



New frontiers in esophageal radiology

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Abstract: Esophageal cancer is the sixth most common cause of cancer related mortality worldwide. Advances in treatment have translated into steadily improving survival rates. Accurate preoperative staging of esophageal cancer is imperative in order to provide an accurate prognosis and direct patients to the most appropriate treatment. Current preoperative staging relies on imaging, most commonly endoscopic ultrasound (EUS), computed tomography (CT) and positron emission tomography (PET). A combination of these modalities should be used in preoperative staging, as each has advantages over another. Magnetic resonance imaging (MRI) has always shown promise in its ability to accurately stage esophageal cancer, though it has not been consistently adopted as a common tool for this purpose. Recent research has demonstrated that MRI can become an integral part of esophageal cancer clinical staging. Advances in MR technology that utilize radial sampling allow for shorter, free breathing techniques without degradation of image quality, resulting in improved capability for T and N staging of esophageal cancer. MRI enhanced with superparamagnetic iron oxide (SPIO) and ultrasmall SPIO (USPIO) nanoparticles has been shown to be useful for the detection of metastatic disease in lymph nodes. This article will review the current evidence in the role that imaging plays in staging esophageal cancer.

Keywords: Esophageal cancer; magnetic resonance imaging (MRI); computed tomography (CT); 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)

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Introduction

Esophageal cancer is the sixth most common cause of cancer related mortality worldwide (1). It makes up approximately 1% of all cancers in the United States, but is much more common in China, India and Iran. While squamous cell carcinoma has long been the most common histologic type, adenocarcinoma has been consistently increasing in western countries. Advances in treatment have translated into steadily improving survival rates, with a 20% 5-year survival for all stages of disease and 47% survival for localized disease in the United States (2). Accurate preoperative staging of esophageal cancer is imperative to determine prognosis and treatment. Staging relies on imaging, most

commonly endoscopic ultrasound (EUS), computed tomography (CT) and positron emission tomography (PET). While magnetic resonance imaging (MRI) has always shown promise in its ability to accurately stage esophageal cancer, it has not been adopted as a common tool for this purpose. However, continued advancements in this imaging technology have demonstrated more promise than ever before in its ability to accurately stage esophageal cancer.

Staging (TNM)

The most recent 8th edition of the American Joint



Figure 1 EUS image of the lower esophagus demonstrates a mass invading the muscularis submucosa (arrow), but not the muscularis propria in this patient with a T1b adenocarcinoma. EUS, endoscopic ultrasound.

Committee on Cancer (AJCC) staging of epithelial cancers of the esophagus and esophagogastric junction separates staging classifications into three groups, clinical (cTNM), pathologic (pTNM) and postneoadjuvant (ypTNM). In order to accurately reflect patient survival, separate groupings based on histologic cell type were created for both clinical and pathologic staging. While pathologic staging is the most accurate predictor of survival, clinical staging is paramount in determining which patients are likely to benefit from neoadjuvant therapy and esophagectomy. Post-neoadjuvant staging (ypTNM) has been introduced by the AJCC, but its role in clinical practice is limited (3). Clinical staging is determined mostly by imaging and criteria include depth of tumor invasion, regional lymph node involvement and distant metastasis. CT has been the most frequently utilized modality for staging, though PET with 2-fluoro-2-deoxy-D-glucose (FDG) and EUS are now also commonly utilized. An approach utilizing a combination of all three modalities is now advocated for, as each modality has advantages over another in the staging workup.

T classification

The T classification is determined by the depth of primary tumor invasion into the esophageal wall and by invasion of adjacent structures. T1 tumors invade the lamina propria or muscularis mucosa (T1a) or submucosa (T1b). T2 tumors invade the muscularis propria. T3 tumors invade the adventitia. T4 tumors invade structures adjacent to the esophagus and have been subcategorized into those that are

still surgically resectable (T4a) and those that are generally not resectable (T4b). T4a tumors invade the pleura, pericardium, azygous vein, diaphragm or peritoneum. T4b tumors invade other structures such as the aorta, vertebral body or trachea/mainstem bronchus (3). Accurate clinical T staging (cT) is imperative, as it has important prognostic and treatment implications. cT1 and cT2 cancers are less likely to have nodal metastases and can be treated with surgical resection alone, whereas cT3 and cT4 cancers are likely to have nodal metastases which would require neoadjuvant therapy (4).

EUS

EUS is the most accurate imaging modality in T staging of esophageal cancers, as it is able to distinguish the layers of the esophageal wall. The normal wall exhibits five alternating hyperechoic (white) and hypoechoic (black) layers. EUS can reliably distinguish between cT1/T2 disease, where there is not invasion beyond the muscularis propria, cT3 disease, where there is invasion beyond the muscularis propria and cT4 disease, where there is invasion beyond the adventitia (*Figure 1*). EUS has demonstrated a performance index of 0.89 at discriminating between T1/T2 esophageal cancers from those that are T3 and T4 (5). EUS alone has not been shown to reliably distinguish between cT1a, cT1b and cT2 disease (6-9). EUS is also limited in its ability to accurately stage stenotic tumors that prohibit endoscope passage (10).

CT

Esophageal wall thickening is a non-specific sign of cancer on CT. A normal esophageal wall should always measure less than 5 mm (11), and less than 3 mm in a distended esophagus (12). Wall thickening is also commonly seen in esophagitis. The inability of CT to distinguish the layers of the esophageal wall limits its ability to accurately discriminate cT1, cT2 and cT3 tumors (*Figure 2*). However, CT is the most accurate imaging modality in assessing the presence of cT4 disease, which is excluded by demonstrating a preserved fat plane between tumor and adjacent structures (13). In addition to loss of adjacent fat planes, displacement or indentation of an adjacent structure is also an additional CT criterion for local invasion (14,15). CT has demonstrated sensitivities and specificities ranging from 85–100% in detecting invasion of adjacent mediastinal

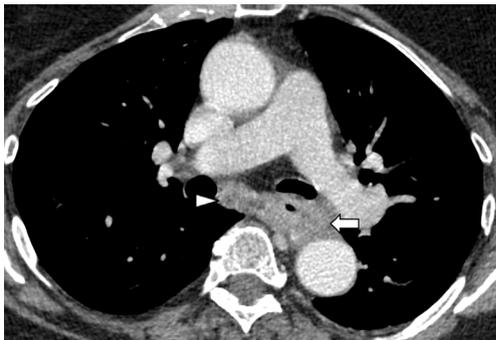


Figure 2 Axial contrast enhanced CT image demonstrates a mid-esophageal mass with circumferential wall thickening and an ill-defined appearance of the adjacent fat in this patient with T3 disease (arrow). Note the enlarged subcarinal metastatic lymph node contributing to N2 disease (arrowhead). CT, computed tomography.

structures (16,17).

FDG-PET

FDG-PET is more sensitive than CT in its ability to detect esophageal cancer (18). However, it has a very limited role in assessing T stage given its inability to accurately assess depth of tumor invasion.

N classification

Pathological nodal status is based on the presence (N1) or absence (N0) of regional periesophageal lymph node involvement. It is the most important prognostic factor in esophageal cancer staging (19). The number of involved nodes determines the N stage, with N1 disease involving 1–2 nodes, N2 disease involving 3–6 regional nodes and N3 involving 7 or more regional nodes. Clinical nodal classification (cN) indirectly assesses the potential for a lymph node to harbor metastatic disease and primarily is accomplished by utilizing EUS, CT and FDG-PET, each of which has its own limitations.

EUS

EUS is able to evaluate the size, shape, border, cortical thickness and internal echotexture of regional lymph nodes. Characteristics which make nodal involvement more likely include larger size, rounded morphology and a well-demarcated hypoechoic appearance. EUS is more

accurate than CT in determining likelihood of lymph node involvement, with accuracy rates of 72–80% (20,21). However, EUS was only 20% specific in a more recent assessment that used criteria of >5 mm in size, round border, smooth shape and hypoechoic center as indicators of lymph node involvement (22).

CT

CT depends primarily on size criteria, where intrathoracic and abdominal lymph nodes larger than 1 cm in short axis and supraclavicular lymph nodes larger than 0.5 cm are considered abnormal (23,24). False negative assessments can occur in normal sized lymph nodes that contain metastatic disease and when positive lymph nodes are in close proximity to and obscured by the primary tumor (25). False positive assessments can occur when reactive lymph nodes become enlarged. CT is therefore less accurate at predicting lymph node involvement than EUS, with accuracy rates of 46–58% (20,21).

FDG-PET

FDG-PET is more specific than CT at predicting lymph node involvement, as it is able to detect both size and degree of hypermetabolic activity. In a meta-analysis FDG-PET was 57% sensitive (range of 43–70%) and 85% specific (range of 76–95%) (26). The lower sensitivity may result from difficulty in distinguishing peritumoral lymph nodes that are obscured by the hypermetabolic primary tumor and from the presence of hypermetabolic reactive nodes. The high specificity of FDG-PET makes it an excellent modality to confirm cN0 disease.

Given the importance of accurate cN staging and the somewhat limited sensitivity or specificity of the imaging modalities, histologic confirmation of cN with EUS-guided fine-needle aspiration (FNA) is critical and is strongly recommended by the AJCC (27).

M classification

Hematogenous metastasis of esophageal cancer to distant organs defines the M classification, designated as absent (M0) or present (M1). Early detection of distant metastatic disease is very important in determining the most appropriate treatment. The presence of metastatic disease has been reported in 20–30% of esophageal cancer patients, with liver, lungs and bones being the most commonly

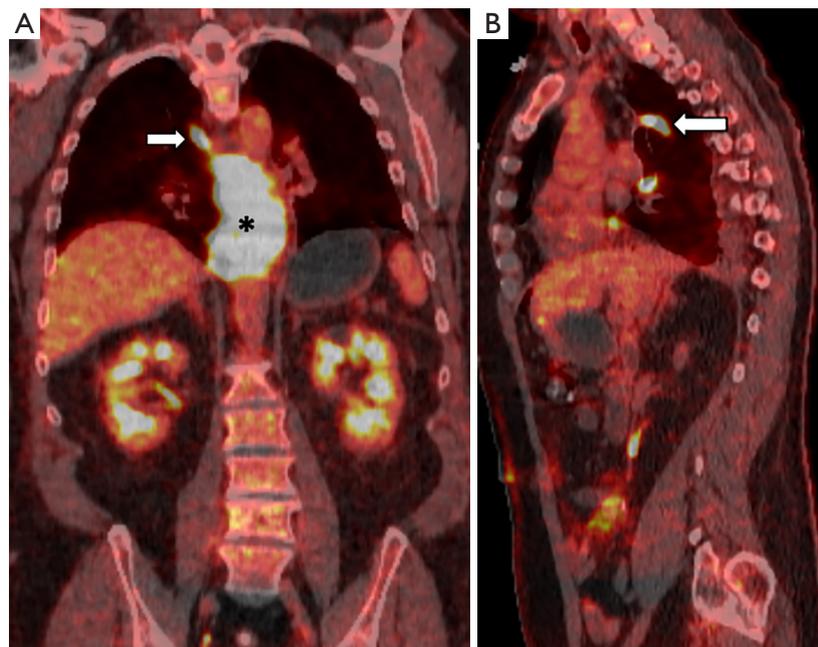


Figure 3 Coronal (A) and Sagittal (B) FDG-PET/CT fused image demonstrates a large mid and lower esophageal hypermetabolic mass extending beyond the adventitia (asterisk). There is also hypermetabolic tumor extending into and along the azygous vein in this patient with T4a adenocarcinoma (arrow). FDG-PET, 2-fluoro-2-deoxy-D-glucose positron emission tomography; CT, computed tomography.

involved organs (28,29).

EUS

The value of EUS in screening for distant metastases is extremely limited, as the distant organ being evaluated must be in direct with the upper gastrointestinal tract.

CT

CT has long been the mainstay for assessment of metastatic esophageal cancer. It has the ability to detect metastasis in the most commonly affected organs, lungs, liver and bones. It has demonstrated a high specificity of 91%, but a low sensitivity ranging from 37–66% (26,30).

FDG-PET

FDG-PET is able to detect additional sites of esophageal cancer metastasis not detected by conventional CT. It has the advantage over CT of offering both total body coverage and functional assessment, allowing detection of unsuspecting metastatic lesions (*Figure 3*). It has a similar specificity of 93%, but markedly improved sensitivity of

71% compared to CT (26). FDG-PET has been shown to affect M stage in 24% of patients, upstaging from M0 to M1 disease in 22% and downstaging from M1 to M0 disease in 2% (31). PET does have limitations, including false positive findings in the setting of infection or inflammation and false negative results in types of esophageal cancer which fail to demonstrate hypermetabolic activity.

MRI

While a combination of EUS, CT and PET have become the standard imaging modalities utilized in esophageal staging, each has its limitations. Continued advancements in MRI have demonstrated more promise than ever before in its ability to accurately stage esophageal cancer. Advantages of MRI include total body coverage, lack of ionizing radiation and contrast agents with lower risk profiles and less restrictions of their use.

Regional MRI

Initial *in vitro* high-resolution MRI of resected esophageal specimens demonstrated the ability to differentiate 8 layers of the esophageal wall, which exhibit alternating low and

high signal intensities from the mucosa to the adventitia (32). Early *in vivo* MRI using a high resolution T2-weighted sequence demonstrated three distinct layers of the esophageal wall, the intermediate signal mucosa, surrounded by the high signal intensity submucosa, followed by the low signal intensity muscularis propria. The high signal intensity periesophageal fat and structures within it were also clearly demonstrated. Esophageal cancers are most commonly of intermediate signal intensity, though tumors with fibrosis demonstrate lower signal intensity and mucinous tumors demonstrate high signal intensity. An initial proposal for MRI criteria for local staging was as follows: T1 exhibits no discernable tumor; T2 exhibits tumor within the submucosa and muscularis propria, but with an intact outer margin of the muscularis propria; T3 exhibits nodular irregularity of the outer margin of the muscularis propria and extension into the periesophageal fat; and T4 exhibits tumor extending into adjacent structures. It was demonstrated that MRI was able to accurately distinguish between T2 and T3 disease and could also clearly diagnose invasion of adjacent structures in T4 disease (33).

A prospective study comparing MRI with diffusion-weighted imaging (DWI) to EUS, CT and PET in preoperative staging of esophageal cancer demonstrated that MRI showed the highest specificity (92%) and positive predictive value (80%) for T-staging, but with a reduced sensitivity of 67%. EUS was the most sensitive (100%) and had the highest negative predictive value (100%) for T-staging. Both MR and EUS demonstrated a 100% sensitivity for N-staging, though with very low specificities of 57% and 36% respectively (34).

MRI is susceptible to motion artifact, namely cardiac and respiratory motion in the case of esophageal cancer imaging. These limitations can be mitigated by applying cardiac and respiratory gating, though with resulting longer acquisition times. Advances in MR technology that utilize radial sampling allow for shorter, free breathing techniques without degradation of image quality (35). Two vendor specific sequences, T2-weighted turbo spin-echo (TSE) BLADE and StarVIBE (Siemens Healthcare, Erlangen, Germany) were used for T-staging of esophageal cancer (Figure 4). A combination of these sequences after neoadjuvant chemotherapy was very accurate in correctly staging T1–T4 lesions, with areas under the curve (AUCs) of 0.886 for T1, 0.917 for T2, 0.943 for T3 and 0.930 for T4. The AUC for T0 tumors was the lowest at 0.667. The high-resolution delayed phase StarVIBE had the highest accuracy in correctly staging T0, T1, T2 and T4 tumors

(AUCs of 0.667, 0.886, 0.917 and 0.930 respectively), while the T2-weighted TSE BLADE was the most accurate sequence for T3 tumors (AUC of 0.952) (36).

Apparent diffusion coefficient (ADC)

DWI is a MR sequence based on the motion of water molecules. The diffusion of water molecules, which is impaired in cancer cells, can be expressed quantitatively as ADC values. There is not a correlation between ADC values and pathologic types of esophageal cancer. However, a correlation between ADC value and histologic grade has been demonstrated, with poorly differentiated tumors exhibiting lower ADC values (37). The degree of change in ADC values before and after neoadjuvant therapy has been shown to correlate with response to treatment, which could potentially be used to determine response to treatment, similar to how standardized uptake values (SUVs) are currently used to measure response to treatment with PET (38,39). There is conflicting evidence on whether pre-treatment ADC values can predict response to neoadjuvant therapy, with one study demonstrating lower ADC values in patients that were likely to respond to neoadjuvant therapy, while others demonstrated higher ADC values predicted a good response (40-42).

Nodal MRI

MRI has been traditionally challenged in its ability to accurately predict nodal metastases given that it relies on size in making this determination. Most of the metastatic lymph nodes in esophageal cancer measure less than 1 cm, below the typical imaging threshold used for suspected lymph node metastases (43). Utilizing a STIR TSE sequence with electrocardiogram (ECG) gating resulted in improved accuracy in predicting lymph node metastases, with a sensitivity of 81% and specificity of 98%, compared to 36% sensitivity and 86% specificity with conventional MRI (44).

ADC values obtained from DWI MR can also improve detection of lymph node metastases, as ADC values are lower in metastatic than in benign lymph nodes (45,46). DWI has been shown to offer similar specificity, but improved sensitivity (67%) compared to conventional FDG-PET (32%) in detecting metastatic lymph nodes in patients with squamous cell esophageal cancer (47).

MRI enhanced with superparamagnetic iron oxide (SPIO) and ultrasmall SPIO (USPIO) nanoparticles has been shown

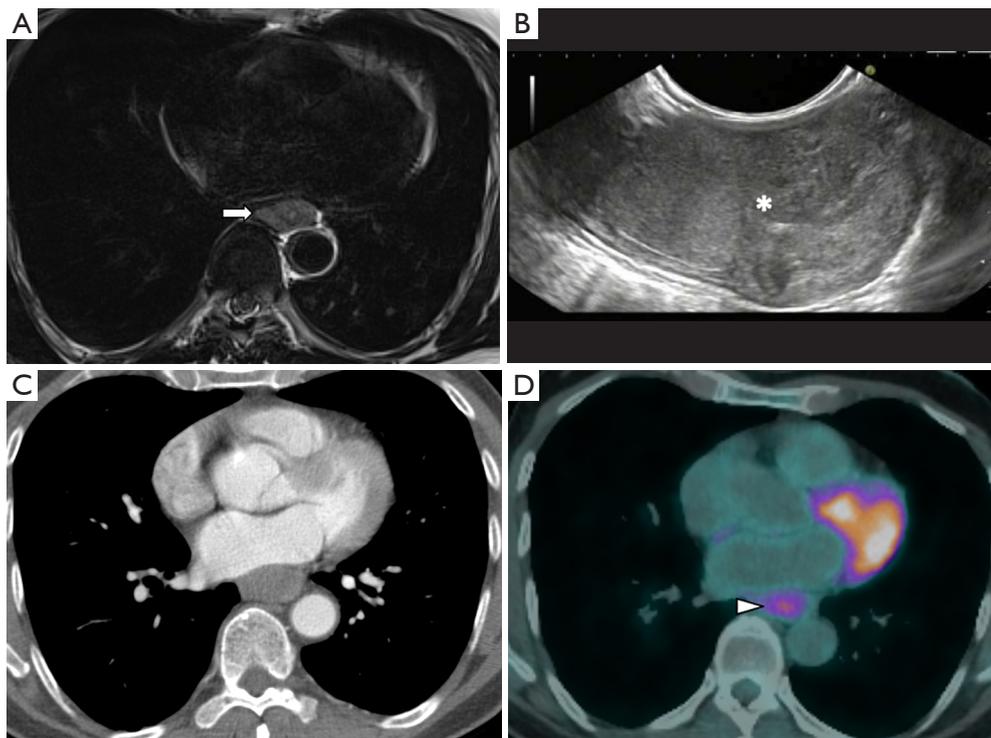


Figure 4 Axial MR T2 BLADE image (A) demonstrating a hyperintense mid-esophageal submucosal mass (arrow) which invades the muscularis propria, but not the adventitia, in this patient with T2 adenoid cystic carcinoma; (B) EUS image in the same patient demonstrates the submucosal mass is fairly homogeneous and well-circumscribed (asterisk); (C) axial contrast enhanced CT image demonstrates the mass does not invade in the peri-esophageal fat nor adjacent structures; (D) FDG-PET/CT fused image demonstrates the mass is metabolically avid (arrowhead) without metastatic disease. MR, magnetic resonance; FDG-PET, 2-fluoro-2-deoxy-D-glucose positron emission tomography; CT, computed tomography.

to be useful for the detection of metastatic tumors in lymph nodes, even in nodes that are not enlarged by traditional criteria. These nanoparticles are unable to phagocytosed by lymph nodes involved by tumor because they lack reticuloendothelial cells. As a result, they appear dark on T2-weighted images because of their superparamagnetic effect (48). Limited feasibility studies in esophageal cancer patients have demonstrated that this technique was able to accurately identify the majority of metastatic mediastinal and celiac axis lymph nodes (49).

Total body MRI

A total body MRI approach with tailored sequences to detect metastasis demonstrated the ability to detect 98% of primary esophageal lesions, compared to 96% for PET/CT. This technique also demonstrated a sensitivity of 27%, specificity of 100% and accuracy of 56% in detecting nodal

metastases, compared to 30%, 100% and 60% respectively for PET/CT. Both modalities detected distant metastases in two patients (42,50).

PET/MR

Previous studies have demonstrated conflicting results as to whether SUV measurements with FDG-PET can predict outcomes in patients with esophageal cancer (51-53). Integrated 18F-PET/MRI combines whole body MRI and PET, which can therefore provide functional information in the form of both ADC values from DWI and glycolytic activity from PET. This functional information has been shown to correlate with TNM staging in patients with esophageal carcinoma. The minimum ADC value exhibited the strongest inverse correlation with SUVs and was lower in higher T-stage tumors. Volume based parameters can also be calculated and include total lesion glycolysis and

metabolic tumor volume, which were more accurate at predicting T- and N-stage respectively, than were ADC values (54).

MRI and response to neoadjuvant chemoradiotherapy

Neoadjuvant chemoradiotherapy can result in a complete pathological response in 25–30% of patients with locally advanced esophageal cancer (55). These patients may not require surgical resection and identifying them is therefore important, though CT, FDG-PET/CT and EUS are limited in their ability to do so given the difficulty in discriminating residual tumor from radiation esophagitis and residual wall thickening (56). MRI utilizing both T2-weighted and DWI sequences demonstrated a higher sensitivity in detecting residual disease at 90–97%, though with a specificity of only 42–50% (57). Use of MRI alone would therefore result in many complete responders being misdiagnosed as having residual disease, and therefore a combination of modalities is therefore needed to correctly diagnose complete responders.

Additional applications

MRI has shown promise in its ability to assess for non-neoplastic diseases. Dynamic or functional MR can assess for gastroesophageal reflux disease, achalasia and other motility disorders (58–61). It can also be used to assess postoperative complications of esophageal surgery such as fundoplication (62). While it offers the advantages of lack of ionizing radiation and increased spatial resolution, the increased time, cost and less availability compared to traditional fluoroscopy make routine and widespread utilization of MRI for these purposes unlikely.

Conclusions

Preoperative staging and assessment of neoadjuvant treatment response in esophageal cancer most often relies on a combination of EUS, CT and/or PET. Each of these modalities has its advantages in being able to accurately determine TNM stage. MRI has always shown promise in its ability to accurately stage esophageal cancer, but it has not yet achieved widespread adoption for this purpose. Technological advancements in MRI have resulted in improved image quality and faster acquisition times and recent research has demonstrated that MRI can be an

integral part in the clinical staging of esophageal cancer.

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