer staging, with encouraging results comparable with CT and EUS. Technical developments that diminish

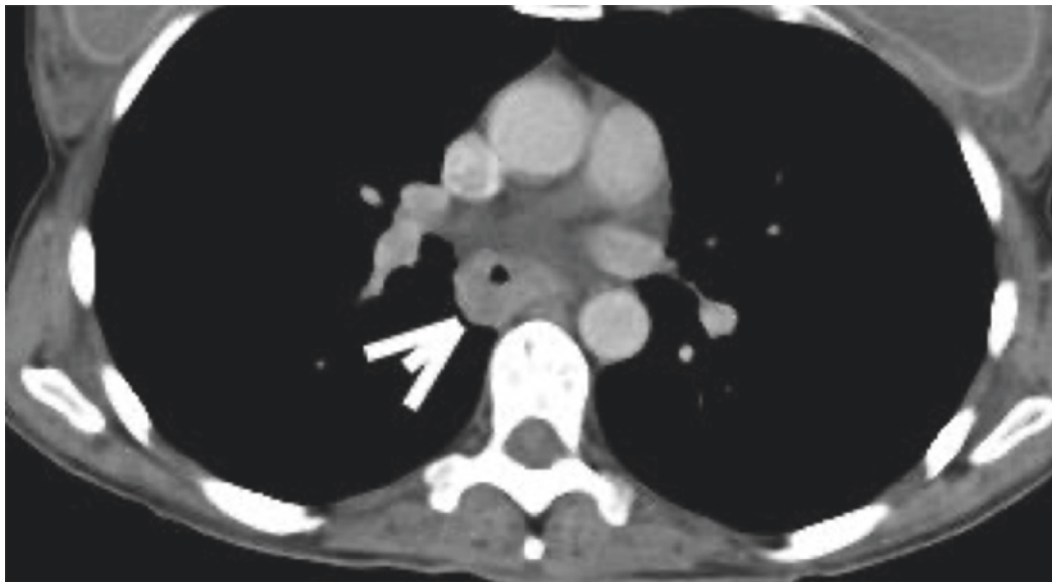

Fig. 1 CT scan showing esophageal tumor with intimal contact with the pericardium (T4a)

motion artifact and optimizes MRI image quality, such as application of high-resolution and ECG-triggered 1.5 T MRI are allowing this method to become increasingly used [16, 17].

With respect to T staging, a previous study showed that with the application of faster imaging sequence and ECG gated technique, accuracy of 1.5 T MRI was 33%, 58%, 96%, and 100% for T1, T2, T3 and T4 stage, respectively [18]. More recently, a study confirmed that high-resolution T2-weighted imaging (T2WI) provides meticulous imaging of the anatomical layers of the esophageal wall and surrounding tissues with an accuracy of 81% for T-staging (according to the signal intensity obtained in each esophageal layer) [19].

Overall, although the diagnostic value of MRI for T staging has significantly improved in recent years, further evidence and standardization of the technique are needed to broadly adopt this imaging method [17].

Endoscopic Ultrasound and "T" Staging

Endoscopic ultrasound (EUS) represents one of the preferred imaging modalities for the assessment of loco-regional disease in esophageal cancer. EUS has the ability to identify the depth of tumor invasion and pathologic regional lymphadenopathies. In addition, it has the possibility to obtain nodal biopsies with fine-needle aspiration (FNA) [8, 20–22].

According to its echogenicity, echoendoscopes can identify 5 layers of the esophageal wall: mucosa (first hyperechoic layer), muscularis mucosa (first hypoechoic layer), submucosa (second hyperechoic layer), muscularis propria (second hypoechoic layer), adventitia (esophageal) or serosa (gastric) (third hyperechoic layer) (Fig. 3).

The overall reported sensitivity and accuracy for assessing the T stage with EUS is 85–90%

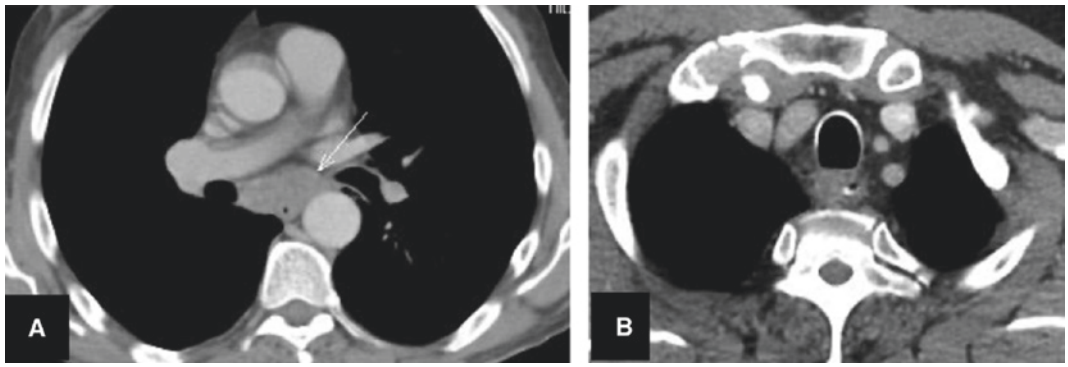

Fig. 2 CT scan showing esophageal tumor in direct contact with the aorta (A) and with the trachea (B)

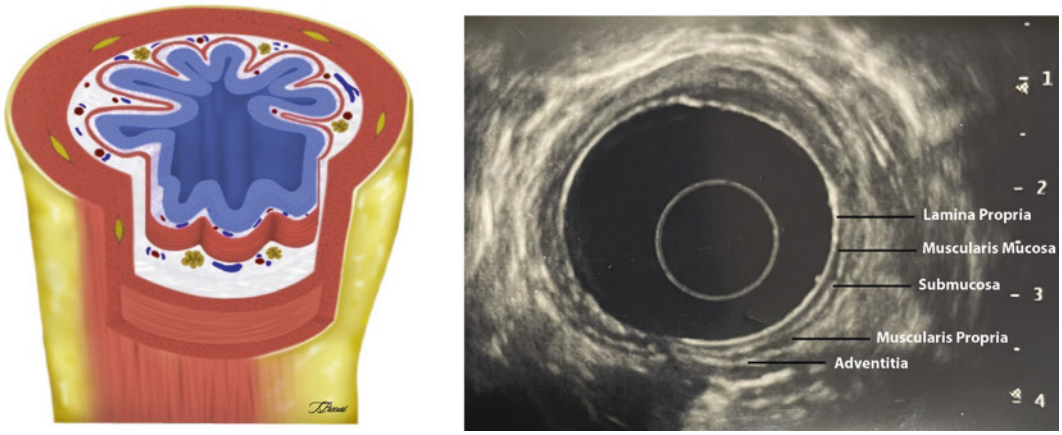

Fig. 3 Esophageal layers (Drawing by Tomás Pascual MD and Endoscopic Ultrasound Image from Stephen Gowing MD)

and 70–80%, respectively [23]. For early tumors, however, accuracy is decreased. Bianco et al. reported that EUS accurately staged 39% of T1a lesions and 70% of T1b lesions [24]. Similarly, another study reported that lesions diagnosed as cT1aN0 by EUS, turned out to be deeper or even pN1 in 15% of patients [25]. Shridhar and colleagues in a series of 1840 patients with T2N0M0 esophageal cancer (EAC or SCC) showed that clinical staging was accurate in only 30.7% of patients, describing tumor length > 3 cm and poor differentiation as risk factors for pathologic upstaging [26]. Likewise, Luu et al. reported understaging by EUS in 21% of patients with stage I or II (14% with unrecognized nodal disease). All these studies suggest that EMR or ESD might be necessary for accurate staging of early superficial tumors [27].

A previous study showed a significant increase in the utilization of neoadjuvant therapy in patients who underwent EUS staging as compared to those that only had a CT as staging modality (32.7% versus 15%). Consequently, an improved overall survival was seen in EUS-staged patients (58.9%) versus CT alone (47.7%) [28].

Overall, current data confirms that EUS is critical for adequate staging in most patients with esophageal cancer, mainly due to its ability to select patients for multimodal therapy and predict patient outcomes.

PET-CT and T Staging

Positron emission tomography (PET) plays a critical role in the staging of esophageal cancer. The study relies on the expression of the GLUT-1 glucose transporter on neoplastic cells for the uptake of fluorodeoxyglucose (FDG). Therefore, it provides information regarding the metabolic activity of the tumor in addition to anatomic features. Currently, PET images are often fused with CT images to more effectively localize sites of abnormal glucose uptake (PET-TC) (Figs. 4 and 5).

The majority of both esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are PET avid. ESCC, however, tends to be more PET avid and around 20% of EAC show little or no FDG avidity. Lack of avidity is more common in poorly differentiated tumors and signet cell lesions [29, 30].

With respect to differentiating between T stages, PET-CT cannot accurately differentiate the depth of invasion of the primary tumor, and thereby has a limited role in T staging. Given the relatively low resolution and detection threshold of the study, this study is less precise for early T1 disease and limited for differentiating between T1 or T2 lesions. Stage specific accuracy is thereby higher for T3 and T4 tumors. In addition, PET-TC provides valuable information regarding T stage in patients with obstructive tumors in whom endoscopy or EUS are not feasible [8, 29, 30] (Fig. 6).

Node "N" Staging

Currently, endoscopic ultrasound, CT and PET CT are commonly used to determine N stage. These modalities have low or moderate sensitivity and moderate-high specificity for assessment of lymph node status.

Lymph node involvement is critical for selecting patients for multimodal therapy. Regional lymph nodes include any paraesophageal lymph nodes from the cervical nodes to the celiac nodes. The N classification comprises N0 (no cancer-positive nodes), N1 (one or two cancer-positive nodes), N2 (three to six cancer-positive nodes), and N3 (seven or more cancer-positive nodes).

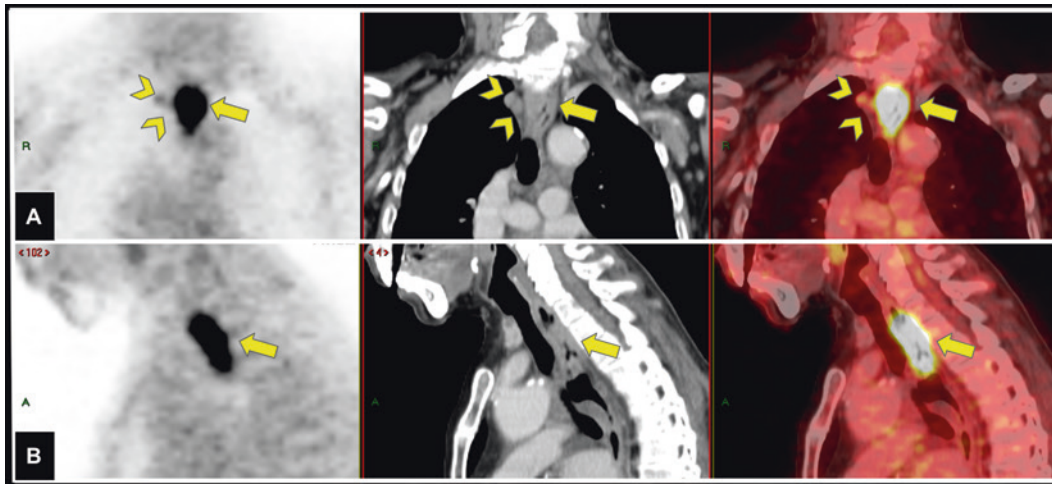

Fig. 4 Squamous cell carcinoma in upper third of the esophagus (T3N1M0). A) PET-CT coronal reconstruction demonstrates esophageal hypermetabolic wall thickening preserving peripheral fat (T3, arrow) and two hypermetabolic infracentimetric nodes to the right (N1, arrow heads). B) PET-CT sagittal reconstruction showing same findings

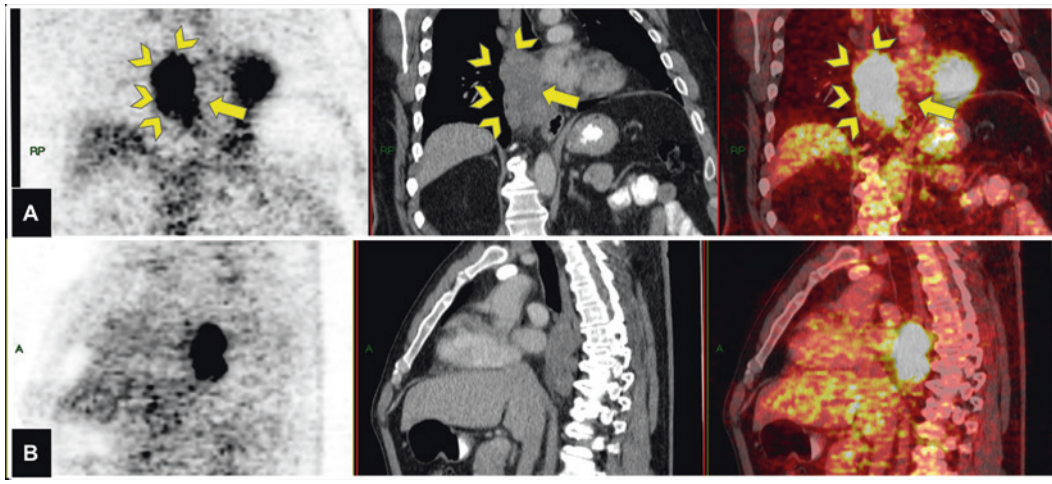

Fig. 5 Adenocarcinoma in lower third of the esophagus (T3N2M0). A) PET-CT coronal reconstruction demonstrates esophageal hypermetabolic wall thickening preserving peripheral fat (T3, arrow) and multiple regional hypermetabolic nodes (N2, arrow heads). B) PET-CT sagittal reconstruction showing same findings

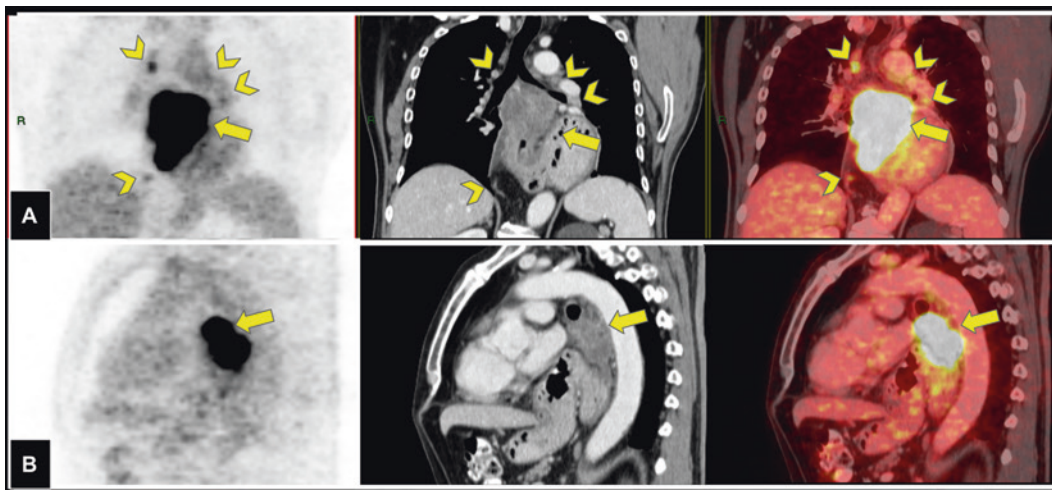

Fig. 6 Adenocarcinoma in middle third of the esophagus (T4N3M0). A) PET-CT coronal reconstruction demonstrates esophageal hypermetabolic wall thickening with periesophageal fat infiltration (T4, arrow) with a maximum SUV of 29.5 and multiple hypermetabolic mediastinal nodes (N3, arrow heads). B) PET-CT sagittal reconstruction showing same findings

CT Scan and N Staging

In CT scan, non-pathologic lymph nodes are usually smaller than 1 cm in short-axis diameter with a smooth well-defined border, uniform homogeneous attenuation, and a central fatty hilum [8].

The detection of metastatic lymph nodes with CT depends primarily on size criteria. In general, intrathoracic and abdominal lymph nodes greater than 1 cm in diameter are considered to be enlarged, and supraclavicular lymph nodes with a short axis greater than 5 mm are considered to be pathologic. However, most studies use the

common size criteria of 1 cm to define a pathological lymph node [8, 9]. Sensitivity and specificity CT for detecting metastatic lymph nodes is somehow limited, with an overall accuracy reported of at best 66% in nodal staging [8, 9].

Unfortunately, even normal-sized lymph node might contain microscopic metastatic foci that are beyond the level of detection offered by CT. Moreover, the presence of reactive enlarged and inflammatory lymph nodes reduces the specificity of the study. Additionally, peritumoral nodes contacting directly with the mass can be indistinguishable from the primary tumor and may induce false-negative results [1, 12].

Luketich and colleagues reported a sensitivity and specificity of CT of the chest and abdomen for lymph node metastasis of 33% and 88%, respectively, proving to be inaccurate in more than 40% of patients [31].

MRI and N Staging

As mentioned above, MRI is not yet widely adopted for esophageal cancer staging. Studies exploring the effectiveness of MRI for N staging have shown heterogenous results. The estimated sensitivity and specificity currently range between 38%–70% and 67%–93%, respectively, owing this variation to diverse methods of image acquisition and threshold size for suspicious lymph nodes [30].

At present, MRI presents some drawbacks as compared to CT, such as higher cost and limited availability. Therefore, its use should be based on institutional experience or equivocal findings from CT.

Endoscopic Ultrasound and N Staging

Endoscopic ultrasound (EUS) is used to determine nodal involvement based on factors such as size, shape, borders, and internal characteristics of the nodes. Malignant lymph nodes are typically identified as round, hypoechoic with smooth borders that may be enlarged (> 10 mm) and are usually located near the tumor [1, 32]. The sensitivity and specificity of EUS range from 59.5%–100% to 40%–100%, respectively. However, more precise estimates have indicated that EUS can differentiate positive from negative nodes with a sensitivity and specificity of 85%–97% and 85%–96%, respectively, and an accuracy of 75%. Nonetheless, the false negative rate for EUS is 18%, while the false positive rate is 9% [8, 9, 20, 21, 31, 33].

Despite the accuracy of EUS, understaging of patients with micro metastatic disease is possible, [34]. FNA is a useful adjunct of the study for sampling suspicious nodes. Furthermore, EUS-CT has been shown to be more accurate than either modality alone for N staging, with EUS-CT even outperforming PET, as the sensitivity of combined EUS-CT was 83% compared to 22% for PET [27, 32].

PET-CT and N Staging

PET-CT is more sensitive than CT for detecting lymph node involvement because alterations in tissue metabolism measured by PET generally precede anatomic changes of affected nodes.

The uptake of the primary tumor, however, might sometimes hamper the identification of peri-lesional nodes.

Tumor metabolic activity might also predict the risk of lymphatic involvement. A previous study included patients with seemingly resectable esophageal cancer and analyzed their standardized uptake value (SUV) max on PET-CT with respect to pathologic stage and survival. Patients in the low SUV group (< 4.5) had earlier T stage tumors and lower incidence of nodal metastasis (8%). On the other hand, 48% of patients with SUV max>4.5 had nodal involvement and this was correlated with poor survival [35].

Overall, one of the main benefits of PET-TC is its improved specificity in detecting lymph node involvement as compared to CT scan

(mainly by detecting abnormal metabolic activity even in normal-sized lymph nodes). The PET SUV max of the primary tumor appears also to predict pathologic stage and overall survival. In addition, PET-CT it is a valuable tool to determine response to preoperative therapy (Fig. 7).

"M" Staging

The M classification designates M0 or M1 according to absence or presence of distant metastasis, respectively.

Distant metastases have been detected at initial presentation in 20–30% of patients with esophageal cancer and are most commonly reported in the liver (35%), lungs (20%), bones (9%), adrenal glands (5%), and, rarely, peritoneum and brain. CT, MRI and PET-CT are useful for determining the M status. EUS has limited value for assessing distant metastases because of the small field of view. This study can only detect distant metastases in direct contact with the upper gastrointestinal tract and ascites as an indirect sign of intraperitoneal metastases.

CT Scan and "M" Staging

CT imaging is highly effective in detecting distant metastases in organs such as the liver or lung. In particular, liver metastases are best seen in the portal venous phase as hypoattenuating

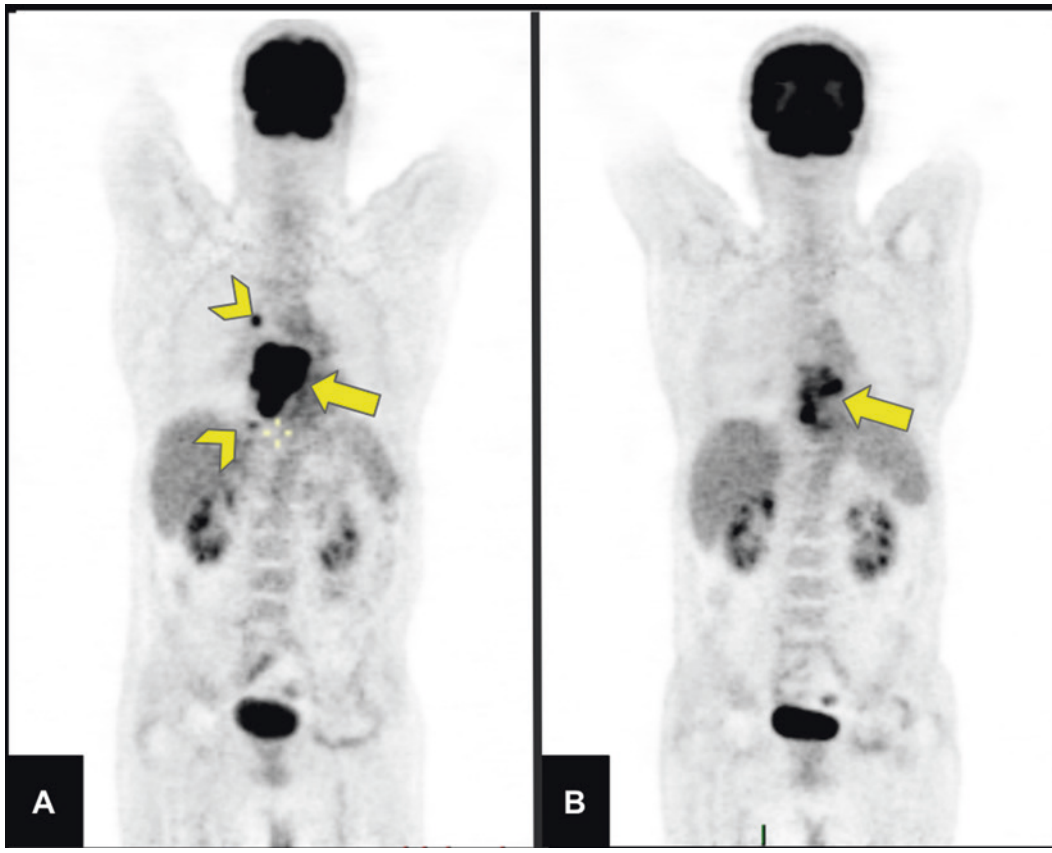

Fig. 7 PET-CT maximum intensity projection (MIP) maps showing tumor downsizing of a patient after neoadjuvant treatment. A) Baseline. Esophageal hypermetabolic wall thickening with periesophageal fat infiltration (T4) with a maximum SUV of 29, 5 and multiple hypermetabolic mediastinal nodes (N3). B) Restaging with partial response. Morphologic and metabolic reduction of the tumor (maximum SUV 8, 8, arrow) and nodal involvement

lesions. While metastatic lung nodules are usually round and smooth-bordered, they might be difficult to diagnose, specially in the absence of prior imaging. In such cases, biopsy by interventional radiology may be helpful.

Compared to PET, CT imaging has reduced sensitivity in detecting bone metastases. Additionally, CT has relatively poor accuracy in identifying peritoneal disease [1, 8, 9, 31, 36].

Accurate determination of M stage with complementary staging modalities such as PET-CT and even diagnostic laparoscopy is needed in some cases [8, 9, 37].

MRI and "M" Staging

Currently, there is scarce data evaluating the efficacy of MRI in detecting distant metastases. Consequently, the precise contribution of MRI for M staging remains uncertain.

PET-CT and "M" Staging

PET-CT is the most accurate imaging method to detect distant metastases. The study covers the entire body and its primary role is to detect distant sites of metastatic disease.

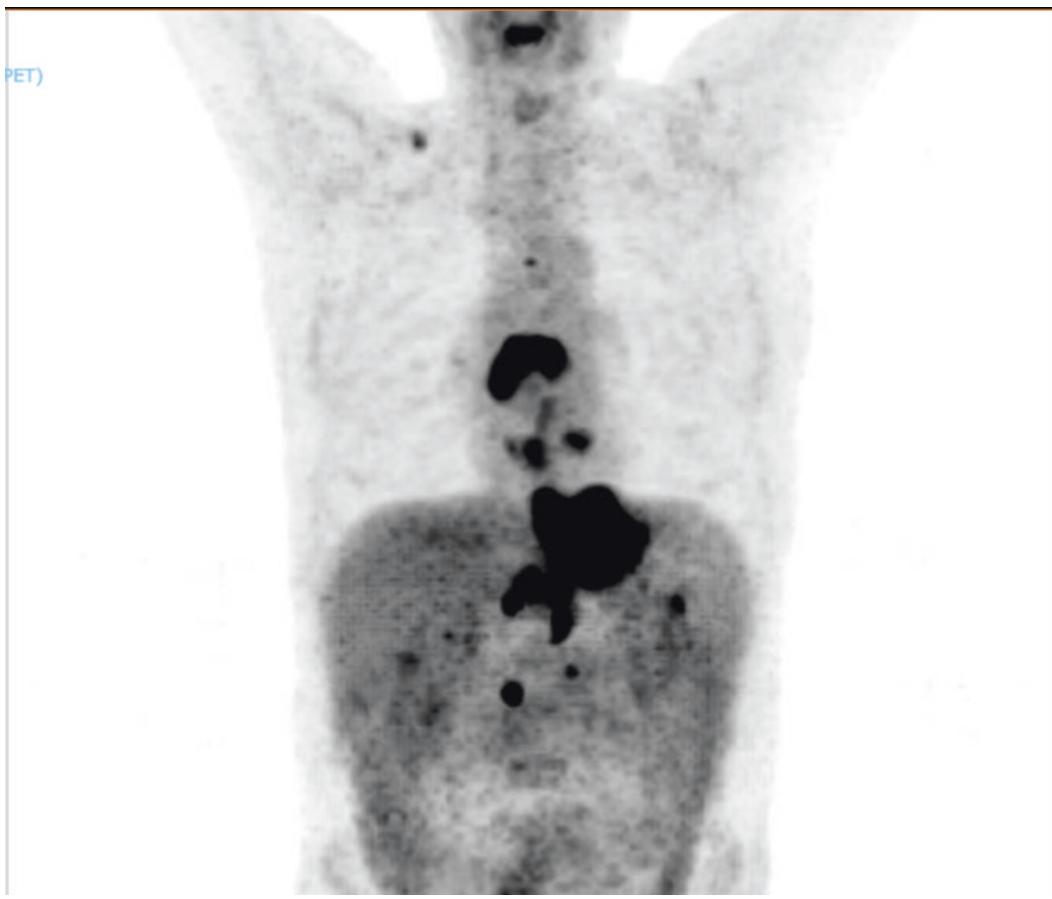

Fig. 8 PET-CT maximum intensity projection (MIP) map of a stage IV esophageal adenocarcinoma of the gastroesophagic junction. Esophageal hypermetabolic wall thickening with a maximum SUV of 22, 2 and multiple sites of distant metastases

Table 2 Performance characteristics of CT, MRI, CT-PET and EUS in the diagnostic workup of esophageal cancer

Modality	Sensitivity	Specificity	Accuracy
CT			
T1, 2, 3, 4	–	–	63%, 72.9%, 75.3%, 74.9% [8]
N	77.2%	78.3%	66.1–87% [8]
M M peritoneum M peritoneum	– 58.8% 66% [39]	– 98.6% [40]	81% [8]
MRI			
T	–	–	81% [41]
T4b	86–100%	67–84%	75–87% [30]
N	25–62%	67–88% [30]	
M	–	–	–
CT-PET			
T 1/2	26–63% [8] 43% [25]	–	–
T 3/4	83–100% [8]	–	–
N	24–99%	46–98% [8]	
M	69–78%	–	82–88% [8]
EUS			
T T1 T2 T3 T4 T0/2vsT/34	27.9% 81.6% 81.4% 91.4% 92.4% 79%	90.9% 99.4% 96.3% 94.4% 97.4% [33] 94%	79.4% [21] 66–97% GEJ 85% [22]
N w/o FNA w FNA N stage in uT1 uT3	73% 35.3% 84.7% 96.7% 0% 83%	77% [22] 90.9% 84.6% 95.5% 90% 55% [33]	57.1% [34]

Obtained from Schlottmann et al. Esophageal Cancer: Diagnosis and Treatment (Springer, 2018)

PET-CT is superior to CT scan in identifying disease in liver and bones and it is also capable of detecting metastases in unusual locations (e.g. skeletal muscles, subcutaneous tissues, thyroid gland or pancreas). The detection of metastatic disease is critical during the initial evaluation of patients because it will direct patients to a palliative treatment pathway rather to an esophagectomy. During treatment, particularly after neoadjuvant therapy (chemotherapy or chemoradiotherapy), PET-CT is also valuable because it provides information regarding response but more importantly it can detect metastases that have developed since the induction therapy (Figs. 7 and 8) [38] (Table 2).

Conclusions

Effective management of esophageal cancer requires a precise staging. An accurate and thorough methodology during the staging process is indispensable for appropriate treatment selection. Each diagnostic method possesses its own distinct benefits and limitations that should be acknowledged when staging esophageal cancer patients.

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